Single Technology Appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including Review of TA594) [ID6334]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Takeda:**
   a. Company submission
   b. Company addendum
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Lymphoma Action

4. **Expert personal perspectives** from:
   a. Dr Cathy Burton – clinical expert, nominated by Takeda
   b. Professor Graham Collins – clinical expert, nominated by Takeda

5. **External Assessment Report** prepared by BMJ Technology
   a. External Assessment Report
   b. EAG critique of company addendum

6. **External Assessment Report – factual accuracy check**

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

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Document B

Company evidence submission

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Tables and Figures

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Abbreviations

A	Brentuximab vedotin
A+AVD	Brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
ADC	Antibody–drug conjugate
AE	Adverse event
AFM	Alternative frontline medication
AIC	Akaike Information Criterion
ALCL	Anaplastic large cell lymphoma
AlloSCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukaemia
ARDS	Acute respiratory distress syndrome
ASCT	Autologous stem cell transplantation
AUC	Area under curve
AVD	Doxorubicin, vinblastine, dacarbazine
BEACOPDac	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BEACOPP-14	14-day bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone regimen
BIC	Bayes Information Criterion
BNF	British National Formulary
BSA	Body surface area
BSH	British Society for Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CDF	Cancer Drugs Fund
CHP	Cyclophosphamide, doxorubicin, and prednisone
CI	Confidence interval
COMP	Committee for Orphan Medicinal Products
CR	Complete remission
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
DCO	Data cutoff
DLBCL	Diffuse large B-cell lymphoma
DS	Deauville score
DSU	Decision support unit
EAG	External assessment group
ECDRP	European Commission Decision Reliance Procedure
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic marketing information tool
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of treatment
esc	Escalated
ESMO	European Society of Medical Oncology
FACIT	Functional Assessment of Chronic Illness Therapy
FACT/GOG-NTx	Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity subscale
G-CSF	Granulocyte-colony-stimulating factor
GHSG	German Hodgkin Study Group
HCRU	Healthcare resource utilisation
HDCT	High-dose chemotherapy
HF	Heart failure
HL	Hodgkin lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HRS	Hodgkin and Reed-Sternberg
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent data and safety monitoring committee

ILD	Interstitial lung disease
INV	Investigator
IPS	International Prognostic Score
IQR	Interquartile range
IRF	Independent review facility
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
LTFU	Long-term follow up
LY	Life year
LYG	Life year gained
MAIC	Matched adjusted indirect comparison
MCM	Mixture cure models
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Multidimensional Fatigue Inventory
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimally important difference
MMAE	Monomethyl auristatin E
NA	Not applicable
NE	Not estimable
NHS	National Health Service
NMB	Net monetary benefit
ORR	Overall response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD	Progressive disease
PET	Positron emission tomography
PET2	Positron emission tomography after cycle 2
PFS	Progression-free survival
PMN	Peripheral motor neuropathy
PN	Peripheral neuropathy
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PTFU	Post-treatment follow-up
PVLE	Present value lifetime earnings
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life questionnaire
QoL	Quality of life
RATHL	Response-Adapted Therapy for advanced Hodgkin Lymphoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
R/R	Relapsed or refractory
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SoC	Standard of care
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTO	Time trade-off
VAS	Visual analogue scale
VHD	Valvular heart disease
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WHO	World Health Organization
WPAI:CG	Work Productivity and Activity Impairment Caregiver questionnaire
WTP	Willingness-to-pay

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

Hodgkin lymphoma (HL) is a rare cancer, comprising fewer than 1% of all new cancer cases, and is caused by malignant B-lymphocytic cells.[1, 2]

- Classical HL, which comprises 95% of all HL cases, is characterised by the presence of the cell membrane antigen CD30.[3–5]
- Patients with HL can experience substantial disease burden, including debilitating B symptoms (night sweats, fever, and unexplained weight loss), anaemia-related fatigue, shortness of breath, pain, and jaundice, depending on the spread and location of malignant cells.[6–9]

Compared with patients with early-stage disease (Stage I and II HL), those with Stage III or IV HL are more likely to experience these B symptoms that impact their daily living, and have poorer 5-year net survival rates of 70–80%, compared with 90% in Stage I–II HL[a].[6, 10]

In England and Wales, there are approximately 820 patients each year with untreated CD30-positive (CD30+) Stage III or IV HL.[11]

The goal of first-line treatment for HL is cure, without the need for additional therapy, particularly in patients with Stage III or IV HL.[6]

- Current standard-of-care (SoC) for untreated patients with HL – typically combination chemotherapy – has remained largely unchanged for nearly 50 years, and regimen adaptations have focused on improving tolerability without losing efficacy.[6, 12–16]
- Combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) – the relevant comparator for this appraisal – is associated with 4- and 10-year progression-free survival (PFS) rates of 73% and 69% in real-world studies, respectively, and 4-year and 5-year overall survival (OS) rates of 87% and 84%, respectively.[17–19]

Current treatment strategies in previously untreated HL are associated with substantial patient burden.

- In particular, long-term treatment toxicities, such as the pulmonary toxicities associated with bleomycin-based regimens, remain an issue in previously untreated CD30+ Stage III or IV HL.[5, 20, 21]
- Treatment for Stage III or IV HL is associated with a high risk of developing second malignancies, which form the largest cause of mortality in long-term HL survivors.[5, 20]

Approximately 20–30% of patients with Stage III and IV[b] HL are not cured at first line and require subsequent treatments.[12, 22, 23]

- Intensive subsequent treatments have the potential to substantially impair the patient's quality of life, and will lead to increased healthcare system burden and additional costs.[20, 24–30]

[a] Proportions shown are sourced from the Office for National Statistics and include all patients, irrespective of whether treatment was administered, treatment type, or baseline characteristics within stage groups.

[b] Note: published data refer to 'advanced stage' HL. This is predominantly patients with Stage III or IV HL, but may also include a small proportion of patients with high-risk Stage II disease, who are typically managed as per Stage III or IV disease.[15]

For patients with previously untreated CD30+ Stage III or IV HL suitable for ABVD[c], brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (AVD) provides the first targeted therapy at first line.[16, 31, 32]

- Brentuximab vedotin is a CD30-targeted antibody–drug conjugate (ADC) therapy that selectively targets the 95% of all HL that express CD30, providing improvements in both PFS and OS while avoiding the bleomycin-related toxicities associated with the current SoC.[3, 4, 31, 33, 34]

B.1.1 Decision problem

The submission covers the technology's anticipated marketing authorisation for this indication, namely brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) as a treatment for adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma (HL).

A summary of the decision problem is shown in Table 1. The company submission is in line with the technology's anticipated marketing authorisation for this indication.

Of note, brentuximab vedotin has previously been assessed by NICE for the following indications:

- Brentuximab vedotin for treating CD30+ Hodgkin lymphoma (TA446; CDF review TA524)
- Brentuximab vedotin for treating CD30+ cutaneous T-cell lymphoma (TA577)
- Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma (TA641)
- Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma (TA478)

[c] A regimen that starts with two or more cycles of ABVD; Section B.1.3.4.

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	People with previously untreated late-stage classical Hodgkin lymphoma	Adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma	The population was adjusted in line with the anticipated marketing authorisation.[35]
Intervention	Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine	Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine	In line with the NICE final scope and marketing authorisation.[35]
Comparator(s)	Single or combination chemotherapy including but not limited to drugs such as doxorubicin, bleomycin, dacarbazine and vinblastine	Combination chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD-based regimens)	The proposed positioning of A+AVD is for the treatment of previously untreated patients with CD30+ Stage III or IV HL who would otherwise be suitable for treatment with ABVD. In current UK clinical practice, patients suitable for treatment with ABVD will receive an ABVD-based regimen, either as six cycles or as per the PET-adapted RATHL approach.[15] While PET-adapted ABVD is commonplace across the UK, there are centres that do not use PET adaptation (i.e. treat with six cycles of ABVD rather than via the RATHL strategy).[36] Therefore, the comparator in the CEM is ABVD-based treatment, comprised of a weighted average of ABVD (six cycles) and PET-adapted ABVD, (10% and 90%, respectively, based on UK clinical expert feedback).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	As per the final scope, the submission considers the following outcomes: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	In line with the NICE final scope.[35]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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, comparator and subsequent treatment technologies will be taken into account.	The analysis performed is in line with the NICE reference case, and the NICE 2022 health technology evaluation manual; the economic analysis is a cost-utility analysis. Costs and QALYs are considered over a lifetime horizon and will be conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The main output of the economic analysis is the incremental cost-effectiveness ratio (ICER). Certain subsequent treatments included in the economic analysis have confidential PASs in the form of simple discounts. The economic analysis has allowed for inclusion of these simple discounts for subsequent treatments, but the base case analysis reflects list prices for these treatments.	In line with the NICE reference case.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CD30, cell membrane receptor 30; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PSS, Personal Social Services; QALY, quality-adjusted life year.

B.1.2 Description of the technology being evaluated

The technology being evaluated in this submission is described in Table 2. The anticipated summary of product characteristics (SmPC) is presented in Appendix C.

Brentuximab vedotin, one of the first antibody–drug conjugates (ADCs) marketed, was first marketed in 2012 in Europe; and has since been used extensively across multiple indications within the UK clinical community.[33, 37–42]

Table 2: Technology being evaluated

UK approved name and brand name	Brentuximab vedotin (ADCETRIS®)
Mechanism of action	Brentuximab vedotin is an ADC composed of an anti-CD30 monoclonal antibody linked with a microtubule-disrupting, antimitotic drug compound, monomethyl auristatin E (MMAE).[3, 4, 33] Brentuximab vedotin selectively binds to 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, 33] The MMAE cytotoxin inhibits tubulin polymerisation, disrupting the microtubule network, effectively arresting the cell cycle, and resulting in apoptotic cell death.[3, 4, 33]
Marketing authorisation/CE mark status	A regulatory submission was made to the MHRA in October 2022 for the anticipated licensed indication and is currently ongoing: brentuximab vedotin for adult patients with previously untreated CD30+ Stage III Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD). Brentuximab vedotin already has existing marketing authorisation, granted by the MHRA in the following indication of relevance to this submission: • Previously untreated CD30+ Stage IV HL, in combination with AVD (06 February 2019) Brentuximab vedotin has also received GB marketing authorisations for HL, as described below. These were granted through the ECDRP based on EMA marketing authorisations. For HL, marketing authorisation of brentuximab vedotin was granted in adult patients for: • As monotherapy for CD30+ HL at increased risk of relapse/progression following ASCT (26 May 2016) • As monotherapy for relapsed or refractory HL following ASCT or ≥2 prior therapies when ASCT/multi-agent chemotherapy is not a treatment option (25 October 2012) The EMA COMP granted brentuximab vedotin orphan medicine product status for: • Treatment of sALCL (15 January 2009; maintenance of orphan status recommended 24 January 2019) [MA in GB and EU] • Treatment of HL (15 January 2009) [MA in GB and EU] • Treatment of CTCL (11 January 2012) [MA in GB and EU] • The amended indication from systemic anaplastic large cell lymphoma to peripheral T-cell lymphoma (21 August 2019)

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Brentuximab vedotin is anticipated to be indicated for: • The treatment of adult patients with previously untreated CD30+ Stage III or IV HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD). Additionally, brentuximab vedotin holds the following indication of relevance to this submission: • The treatment of adult patients with previously untreated CD30+ Stage IV HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD). Brentuximab vedotin is also indicated for: A. The treatment of adult patients with relapsed or refractory CD30+ HL (R/R HL): (i) following ASCT or; (ii) following ≥2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. B. The treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT. C. The treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL). D. The treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) in combination with cyclophosphamide, doxorubicin and prednisone (CHP). E. The treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after ≥1 prior systemic therapy.
Method of administration and dosage	In the indication of interest for this appraisal, the recommended dose of brentuximab vedotin is 1.2 mg/kg administered as an IV infusion over 30 minutes on days 1 and 15 of each 28-day cycle for six cycles.[43] Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should be administered through a dedicated IV line and it must not be mixed with other medicinal products.[43] Doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 are administered by IV infusion on the same days as brentuximab vedotin for 6 cycles.
Additional tests or investigations	None; CD30 testing is routine NHS practice during HL diagnosis.
List price and average cost of a course of treatment	NHS list price: £2,500 per 50 mg vial Cost per 28-day treatment cycle: £11,231 Average cost per course of treatment (based on 5.5 cycles of brentuximab vedotin and 5.6 cycles of AVD observed in the ECHELON-1 trial and the duration of treatment applied in the CEM): £61,793
Patient access scheme (if applicable)	Unless otherwise stated, the analyses in this submission reflect the 'with PAS' price of brentuximab vedotin. PAS price: [redacted] Cost per treatment cycle: [redacted] Average cost per course of treatment (based on 5.5 cycles of brentuximab vedotin and 5.6 cycles of AVD observed in the ECHELON-1 trial and the duration of treatment applied in the CEM): [redacted]

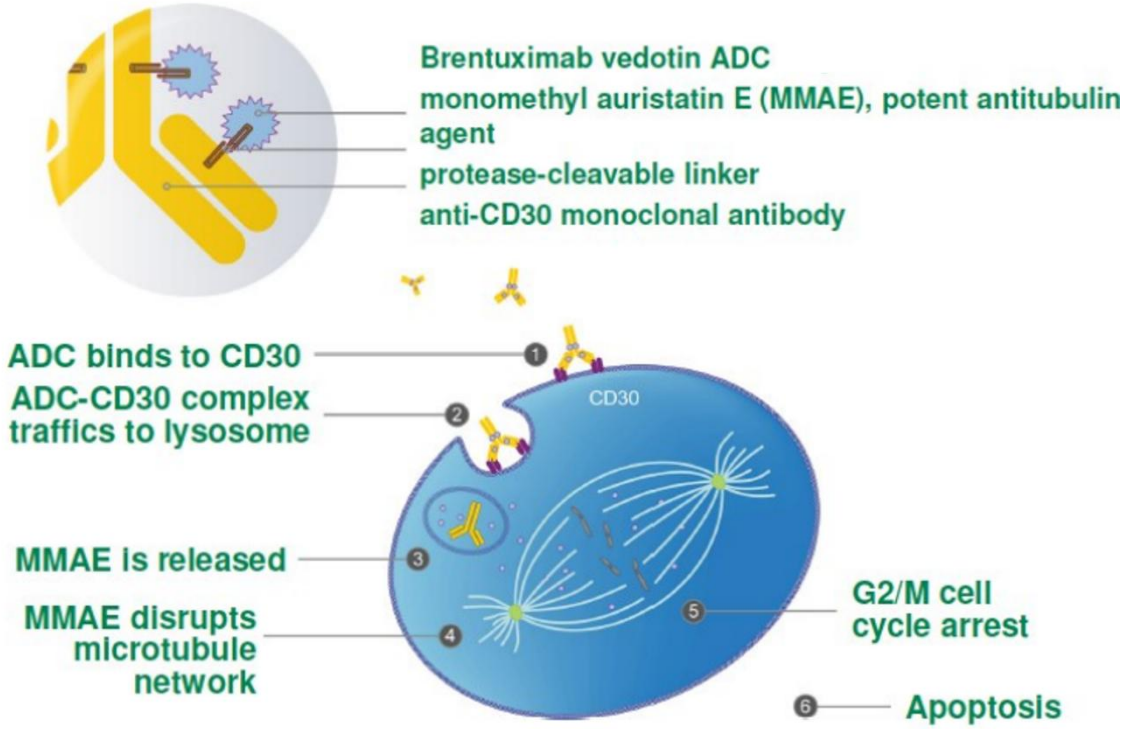
Abbreviations: ADC, antibody–drug conjugate; ASCT, autologous stem cell transplant; AVD, doxorubicin, vinblastine, dacarbazine; CD30, cell membrane receptor 30; CE, European conformity; CEM, cost-effectiveness model; CHP, cyclophosphamide, doxorubicin and prednisone; COMP, Committee for Orphan Medicinal Products;

CTCL, cutaneous T-cell lymphoma; ECDRP, European Commission Decision Reliance Procedure; EMA, European Medicines Agency; EU, European Union; GB, Great Britain; HL, Hodgkin lymphoma; IV, intravenous; MA, marketing authorisation; MHRA, Medicines and Healthcare Products Agency; MMAE, monomethyl auristatin E; NHS, National Health Service; PAS, patient access scheme; R/R, relapsed or refractory; sALCL, systemic anaplastic large cell lymphoma; SmPC, summary of product characteristics; UK, United Kingdom.

Brentuximab vedotin is an ADC composed of an anti-CD30 monoclonal antibody linked with a cytotoxic anti-mitotic drug compound, monomethyl auristatin E (MMAE).[3, 4, 33] Brentuximab vedotin selectively binds to 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).[3, 4, 33]

The CD30 cell surface antigen is expressed in classical HL, also called CD30-positive (CD30+) HL, which comprises 95% of all HL cases; the expression of the CD30 is independent of the disease stage, line of therapy, or transplant status.[3–5, 44] Therefore, CD30-targeting treatments, such as brentuximab vedotin, have the potential to be effective treatments in patients with CD30+ HL. Targeted delivery of MMAE to CD30-expressing tumour cells is the primary mechanism of action of brentuximab vedotin that results in tumour cell death. Additional mechanisms for tumour cell death that contribute to its clinical activity may include antibody-dependent cellular phagocytosis, immunogenic cell death, and bystander effect, as it is the case with the medical effect of an ADC.[3]

Figure 1: Brentuximab vedotin mechanism of action



Abbreviations: ADC, antibody–drug conjugate; CD30, cell membrane antigen 30; MMAE, monomethyl auristatin E; G2, G2 phase of the cell cycle; M, mitosis phase of the cell cycle.
Source: NICE 2020 (TA641).[40]

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

B.1.3.1 Disease overview

Lymphoma is blood cancer that affects white blood cells of the lymphatic system, called lymphocytes.[45] It is divided into two main types: HL and non-HL.[2, 45] In HL, the cancer cells form a minority of the tumour and are surrounded by a reactive inflammatory milieu comprising lymphocytes, eosinophils, neutrophils, histiocytes and plasma cells. The malignant lymphocytes found in HL are referred to as Hodgkin Reed-Sternberg (HRS) cells.[5] HL is subdivided into classical HL and nodular lymphocyte-predominant HL, based on morphology and immunohistochemistry.[2, 5] Classical HL is further divided into four subgroups: nodular sclerosis, lymphocyte-rich, mixed cellularity, and lymphocyte-depleted, of which nodular sclerosis is most common; all subtypes have similar management and prognosis.[6, 46] The malignant HRS cell in all classical HL subtypes exhibits a characteristic immunophenotypic pattern of CD30+, CD15+, and CD45+.[5] Due to expression of CD30, classical HL is also referred to as CD30+ HL; hereafter, classical HL will be described as CD30+ HL.

The most common symptom of HL is lymph node swelling, typically in the neck, armpit, or groin. In the healthy general population, lymph nodes swell when there is an infection, but are usually restored over a short time.[9] With lymphoma, the lymph nodes continue to grow due to the accumulation of excess malignant lymphocytes, which can affect a range of organs and tissues which may be compressed due to the swelling, e.g. persistent nerve pain, breathlessness, or indigestion.[47] Depending on disease severity at diagnosis, patients may also present with potentially debilitating B symptoms, including unexplained profound weight loss (>10% of body weight in 6 months), high fevers, and drenching night sweats.[5, 6] B symptoms are present in up to 30% of patients with HL, are frequent in patients with Stage III or IV HL, and have a substantial negative impact on patient quality of life and activities of daily living.[5, 6]

Patients undergoing first-line treatment for HL commonly experience side effects of the standard of care (SoC) chemotherapy , such as nausea, appetite loss, infections, diarrhoea, constipation, hair loss, and fatigue, negatively impacting their day-to-day lives.[48–51] However, over the longer term, HL treatment is also associated with potentially long-lasting toxicities, including pulmonary toxicities and second malignancies.[21, 29, 32, 51–55]

Factors associated with an increased risk of HL diagnosis include male gender, age, living in a highly developed country, family history of lymphoma, history of illness caused by Epstein-Barr virus, and a compromised immune system.[2, 5, 56–60] Environmental factors (radiation or smoking) and reduced microbe exposure in childhood have also been shown to be associated with an increased risk of HL.[61, 62]

Diagnosis and staging

In the UK, referral for investigation of significant lymphadenopathy may come from general practitioners after patients present with an enlarged lymph node, or from specialist medical or surgical teams. Rapid referral from primary care via a two-week wait pathway is recommended.[63] Pathological diagnosis of HL requires a core-needle biopsy, an adequately

sized surgical specimen, or excisional lymph node biopsy.[28, 63] CD30+ HL is identified by the presence of the cell membrane antigen CD30 and HRS cells, both detected by immunostaining in NHS routine practice.[28, 39, 63]

Following an HL diagnosis, blood evaluation is recommended in the UK during pre-treatment evaluation, to include full blood count, erythrocyte sedimentation rate, renal and liver function, and serology.[15] Patients are then staged using a positron emission tomography (PET) scan, which can accurately detect spread to lymph node(s) and bone marrow involvement – negating the need for bone-marrow biopsy in most cases – and determine the optimal treatment strategy based on disease stage and spread.

Internationally and in the UK, HL is staged using the modified Ann Arbor staging system (also called "Lugano staging system", which is based on the Ann Arbor staging system for lymphomas), based on the number of lymph nodes affected and where the lymphoma is in the body in relation to the diaphragm.[63, 64] In Stage I, HL is limited to one group of lymph nodes, either above or below the diaphragm; in Stage II, the lymphoma is likewise present on one side of the diaphragm (above or below), but in two or more groups of lymph nodes. In Stage III HL, lymph nodes that contain lymphoma are found on both sides of the diaphragm, while in Stage IV HL, the lymphoma has spread to ≥1 body organ outside the lymphatic system (Figure 2).[64]

Following classification of stage by number (I–IV), further staging of disease based on additional risk factors takes place, accounting for the presence of B symptoms and extranodal disease. The letter "A" indicates that there are no systemic symptoms present. The letter "B" indicates the presence of B symptoms (outlined in Section B.1.3.3.1). "E" indicates the presence of extranodal disease, "S" indicates that HL is present in the spleen and thymus, and "X" indicates the presence of bulky disease (Figure 2).[64] In advanced-stage HL, risk can be further assessed using the patient's International Prognostic Score (IPS)[d], of which stage is a component.

Disease stage is critical for the selection of appropriate therapy: Stages I and II are treated as "early-stage" disease, and Stages III and IV are treated as "advanced-stage" disease (Section B.1.3.4.1).[15, 58] In the UK, patients with Stage IIB who have either large mediastinal adenopathy or extranodal disease are typically managed with protocols for advanced-stage disease.[15]

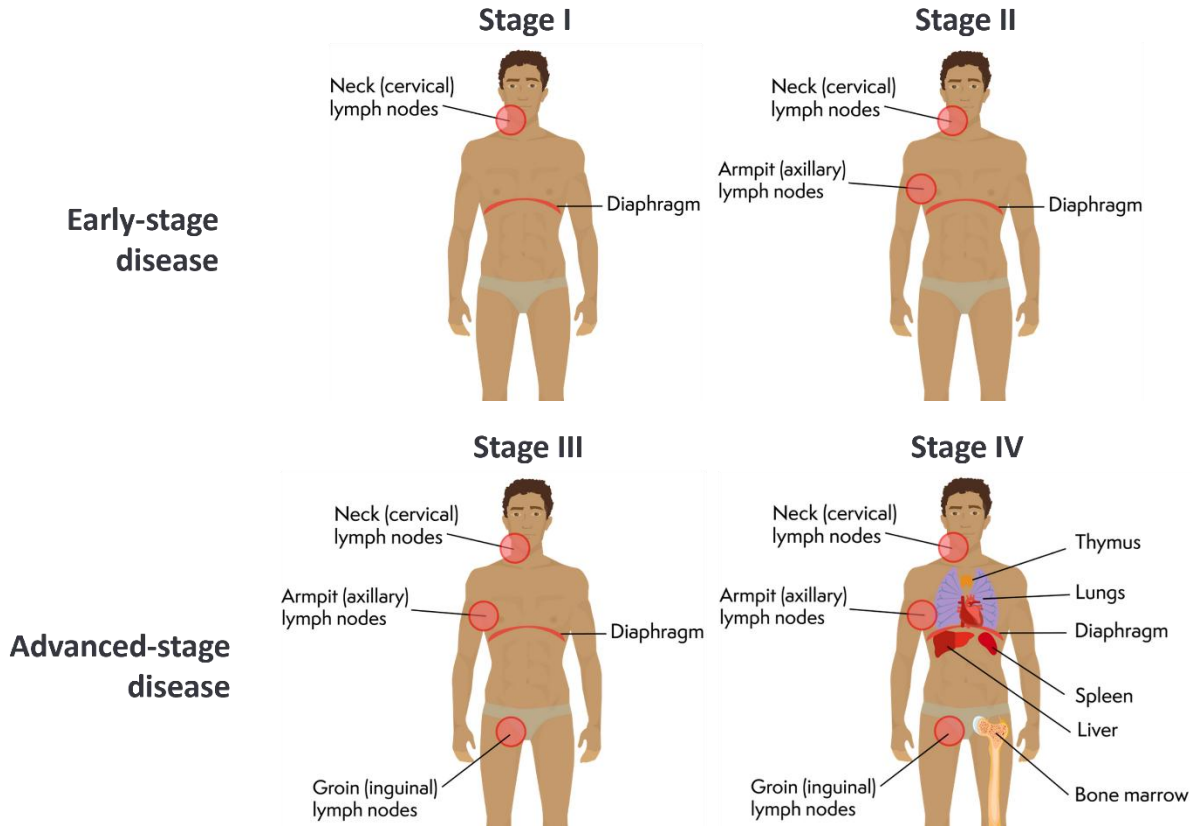
Additionally, staging at diagnosis can predict the patient's risk of dying due to HL. In patients with Stage I or II disease, HL can be curable, with 5-year OS rates of 90%.[10] However, prognosis is worse for patients with Stage III or IV HL, with 5-year OS rates that are 10−20%-points lower than for Stage I or II HL.[6, 10, 12, 14, 36, 56] Approximately 20−30% of patients with Stage III or IV HL are not cured at first line with current SoC treatments (Section B.1.3.4), and need to undergo further treatments upon disease progression[e].[12, 22, 23] Subsequent treatments increase the cumulative dose of chemotherapy, and are therefore associated with an increased risk of second malignancies (Section B.1.3.3.2) in patients with

[d] IPS includes seven factors: (1) Stage IV disease; (2) age ≥45 years; (3) male gender; (4) white blood count ≥15,000/mm^3; (5) lymphocyte <600/mm^3; (6) albumin <4.0 g/dL; (7) haemoglobin <10.5 g/dL.[6, 15, 65]

[e] Note: published data refer to 'advanced stage' HL. This is predominantly patients with Stage III or IV HL, but may also include a small proportion of patients with high-risk Stage II disease, who are typically managed as per Stage III or IV disease.[15]

HL, compared with patients who receive a low cumulative dose (e.g. those who are cured by a single line of therapy); additionally, subsequent treatments are associated with a burden upon the healthcare system (Section B.1.3.3.4).[20, 24, 26–30, 66] Moreover, prognosis worsens with each subsequent line of treatment, and relapsed or refractory (R/R) HL has a cure rate of approximately 50% (Section B.1.3.3.1).[12, 28, 67]

Figure 2: Staging of HL in adults



Stage I: lymphoma only extends to one group of lymph nodes, e.g. the cervical lymph nodes.
Stage II: lymphoma is in two or more groups of lymph nodes, which are both on the same side of the diaphragm, e.g. the cervical and axillary nodes. **Stage III:** lymphoma is in lymph nodes on both sides of the diaphragm. **Stage IV:** lymphoma has spread to ≥1 organ outside the lymphatic system. **Stage (N)A:** no B symptoms present. **Stage (N)B:** B symptoms are present. **Stage (N)E:** the origin of the lymphoma was extranodal, e.g. digestive or salivary glands. **Stage (N)S/T:** lymphoma is present in the spleen/thymus. **Stage (N)X:** presence of bulky disease.
Abbreviations: HL, Hodgkin lymphoma.
Source: adapted from Lymphoma Action, 2022.[64]

B.1.3.2 Epidemiology

HL comprises 10–15% of all lymphomas, and approximately 95% of all HL cases are CD30+ HL.[56, 68] HL is a rare cancer, accounting for less than 1% of all new cancer cases, with approximately 2,100 new cases of HL diagnosed in the UK every year;[1] however, it is the most common cancer in teenagers and young adults globally.[2, 69] Incidence is bimodal, with incidence peaking at ages 20–24 years and 75–79 years; though cases are highest in young patients, age-specific incidence rates are highest in patients aged 75–79 years.[1, 69] As such, treatment choice depends on a careful assessment of the patient's risk profile, fitness, and personal priorities.[15] For example, the potential for impaired fertility and late second

malignancies in young patients, or the impact of short-term toxicities in elderly and/or "frail" patients (Section B.1.3.3.2).[15, 70]

According to Cancer Registration Statistics, there were 1,861 new cases of HL in England in 2021, of which 822 were Stage III or IV.[11] Welsh Cancer Intelligence and Surveillance Unit (WCISU) indicate 85 new cases of HL diagnosed in Wales in 2020, of which 13 were Stage III and 27 were Stage IV.[71] Considering that 95% of HL is CD30+, it is estimated that 781 and 38 patients with CD30+ Stage III or IV HL were diagnosed in England and Wales in 2021 and 2020, respectively.[28]

B.1.3.3 Burden of CD30+ HL

B.1.3.3.1 Clinical burden

Disease symptoms

At diagnosis, the most common symptom of HL is swelling in lymph nodes, but approximately 30% of patients experience potentially debilitating B symptoms, including unexplained profound weight loss, high fevers, and drenching night sweats.[6–9]

"I had been gradually losing weight, and I'd had a couple of infections needing antibiotics. I put those down to stress, but then I felt a hard lump on my neck just above my collar bone. This definitely set the alarm bells ringing, but the final straw came when I started to feel pain in my chest whenever I took a deep breath." Sarah, diagnosed with HL at age 26.[72]

Other symptoms include fatigue, itching, coughing or shortness of breath, abdominal pain, or vomiting after drinking alcohol.[6, 9] Enlarged lymph nodes can lead to pain from nerve compression, cause swelling in arms or legs, and cause yellowing of skin and eyes (jaundice).[6, 9] Patients with HL also report high levels of fatigue (Section B.1.3.3.3).[73]

Presence of B symptoms is more frequent in patients with Stage III or IV HL than in Stage I and II HL.[5, 6] Likewise, patients with Stage III or IV HL more often experience symptoms such as severe dyspnoea and appetite loss than patients with early-stage disease (Section B.1.3.3.3).[74]

Survival outcomes

For patients who are not cured of HL, the most detrimental impact is increased mortality, particularly in patients with Stage III or IV HL, where cure rates may be as low as 70%, increasing the likelihood of patients progressing or dying due to their disease (Section B.1.3.1).[12, 22, 23] In 2022 alone, over 22,000 people died from HL worldwide, of whom 301 were in the UK, representing approximately 14% of the number of HL cases diagnosed in the UK each year.[1, 75, 76]

Long-term survival outcomes vary depending on disease stage at diagnosis and worsen if patients present with Stage III or IV disease vs. early stages. More advanced disease stage at baseline is associated with an increased risk of disease progression, with 3-year PFS rates of 90.0%, 83.1%, and 79.6% for UK patients with Stage II, III, and IV HL, respectively ($p<0.001$).[77] Survival outcomes (both PFS and OS) deteriorate the more lines of treatment patients receive, and even cured patients may face increased mortality vs. the general population.[67]

Treatment of HL with ABVD was first described nearly 50 years ago, and its use is therefore well established for patients with previously untreated CD30+ Stage III or IV HL (Section B.1.3.4).[16] In two separate real-world studies, ABVD is associated with 4- and 10-year progression-free survival (PFS) rates of 73%[f] and 69%[g], respectively.[17, 19] OS rates have been reported as 87%[f] and 84%[g] at 4 and 5 years, respectively, and the HD2000 trial reported a 10-year OS rate of 85%[g], albeit for a patient population that included some Stage II HL patients.[17–19, 78] However, the similarity between 5- and 10-year OS rates across studies may also reflect the sustained survival outcomes that result from curative treatments in HL.[6, 36]

Impact of subsequent treatments

Approximately 20–30% of patients with Stage III or IV disease[h] experience disease progression following first-line treatment and require further treatments, which may include high-dose chemotherapy and stem-cell transplantation (SCT), both of which are associated with substantial treatment burden.[12, 22–24, 28, 79] Although the impact of second-line multiagent chemotherapy in HL is not well documented, it is likely to be similar to or greater than that of first-line multiagent chemotherapy; for example, fatigue and the associated quality of life (QoL) impairment, nausea and appetite loss, increased infection risk, alopecia, constipation and diarrhoea.[48–51] In addition, cumulative chemotherapy and its associated toxicities in HL is likely to be similar to other types of cancer and is expected to be associated with cardiac toxicities, impair fertility in young patients, and cause second malignancies, as with first-line chemotherapy; though limited, data in HL support an association between cumulative dose and risk of second malignancies or cardiovascular disease.[29, 32, 48–50, 53, 66, 80]

Subsequent SCT may also impose a substantial HRQoL burden and is associated with cure rates as low as 50%.[12] For example, patients with relapsed or refractory (R/R) HL who receive subsequent SCT have up to an eight-times higher risk of second malignancies vs. patients who are cured at first line, with a reported incidence rate of 4–15% after 15 years (Section B.1.3.3.2).[24, 26–28] Furthermore, survival outcomes in patients with HL worsen in patients who experience disease relapse. In previously untreated advanced HL, 10-year PFS and OS rates of 69% and 85% are reported, as discussed in the previous Section.[17–19, 78] In a long-term analysis[i] of patients with R/R HL after first-line treatment, 10-year PFS and OS was 48.2% and 59.4%, respectively.[67] Though survival outcomes for each line of treatment are not well documented, these data indicate declining survival outcomes in patients who are not cured at first line, highlighting the importance of a first-line cure for patients' overall survival.

B.1.3.3.2 Treatment burden

First-line chemotherapy for HL imposes a substantial side effect burden on patients, with common side effects of current first-line treatments including feeling sick, loss of appetite,

[f] Patients in the study received eight cycles of ABVD.

[g] Patients in the study received six cycles of ABVD.

[h] Note: published data refer to 'advanced stage' HL. This is predominantly patients with Stage III or IV HL, but may also include a small proportion of patients with high-risk Stage II disease, who are typically managed as per Stage III or IV disease.[15]

[i] Based on an analysis of 409 patients evaluable for first relapsed or refractory HL occurring between May 2003 and March 2018 followed from HD13 trial (early-stage, favourable HL, HD14 trial (early-stage unfavourable HL), HD15 trial (advanced-stage HL), and HDR3i trial (R/R HL). Median age at relapse was 38.6 years old (range: 18.4–76.8). At the time of relapse, 80 patients (20%) were not considered for ASCT whereas 329 patients (80%) were intended to receive ASCT.[67]

increased risk of infections, diarrhoea, constipation, and hair loss, all of which are considered to negatively impact the day-to-day lives of patients (Section B.1.3.3.3).[51] Fatigue, a common side effect with HL chemotherapy, is associated with impaired QoL in people with HL.[48–50] For patients who are not cured by first-line treatments and require chemotherapy on disease progression or relapse, the burden of their initial treatment will be repeated.

"I started treatment with ABVD chemotherapy. The first session knocked me off my feet and I felt tired and emotional." Cassi, diagnosed with HL at age 24 years.[72]

Beyond this, first-line treatment for HL is associated with additional side effects impacting major organs, particularly cardiac and pulmonary toxicities.[29, 32, 53–55] Pulmonary toxicities, associated with bleomycin, are of particular importance, as they are likely to persist long term and be only partially reversible, resulting in adverse consequences on pulmonary function in later years for patients who have been cured of HL.[21] HL treatments are also associated with an increased risk of developing second malignancies.[51, 52]

Impaired fertility associated with HL treatments has the potential to create a major psychosocial burden in patients and their relatives, making starting a family an uncertainty or impossibility for survivors.[50, 81, 82] Treatment at first line (ABVD- or bleomycin, etoposide, doxorubicin hydrochloride [Adriamycin], cyclophosphamide, vincristine [Oncovin], procarbazine and prednisone [BEACOPP]-based regimens) can result in reduced fertility in both men and women, and treatment with BEACOPP-based regimens is more likely to persist long term compared with treatment with ABVD, due to the inclusion of procarbazine (a component of the escalated [esc]BEACOPP regimen used by some UK centres for escalation of treatment from ABVD in patients who fail to achieve sufficient response after two cycles), which is associated with an increased risk of infertility (Section B.3.12).[15, 48–50, 81] Therefore, the ability to improve cure rates at first line, whilst simultaneously avoiding the need for treatment escalation to escBEACOPP regimens, is of high importance, especially for patients with fertility considerations.

Consequently, the cumulative impact of HL treatments results in substantially increased morbidity whilst on treatment, and results in morbidity and mortality after treatment vs. the general population.[15] A more pronounced impact is anticipated in patients who relapse and require subsequent treatment compared with those cured at first line, due to the potential for accumulated toxicities across multiple lines of treatment. Despite limited data on the impact of subsequent treatment in HL, it is well established that minimising the number of chemotherapy cycles minimises toxicity.[15] Due to the toxicity burden of first-line treatments in HL, clinical attention in recent years has aimed to maximise tolerability, especially through reduced use of bleomycin and replacement of procarbazine, while maintaining survival outcomes.[15, 21] The ability to improve cure rates at first line, and therefore avoid the need for subsequent treatments, remains an unmet need.

Pulmonary toxicities

ABVD treatment can cause pulmonary toxicities, due to bleomycin, and this is a key treatment consideration for clinicians and patients. Concerns about long-term toxicities around lung function have led to efforts from the clinical community to minimise bleomycin use.[15, 21, 32, 54, 55, 70] The severity of adverse events (AEs) associated with bleomycin-induced

pulmonary toxicity varies, from dyspnoea to interstitial pneumonitis and lung fibrosis, meaning the patient impact extends from limiting daily activity and reducing QoL, to death.[54, 83]

Recent data from the RATHL trial (Section B.1.3.4) in the UK have shown reduced lung diffusion capacity in patients treated with ABVD- (69.6%; 95% CI: 64.9–74.1%) or BEACOPP-based treatments (68.5%; 95% CI: 59.8%–76.9%) vs. treatment with AVD (i.e. omission of bleomycin; 81.4%; 95% CI: 77.4–85.2%) after 2 years since end of treatment.[21] Additionally, patients treated with ABVD showed slower recovery in lung diffusion capacity compared with those treated with AVD (hazard ratio [HR]: 0.71; 95% CI 0.57–0.90; p=0.004) with reduced diffusion capacity persisting at 5 years.[21] In another retrospective analysis of 126 ABVD-treated patients with HL, OS was negatively impacted by bleomycin-induced pulmonary toxicity (HR: 3.6; 95% CI: 1.2–10.6), but not bleomycin omission (HR: 1.3; 95% CI: 0.5–3.7).[83] These data suggest that even two cycles of ABVD treatment may result in long-term consequences on pulmonary function, and support avoidance of bleomycin in HL treatment regimens where possible.[21, 83]

In patients aged >60 years, who are fit enough to receive combination chemotherapy, the use of bleomycin requires caution, and omission of bleomycin from ABVD (i.e. treatment with AVD) is recommended by the BSH (Section B.1.3.4.1).[15] The incidence of bleomycin-related lung toxicity ranges from 5–31% in older patients with HL (age ≥60 years), with increased risk seen in those aged >70 years vs. 60–69 years.[84]

Second malignancies

After treatment for HL, there is a high risk of second and multiple cancers, forming the largest cause of mortality in long-term survivors of HL.[5] The most commonly-reported second malignancies include solid tumours, such as breast and lung cancer, whereas development of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) are also of major concern following treatment with alkylating agents, including procarbazine.[6, 31, 85] In HL survivors who received first-line treatment, a study from the Netherlands reported that the risk of being diagnosed with any type of cancer was almost five times higher in HL survivors vs. the general population (Standardised Incidence Ratio [SIR]: 4.6; 95% CI: 4.3−4.9).[86] Risks that were more than 10 times as high as those observed in the general population were seen for thyroid cancer, soft-tissue sarcoma, mesothelioma, and non-HL, whereas risks were 5–10 times as high for oesophageal, stomach, pancreatic, lung cancer, and leukaemia.[86] Likewise, 5% of patients who received first-line treatment for advanced HL pooled across four randomised trials had developed a second malignancy by 7 years' follow-up.[87] Similar results were observed in the 7-year follow-up of the RATHL trial, where the cumulative incidence of second malignancies was 5.5% (95% CI: 4.0–7.5%) in patients with HL treated at first line with ABVD, with or without de-escalation (incidence in patients receiving ABVD: 7%; incidence in patients receiving AVD: 5%)[j].[88] Second malignancies are associated with an inherent impact on prognosis, given that they form the largest cause of mortality in long-term survivors of HL.[5, 6]

[j] Patients received 2 cycles of ABVD; those who were subsequently PET negative were randomised to either a further four cycles of ABVD or de-escalation to four cycles of AVD.[88]

Due to the cumulative effect of treatment, second malignancies are expected to occur at higher rates in patients who are not cured at first line and receive subsequent treatment, compared with patients who achieve first-line cure.[66, 89] For example, patients who receive subsequent SCT (of any type) are associated with a higher long-term risk of developing second malignancies vs. patients who are cured following first line treatment.[24, 26–28] Whether due to the cumulative impact of multiple rounds of therapy or the high-dose conditioning regimens required for SCT, the rates of second malignancies post-SCT are higher than those reported above after first-line treatment: approximately 10–12% of patients receiving SCT develop second malignancies after 15 years, and second cancers account for 5–10% of deaths among recipients who survive for ≥2 years.[24, 26]

Cardiac toxicities

Chemotherapy is associated with a significant 50% increased risk of cardiovascular disease compared with the general population[k], particularly valvular heart disease (VHD; 50% increased risk) and heart failure (HF; three-fold increased risk)[l].[29, 53] However, cardiac toxicity can also occur in the long term, with cumulative mortality in survivors of HL[m] due to cardiovascular disease exceeding that of the general population.[20] Across HL patients (irrespective of disease stage and number of treatment lines received) the anthracycline-associated risk of cardiac toxicity is still significantly elevated after 20 years in HL survivors, for any cardiovascular disease, including VHD and HF.[29]

B.1.3.3.3 Humanistic burden

Patients with HL have a substantial QoL burden from the time of diagnosis and during treatment.[74] Initially, patients experience a negative impact on QoL upon receiving a diagnosis, as well as additional burden from the disease and associated symptoms, and the chemotherapy regimens used to treat it.

Burden of disease on patients' QoL

The patient impact of receiving a diagnosis of HL can include the sudden, emotional challenge of receiving a diagnosis.[90] A European study reported greater impacts upon emotional functioning scores than physical scores, with women with HL reporting lower health-related quality of life (HRQoL) and increased symptom distress than men based on both the EORTC QLQ-C30 and the Multidimensional Fatigue Inventory (MFI) instruments.[91]

"When I first received my diagnosis, it was very overwhelming. I felt frightened about what would happen to me, and anxious at the thought of starting treatment." Paris, diagnosed with HL at age 28 years.[92]

[k] The study included patients with HL treated from 1965 to 1995. From the 1960s to the 1980s, chemotherapy consisted mainly of mechlorethamine hydrochloride, vincristine sulphate [Oncovin], procarbazine, and prednisone (MOPP). In the 1980s, anthracycline-containing regimens, such as MOPP and ABV or ABVD were introduced as part of primary treatment. Standard doses of anthracycline per regimen per cycle were 25 mg/m^2 at days 1 and 15 for ABVD and hybrid MOPP-ABV and 35 mg/m^2 at Day 8 for alternating MOPP-ABVD.[29]

[l] Increased risk of cardiovascular disease compared with the general population (HR: 1.5; 95% CI: 1.2–1.8; p<0.05); increased risk of valvular heart disease (HR: 1.5; 95% CI: 1.1–.2.1; p<0.05) and heart failure (HR: 3.0; 95% CI: 1.9–4.7; p<0.05).[29]

[m] Based on a multicentre cohort of 4,919 patients with any-stage HL in the Netherlands, treated between 1965 and 2000, of which 2,632 (53.5%) were alive at the end of follow-up (median follow-up after HL treatment: 20.2 years; range: 12.1–28.6). Treatment for HL included radiotherapy alone (n=1,175; 23.9%), chemotherapy alone (n=668, 14%), or radiotherapy plus chemotherapy (n=3,056; n=62.1%). Median age at HL treatment was 27.8 years (IQR: 21.4–36.4).[20]

"Hearing the words 'you have cancer' is the most terrifying thing anyone can ever say to you, and not something you expect to hear at the age of 21. Asking a doctor if I'm going to die was the most frightening thing." Faye, diagnosed with HL at age 21 years.[93]

The burden of HL at diagnosis is evidenced by clinically relevant impairments across most functional and symptom scales of EORTC QLQ-C30, for patients with all stages of HL.[74] In one study, substantially poorer QoL was reported by patients with HL vs. both the general population and HL survivors, via lower mean scores in Physical, Role, and Social Functioning subdomains of the EORTC QLQ-C30[n].[94] The greatest decrement (highest mean scores) reported by patients with HL were fatigue (mean: 50.0; SD: 27.2), insomnia (mean: 49.4; SD: 36.7), and pain (mean: 34.2; SD: 32.2).[94]

Compared with the general population, patients with HL report higher rates of anxiety (23% vs. 13%) and depression (18% vs. 12%)[o].[95] In a Danish study of 945 patients with HL and 4,725 matched persons, the use of psychotropic drugs was higher among patients with HL vs. the matched population (21.5% vs. 8.4%; HR: 2.6; 95% CI: 2.2–3.1; p<0.001).[96] In addition, rates of psychotropic drug prescriptions were significantly higher in patients with advanced disease than those with early-stage HL (HR: 1.8; 95% CI: 1.4−2.4; p<0.001), driven largely by increased antidepressant use. Disease relapse is also associated with an increased patient burden.[96, 97] Most physical, psychological, and socio-economic sequelae are significantly more frequent among relapsed than cured patients (p<0.05).[97]

Burden of treatment on patients' QoL

First-line and subsequent treatment for HL (Section B.1.3.4) is associated with short- and long-term QoL decrements, which can drastically impact how patients live their day-to-day lives.[74, 98] Irrespective of disease stage, HRQoL worsens in most domains during treatment; a recent European study reported that fatigue, role functioning, and social functioning were the aspects most affected by treatment.[74] Such data are consistent with previous studies, showing a reduction in role functioning during treatment compared with the general population, and poorer cognitive and social function in patients receiving ASCT (all p<0.01).[98]

As described in Section B.1.3.3.2, reduced fertility in both men and women, and early menopause, are often seen in HL survivors treated with chemotherapy regimens, which can bring substantial humanistic burden to patients.[48–50] The potential impact of chemotherapy on ovarian function can be a major worry, causing substantial distress to patients, and potential loss of fertility can cause strain on personal relationships.[50, 81, 99]

"*Sadly, relationships I've been in have fallen apart as a result of having that conversation about my fertility."* Federica, diagnosed with HL at age 20 years.[99]

After the end of treatment, HRQoL begins to improve and generally remains largely stable from the timepoint of 2 years after end of treatment, highlighting the value of efficacious

[n] The review included five studies: one study included patients with Stage III or IV HL, one study included survivors of Stages IIIb–IV HL, and three studies included survivors of Stages I–II HL.[94]

[o] Based on a Danish cross-sectional survey among in 180 HL survivors and 327 people representing the general population, with a mean time since diagnosis of 4.6 years (SD: 2.9 years; range: 6–122 months) in 180 patients diagnosed with HL between 01 January 1999 and 01 December 2010. Mean time since diagnosis was <5 years in 57% of responders, 5–10 years in 42% of responders and >10 years in 1% of responders.[95]

treatment.[74] However, some aspects of patients' lives can remain affected in the first 2 years after treatment ends.[74, 95, 96] These include fatigue, dyspnoea, sleeplessness, anxiety, depression, and financial problems. In a study of 5,277 patients with HL included in three randomised clinical trials (HD13, HD14, and HD15), financial problems was the most affected domain of HRQoL in the first year of follow-up after end of treatment (EORTC QLQ-C30 deficit scores: 29.1–36.8).[74]

In patients who are not cured at first line, the burden of subsequent treatments – such as SCTs – is substantial. Patients who relapse on first-line treatments require further treatments, including SCT, and cure rates decrease with increasing lines of treatment (Section B.1.3.3.1).[12, 14, 28] Hearing the news that the cancer has come back can be hard for people to cope with, resulting in feeling shocked or anxious.[100]

"(After being) initially told that I needed 6 months of treatment and then to find that it had not worked was fairly emotional; it was quite a roller coaster… with loads of uncertainty". Hannah, diagnosed with HL.[101]

Fear of late effects and relapse can exert a substantial psychological toll. After a median follow-up of 106 months in the German Hodgkin Study Group (GHSG)'s HD13–15 trials, 40% of relapse-free and >60% of relapsed survivors were still worried about the late effects of treatment and possibility of relapse.[97]

Although there is limited evidence on the impact of second-line chemotherapy, it is likely to have a similar or greater impact than first-line chemotherapy. Patients must not only handle the awareness that their disease has relapsed, but potentially also the adverse effects of a second line treatment while they recover from the physical effects of the first. Likewise, there are minimal data reporting the burden for previously untreated patients undergoing first-line treatment vs. those who receive an SCT at a later line, but the burden for the latter is known to be extensive. Cancer patients who receive subsequent SCT report a substantial QoL burden; specifically, poorer cognitive and social function ($p<0.001$), and significantly more dyspnoea ($p<0.001$) compared with the general population were reported in a Norwegian study[p].[98] Notably, this patient group also reported significantly more physical, mental, total, and chronic fatigue compared with the general population ($p<0.01$–0.001).[98]

Taken together, these data indicate the importance of a successful cure at first line.

Burden of disease on caregivers of patients with HL

High levels of emotional stress and financial strain are reported by caregivers of patients with cancer.[102]

"As we went through the lengthy staging process, I felt like I became an online doctor. I was checking his vitals with my…thermometer, blood pressure machine, and pulse oximeter. My soulmate, the love of my life, my life partner was sick." Fallon, HL caregiver.[103]

HL can affect work and productivity of caregivers, whose time is absorbed by looking after the patient, particularly if the patient is undergoing treatment. In a survey of 209 caregivers,

[p] Based on a Norwegian prospective study with a 3–5-year follow-up in 40 patients who received autologous SCT, of whom nine were diagnosed with Hodgkin lymphoma, compared with 1,806 people representing the general population, from matched reference values from three Norwegian general population surveys.[98]

those who were employed and caring for patients on treatment were more likely to report work absences (p=0.02) and work impairment (p=0.054) than those who were employed and caring for patients off treatment (as measured by the Work Productivity and Activity Impairment Caregiver questionnaire [WPAI:CG]).[102] Additionally, 29% of the employed caregivers reported work impairment (PROMIS-Global score) regardless of their relation to the patient.[104] The observed work impairment was due to caregiving activities (PROMIS-Global score).[104] As such, caregivers who are employed may require work flexibility to provide care, such as different start and stop times, time off, reduced working hours, or a leave of absence.[102]

"Becoming a caregiver overnight was hard. You're in survival mode from the time you hear what's going on until treatment ends and living in survival mode for so long was definitely a challenge." Carley, wife of HL survivor.[105]

B.1.3.3.4 Economic burden

Malignant blood cancers, including HL, are responsible for the second highest healthcare expenditure in EU countries, accounting for 12% of total healthcare costs in the 28 EU countries (second to breast cancer) and 14% of morbidity costs.[106] HL is also one of the most expensive cancers based on cost per death, due to its relatively young age distribution and significant proportions of deaths occurring in young people of working age where wages are highest.[107] HL had the second highest cost per death in Europe in 2014 (€306,628) and in the US between 2000–2020 ($544,118).[107, 108] Using an oncology simulation model to estimate the impact of first-line treatment choice on mortality and productivity, a US study has shown an estimated 2,650 deaths over 10 years (from 2021 to 2031) and a total present value lifetime earnings (PVLE) loss of $1,664 billion (Section B.3.12).[109]

HL can impose a financial burden due to HRQoL impairments resulting from treatment toxicity.[74] Diagnosis of HL also often interrupts education or work; among survivors who had been studying at time of diagnosis, 52% interrupted their education, and treatment with chemotherapy was not associated with a high resumption rate.[110] Likewise, among survivors working at the time of diagnosis, 77% interrupted their work.[110]

Substantial costs are also incurred to the NHS by failure of first-line HL treatment.[30] Though no UK-specific cost data are available, a US study reported significantly higher healthcare costs in patients who had first-line treatment failure compared with those who did not ($29,040 vs. $16,369 per person per month; p<0.05).[30] The difference in costs in patients who had first-line treatment failure vs. those who did not were driven by outpatient services (62% vs. 83%) and inpatient admissions (32% vs. 12%). Among patients who had moved to a second- or third-line treatment, total costs were almost twice as high compared with first line (first line: $29,040; second line: $38,918; third line: $37,388), and almost three times the cost compared with patients who had a successful first-line treatment ($16,369).[30] Treatments for patients who relapse after autologous SCT (ASCT) are also particularly resource intensive: in a UK retrospective study, allogeneic SCT (alloSCT) and palliative chemotherapy were associated with the highest number of outpatient visits, longest durations of hospitalisation and highest number of scans of any intervention after post-ASCT recurrence, and alloSCT was the most costly intervention overall (mean: £110,374 per

patient).[111] Therefore, a successful cure at first line may substantially lessen the financial burden of CD30+ Stage III or IV HL.

B.1.3.4 Clinical pathway of care in the UK

To further understand the current UK clinical practice, three advisory boards were conducted, each with a unique objective: one discussing clinical experience with first-line treatments for HL and providing expert insights into possible positioning of A+AVD in this patient population (2022); one providing insights regarding the evolving and potential future first-line treatment landscape of advanced-stage HL in the UK, based on recent data releases (2023); and one focusing on the current HTA submission, discussing the applicability of ECHELON-1 (Section B.2.3) in the context of the UK clinical practice for HL and the approach to modelling its cost-effectiveness for this submission (2024).[13, 36, 70]

The goal of first-line treatment for patients with Stage III or IV HL is cure, without the need for additional therapy.[6, 36, 112] Clinical feedback elicited is that patients with Stage III or IV HL are generally considered to be cured of their HL if they have not relapsed within approximately 2 years from the end of treatment, as the majority of relapses will occur within this timeframe.[36] Relapses after 5 years are described as “late” or “very late” relapses and occur in a minority of patients[q].[113, 114] Thus, in the absence of disease progression, patients are generally discharged at 2 years after the end of treatment.[15, 36]

B.1.3.4.1 Current treatment guidelines

Two clinical guidelines are relevant for the management of untreated HL: the British Society for Haematology (BSH) guidelines, published in 2022, and the European Society of Medical Oncology (ESMO) guidelines, published in 2018 (Appendix M).[15, 28] Of these, the BSH guidelines focus on treatment of previously untreated HL, whereas the ESMO guidelines include recommendations for both untreated and R/R HL from a European perspective.[15, 28] Other British guidelines for R/R HL are available but are outdated and not relevant to the population under consideration in this submission.[115] To date, NICE have not published a clinical guideline for HL. No NICE technology appraisal (TA) guidance has been published for treatment of previously untreated advanced HL patients, because current first-line treatment is largely based on chemotherapy regimens that were first described nearly 50 years ago.[16] Four NICE technology appraisals for the treatment of R/R HL have been published.[116–119]

UK-based clinical experts have advised that the BSH guidelines are used in the UK, along with local trust guidelines and protocols at each centre.[15, 36] For previously untreated Stage III or IV HL (and patients with Stage IIB who have either large mediastinal adenopathy or extranodal disease, whose disease is considered unfavourable), the BSH guidelines recommend initiating treatment with either ABVD or escBEACOPP; in older patients or those with comorbidities, ABVD, AVD or alternative anthracycline-containing regimens[r] are recommended.[15] Due to concerns over gonadal and haematopoietic stem cell toxicity from procarbazine (Section B.1.3.3.2), clinicians in the UK routinely use escBEACOPP with a

[q] Two studies in patients with HL (any stage) diagnosed 1982–2018 and 1976–2016 reported a 10-year cumulative incidence of late relapses of 2.7% and 3.6%, respectively.[113, 114]

[r] E.g. cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (ACOPP).[15]

dacarbazine substitution for procarbazine suggested by the BSH guidelines, hereafter referred to as escBEACOPDac.[15, 36]

Following the first two cycles of ABVD or escBEACOPDac, the guidelines recommend PET-adapted treatment based on the findings of an interim PET scan (PET2).[15] Interim PET scans can inform treatment adaptation, including treatment escalation and de-escalation, and thus reduce the risk of treatment toxicities; however, notably, this approach is not SoC globally (Appendix M), and some treatment centres across the UK do not use a PET-adapted approach.[28, 36, 120] PET-adapted treatment strategies recommended by the BSH guidelines are:[15]

- **Starting with two cycles of ABVD – the RATHL trial strategy/protocol**
  The RATHL trial was conducted in 1,201 patients with previously untreated CD30+ advanced HL, which included patients with Stage IIB–IV HL or Stage IIA with adverse features (bulky disease or ≥3 involved sites).[77, 88] Patients received an initial two cycles of ABVD and then followed an adapted approach based on the outcome of an interim PET scan (PET2); PET2-negative patients (Deauville score [DS] 1–3; n=935) were randomised to receive four cycles of ABVD (n=470) or AVD (n=465), i.e. omitting bleomycin, while PET2-positive patients (n=172; DS 4–5) were escalated in a non-randomised fashion to receive four cycles of escBEACOPP or BEACOPP-14.[77] In the UK, the recommended strategy based on the RATHL trial is de-escalation to AVD or escalation to escBEACOPDac, depending on PET2 status, after two initial cycles of ABVD.

- **Starting with two cycles of escBEACOPP/Dac**

  - **The HD18 trial strategy**
    After two initial cycles of escBEACOPP, the HD18 trial randomised patients with a PET2-negative (DS<3) scan to either two, or four to six further cycles of escBEACOPP (i.e. four or six to eight cycles in total). Patients with a PET2-positive (DS≥3) scan received four to six further cycles of escBEACOPP (i.e. six to eight cycles in total). No significant difference was observed in PFS or OS with four cycles compared with six or eight cycles of escBEACOPP in PET2-negative patients, indicating that the total number of cycles could be reduced to four.[121] Consequently, the recommended approach based on the HD18 trial after an initial two cycles of escBEACOPDac is two additional cycles of escBEACOPDac in PET2-negative patients, or four additional cycles of escBEACOPDac in PET2-positive patients.

  - **The AHL2011 trial strategy**
    After two initial cycles of escBEACOPP, the AHL2011 trial randomised PET2-negative patients to either de-escalation to four cycles of ABVD or a further four cycles of escBEACOPP[s]. The recommended strategy based on this trial is therefore de-escalation to four cycles of ABVD or AVD in PET2-negative

[s] The AHL2011 trial also used a different definition for PET positivity to the HD18 trial (defined as standardised uptake value was greater than 140% compared against the liver).

patients; however, across the UK this is by far the least-widely used of the three PET-adapted strategies detailed.

The choice of initial treatment strategy is described in Section B.1.3.4.2.

After any of these treatment strategies, end of treatment radiotherapy can be considered, but is infrequently used in patients who initiate treatment with ABVD, and almost never used in patients who initiate escBEACOPDac.[15, 36]

Patients are typically followed up for 2 years after first-line treatment, in line with BSH guideline recommendations and clinical experience.[15, 36] Follow up depends on patient and clinician preference with no evidence supporting computed tomography (CT) or PET surveillance.[15] As noted above, clinicians consider 2 years from end of first-line treatment to be the timepoint within which the majority of relapses will occur.[36]

B.1.3.4.2 Choosing an initial treatment strategy

The choice between starting with ABVD or escBEACOPDac varies across the UK due to regional or centre-based preferences, and depends on multiple factors, including the patient's risk profile and toxicity/efficacy balance of the recommended treatment regimens.[15, 36]

Broadly speaking, escBEACOPDac is offered from the start to patients who are deemed able or willing to tolerate a heavier toxicity burden and hospitalisation risk, and those deemed to have higher-risk disease and a poorer prognosis.[36] By contrast, ABVD is generally offered from the start to those who are unsuitable or unwilling to accept the greater toxicity of up to six cycles of escBEACOPDac, or who do not require such an intensive regimen.[36] The threshold for this choice differs by centre, meaning some centres initiate treatment primarily with escBEACOPDac, and others with ABVD, as well as choices by the treating physician or patient[t].[36]

Importantly, as noted above, while PET2 adaptation is common in many UK centres, there are some centres that do not adapt treatment according to PET2 results (i.e. would treat with six cycles of ABVD rather than adapting treatment as per the RATHL strategy).

B.1.3.4.3 Proposed positioning of A+AVD in therapy

The proposed positioning of A+AVD is for the treatment of previously untreated patients with CD30+ Stage III or IV HL who would otherwise be suitable for treatment with ABVD, as described in Section B.1.3.4.2 (Figure 3). In current UK clinical practice, many patients starting on ABVD will be treated in a PET-adapted fashion based on the RATHL approach, as described above; however, this approach is not universal and, in some centres, patients may receive six cycles of ABVD without PET adaptation.

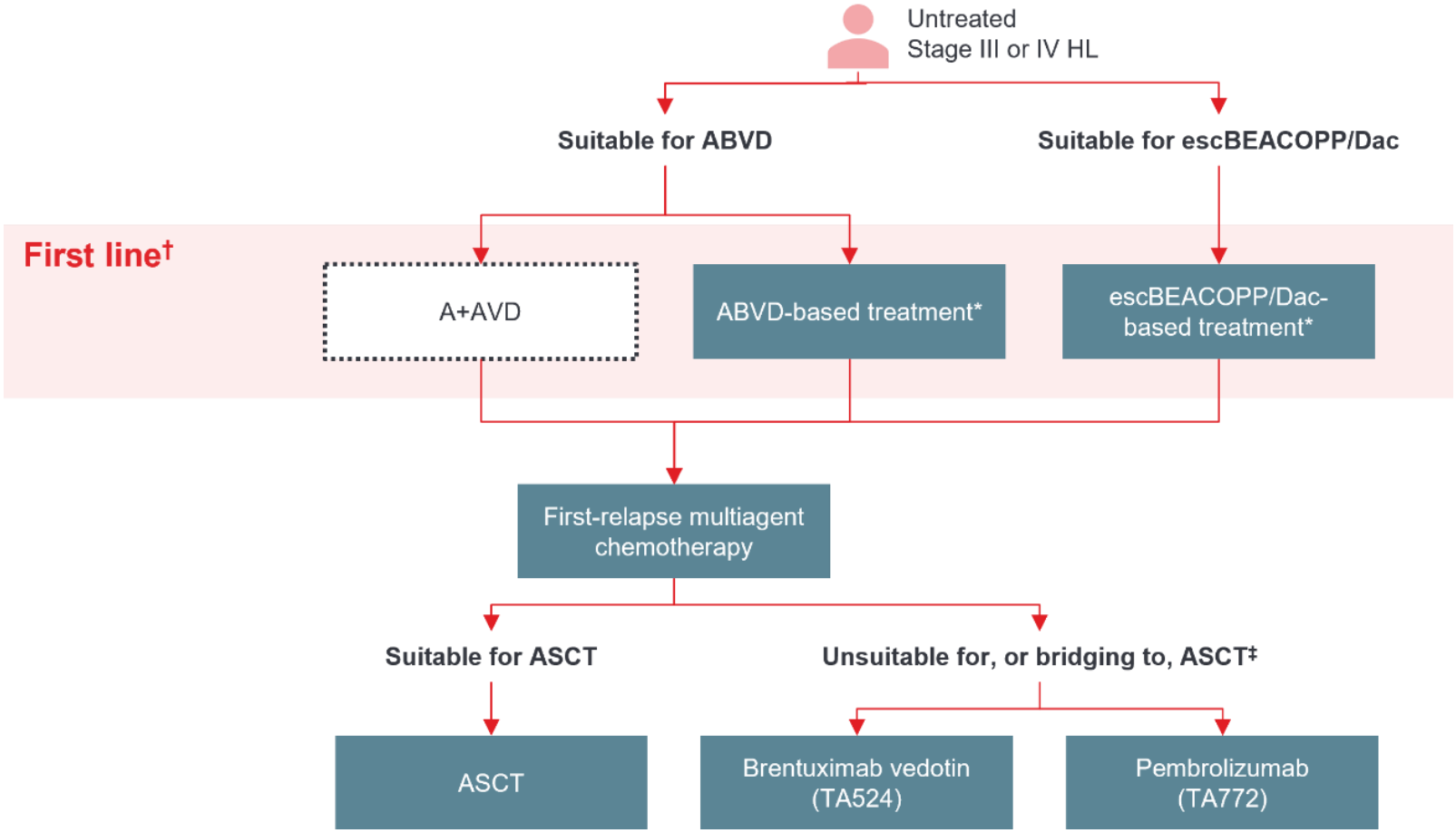
Clinicians who follow a PET-adapted approach with ABVD may de-escalate treatment to AVD in patients who are PET2 negative after the two initial cycles of ABVD, as per the RATHL trial; this approach has demonstrated improved safety, with similar OS and non-inferior PFS rates when compared with continued treatment with ABVD.[15, 88] Alternatively,

[t] Clinical experts described a small minority of patients they considered 'borderline' for initiating treatment with escBEACOPP/Dac or ABVD, for whom the preferred treatment would be less clear than for the broader patient population. Treatment of these patients might be guided by the patient's wishes.[36]

clinicians may escalate treatment to escBEACOPDac in patients who are PET2 positive after the two initial cycles of ABVD (per treatment escalation to escBEACOPP or BEACOPP-14 in the RATHL trial).[15, 88] However, the PET2-positive treatment arm of the RATHL trial was not randomised; therefore, it is unknown whether such escalation leads to better outcomes when compared with continuing therapy with ABVD in these patients.[88] Additionally, clinical experts consulted at the 2024 advisory board noted that the outcomes seen with escalation to BEACOPP-based regimens among PET2-positive patients in the RATHL trial were somewhat disappointing.[36, 88] Based on all of the above, it is reasonable to infer that the efficacy of the ABVD arm in ECHELON-1 (i.e. six cycles of ABVD without PET-adaptation) can be considered equivalent to ABVD administered as per the PET-adapted RATHL trial protocol (Section B.3.2.3.2), which was supported by the clinicians at the 2024 access advisory board.[36]

Clinicians at the advisory boards conducted by Takeda, as described above, agreed with the proposed positioning and stated that it is in line with their expected use of A+AVD within the treatment pathway for previously untreated HL, based on the ECHELON-1 trial.[70] Thus, the relevant comparator for this appraisal is ABVD-based treatment.

Figure 3: Current treatment pathway for untreated Stage III or IV HL in England and Wales, and proposed positioning of A+AVD



Dashed box denotes proposed place of A+AVD in therapy.
*Treatment may be PET-adapted (e.g. RATHL) or not PET-adapted. †Alternative treatment options (e.g. AVD, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone [ACOPP]) may be used in some patients where age or frailty precludes standard therapeutic options. ‡In transplant-naïve patients, treatment with pembrolizumab or brentuximab vedotin may be used as a bridge to ASCT.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplantation; CD30, cell membrane receptor 30; escBEACOPP/Dac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, prednisolone, procarbazine or dacarbazine; HL, Hodgkin lymphoma; PET, positron emission tomography; RATHL, response-adapted therapy for advanced Hodgkin lymphoma; TA, technology appraisal.
Sources: NICE 2021 (TA772 public committee slides);[122] British Society for Haematology guidelines;[15] Takeda, Medical Advisory Board (2023).[13]

B.1.3.5 Unmet need

For patients with previously untreated CD30+ Stage III or IV HL who are suitable for treatment with ABVD, there remains an unmet need for improved cure rates and PFS and OS.[16, 88] Improved survival outcomes should not, however, come at the cost of an increase in toxicity.[21, 36, 49, 50] Despite attempts to improve the efficacy of first-line therapy, prior to the ECHELON-1 trial, no regimen had been shown to offer an OS advantage compared with ABVD (PET-adapted or six cycles) in patients with previously untreated Stage III or IV HL. Through trials such as RATHL, the focus has largely been on improving tolerability without losing efficacy, for example via the de-escalation approach in patients who are PET2-negative.[18, 19, 78] There remains an unmet need for a well-tolerated first-line treatment that can improve survival outcomes in patients with CD30+ Stage III or IV HL who would otherwise be suitable for an ABVD-based regimen.

Despite attempts to improve tolerability, current first-line combination chemotherapies still impose burdensome toxicity, particularly toxicities associated with bleomycin, a component of ABVD. For patients treated with ABVD per the RATHL strategy, all patients will receive bleomycin as part of their first two cycles, and a small minority who are PET2 positive will receive it as a component of escBEACOPDac.[15, 77] While the severity of bleomycin-related lung toxicity varies, with AEs ranging from dyspnoea to lung fibrosis, its impact is likely to persist long term, resulting in impaired pulmonary function in later years, resulting in a treatment burden even in cured patients who have completed their HL treatment.[15, 54, 70] Hence, although the RATHL approach has reduced exposure to bleomycin, it has not completely eradicated its use, and even the reduced bleomycin exposure in RATHL is associated with long-term pulmonary toxicity.[21]

Moreover, while first-line treatment is curative for 70–80% of patients with advanced stage disease, the remainder experience disease progression after treatment.[22, 23] These patients are likely to require subsequent therapy, and each treatment line has diminishing likelihood of a cure and reduced PFS and OS; 10-year OS is lower than 60% after first relapse.[67] Patients receiving subsequent treatments will also incur cumulative treatment toxicity, as further chemotherapy and/or SCT is likely to be needed.[24–27] The burden of SCT is particularly extensive, due to burden of the treatment itself, the significant QoL decrement (particularly in fatigue levels compared with the general population), and the high rate of second malignancies associated with transplantation.[24, 26, 27]

Therefore, there remains a significant unmet need for a treatment with the potential to improve PFS and OS, while minimising the toxicity burden, particularly bleomycin-associated toxicities. This is especially true for patients who currently start treatment with ABVD, who may be less able to tolerate toxicities compared with those suitable for starting treatment with escBEACOPDac. Such a treatment would provide a cure for more patients without increasing treatment burden.

B.1.4 Equality considerations

No equality considerations relating to the use of brentuximab vedotin have been identified.

B.2 Clinical effectiveness

ECHELON-1 was a multicentre, randomised, open-label, Phase III trial of A+AVD vs. ABVD in patients with untreated CD30+ Stage III or IV HL.[31]

- ECHELON-1 represents the most robust evidence available for A+AVD in previously untreated Stage III or IV HL, with 1,334 enrolled patients and over 7 years of follow-up.[123]

At the 11 March 2023 data cutoff, progression-free survival was longer with A+AVD compared with ABVD (p=0.001).[123, 124]

- The 7-year PFS estimates were 82.3% (95% CI: 79.1–85.0%) in the A+AVD arm and 74.5% (95% CI: 70.8–77.7%) in the ABVD arm. Median PFS was not estimable (NE) in either arm (95% CI: NE–NE in either arm) and a 32.3% reduction in risk of progression or death was observed with A+AVD compared with ABVD (HR: 0.677; 95% CI: 0.532–0.863; p=0.001).[123, 124]

Similarly, treatment with A+AVD led to a statistically significant difference in overall survival compared with ABVD in the intention-to-treat (ITT) population.[123, 125]

- The 7-year OS estimates were 93.5% (95% CI: 91.1–95.2%) in the A+AVD arm and 88.8% (95% CI: 85.8–91.1%) in the ABVD arm. Median OS was NE in either arm (A+AVD 95% CI: 115.1–NE; ABVD 95% CI: NE–NE; HR: 0.617; 95% CI: 0.423–0.899; p=0.011). A significant 38.3% reduction in the risk of death was observed with A+AVD compared with ABVD (HR: 0.617; 95% CI: 0.423–0.899; p=0.011).[123, 125]

Across both treatment arms, mean patient-reported outcome (PRO) scores (EORTC QLQ-C30 subscales and Global scores, and EQ-5D-3L) improved after treatment compared with baseline scores.[34]

During the treatment period in ECHELON-1, six cycles of A+AVD was a well-tolerated regimen with a manageable safety profile.[34, 112, 123, 126]

- A similar proportion of AEs of any grade (99% vs. 98%) and drug-related AEs (97% vs. 94%) were reported for the A+AVD and ABVD arms.[34]
- Fewer patients had a pulmonary toxicity event in the A+AVD arm compared with the ABVD arm (2% vs. 7%). In the ABVD arm, one fatal pulmonary toxicity event was observed and 11 of 13 deaths during treatment were due or related to pulmonary toxicity, but no deaths due or related to pulmonary toxicity occurred in the A+AVD arm.[127]
- A higher incidence of peripheral neuropathy (PN) was observed with A+AVD vs. ABVD during treatment (67% vs. 43%), which is consistent with the safety profile of brentuximab vedotin.[34, 38, 43] However, in the latest follow-up, 86% and 87% of patients who had PN had complete resolution or amelioration of symptoms in the A+AVD and ABVD arms, respectively.[123]
- Patients treated with A+AVD who received primary prophylaxis with granulocyte-colony-stimulating factor (G-CSF) experienced a lower incidence of Grade ≥3 neutropenia (29% vs. 70%) and febrile neutropenia (11% vs. 21%).[126]
- Second malignancies were reported in fewer patients treated with A+AVD compared with ABVD (33 vs. 39).[123]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant published evidence on the clinical efficacy, safety, tolerability, HRQoL and costs associated with first-line treatments in the management of patients with advanced HL (defined as Stage IIB, III, or IV). Initial searches were conducted on 29 July 2016, followed by updates on 23 May 2018, 22 June 2022, and 19 and 27 December 2023; the December 2023 search dates correspond to searches for randomised controlled trial (RCT) and non-RCT data, respectively. Full details of the methodology and results of the SLR are provided in Appendix D.

The SLR identified relevant evidence evaluating the efficacy, safety, and tolerability of A+AVD, based on the current submission scope, and of ABVD as used in UK clinical practice in newly diagnosed patients with advanced HL (defined as Stage IIb, III, and IV in the SLR).

One unique study was identified as reporting effectiveness evidence for brentuximab vedotin: ECHELON-1 (23 publications), an RCT conducted in 1,334 patients with previously untreated CD30+ Stage III or IV HL, of whom 664 were treated with A+AVD and 670 were treated with six cycles of ABVD (Section B.2.3).

Evidence relating to ABVD per the RATHL protocol, as used in UK clinical practice, was also identified via the SLR. One unique study was identified: RATHL (five publications), an RCT conducted in 1,201 patients with previously untreated advanced-stage HL (Stage IIb, III, and IV), as described in Section B.1.3.4. No other trials were identified that assessed the efficacy of ABVD using a regimen(s) considered reflective of the current UK clinical practice, as guided by expert clinical opinion.[36]

B.2.2 List of relevant clinical effectiveness evidence

One RCT evaluating A+AVD was identified by the SLR (ECHELON-1). ECHELON-1 was used to inform the marketing authorisation of A+AVD, forms the main evidence base for this appraisal, and was used to inform the economic model (Table 3).

Table 3: Clinical effectiveness evidence

Study	**ECHELON-1; NCT01712490**
Study design	International, open-label, randomised, multicentre, two-arm, Phase III trial
Population	Treatment-naïve, adult patients (≥18 years old) with histologically confirmed CD30+ Stage III or IV* HL
Intervention(s)	A+AVD: brentuximab vedotin (A) plus doxorubicin (A; also called Adriamycin), vinblastine (V), and dacarbazine (D)
Comparator(s)	ABVD: doxorubicin (A), bleomycin (B), vinblastine (V), and dacarbazine (D)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes

Rationale for use/non-use in the model	ECHELON-1 is the pivotal Phase III study of A+AVD vs. ABVD. It is the most robust evidence available for A+AVD in previously untreated CD30+ Stage III or IV HL, with over 7 years of follow-up (median follow-up for PFS: 89.2 months; 95% CI: 86.4–90.1), which included 154 patients from 23 centres in Great Britain. ECHELON-1 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** • Response rates‡ • **Adverse effects of treatment** • **Health-related quality of life**
All other reported outcomes§	• Modified progression-free survival • PET status after Cycle 2
Key publications**	**Protocol, modified PFS, and interim OS analysis |** Connors *et al. N Engl J Med*. 2018;378(4):331–344.[112] **3-years' follow-up; PFS (per INV) |** Straus *et al. Blood*. 2020; 135(10):735–742.[127] **5-years' follow-up; PFS (per INV) |** Straus *et al. Lancet Haematol*. 2021;8(6):e410–e421.[128] **6-years' follow-up; OS |** Ansell *et al. N Engl J Med*. 2022;387(4):310–320.[31] **Safety outcomes** | Straus *et al. Blood*. 2020;135(10):735–742;[127] Ansell *et al. N Engl J Med*. 2022;387(4):310–320.[31]

*Based on Ann Arbor staging system. †Outcomes **in bold** are those incorporated in the economic model. ‡Objective response rate and complete remission rate are shown in Appendix N.1.3. §Other reported outcomes in ECHELON-1 not presented in this submission include event-free survival, disease-free survival, duration of response, duration of complete remission, rate of patients receiving irradiation for HL not in complete remission, immunogenicity, patients alive without HL at 3 and 5 years, pharmacokinetics, tumour biomarker expression changes, and medical resource utilisation. **Publications list not comprehensive, and additional publications of ECHELON-1 trial data are available; shown are those which present key data cutoffs and outcomes of interest for this submission.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CD30, cell membrane receptor 30; CI, confidence interval; HL, Hodgkin lymphoma; INV, investigator; OS, overall survival; PET, positron emission tomography scan; PFS, progression-free survival.

Sources: Connors *et al* (2018);[112] Takeda ECHELON-1 CSR (2018).[34]

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

B.2.3.1 Trial design

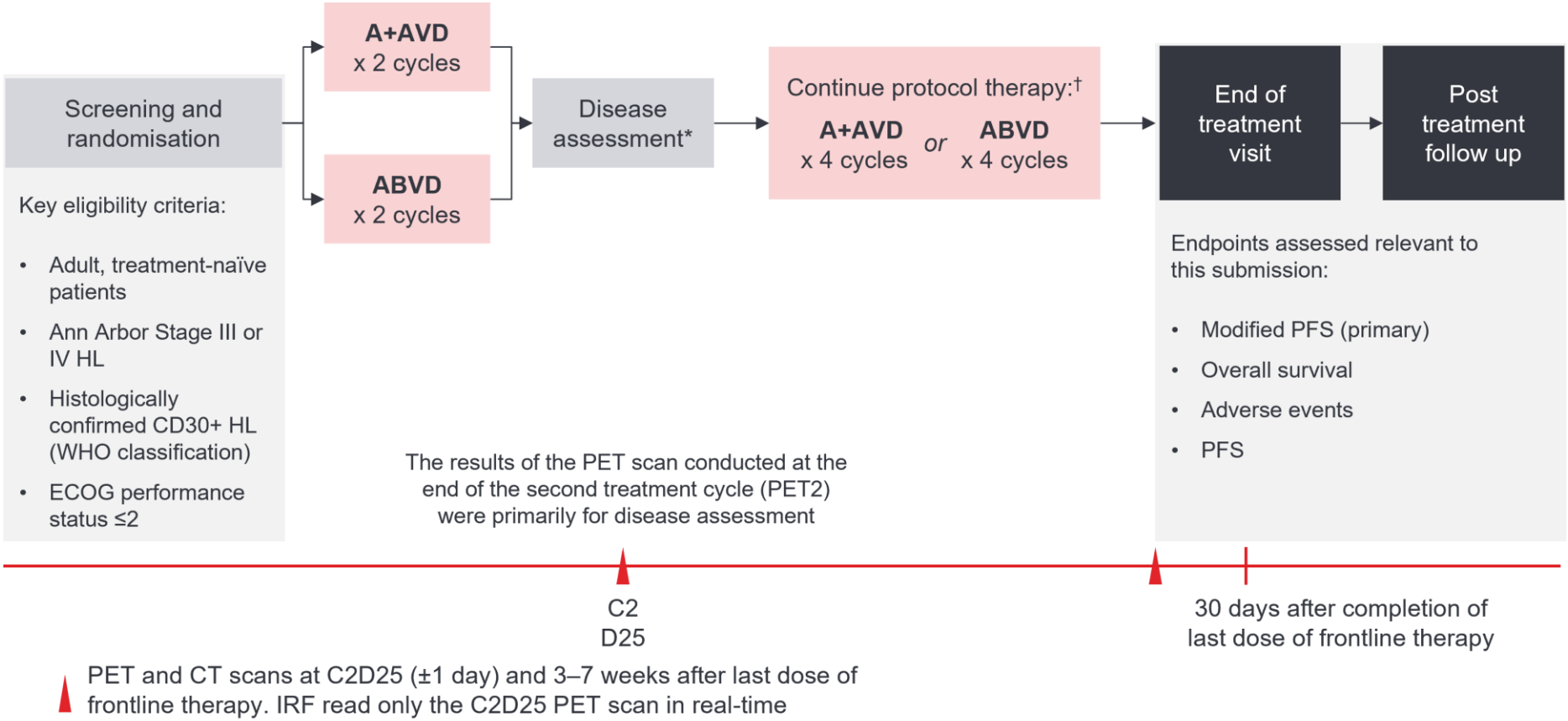
ECHELON-1 was an international, open-label, randomised, Phase III trial, conducted across 218 sites in 21 countries (Section B.2.3.2; Figure 4; Table 4). Of the 1,334 patients enrolled, 154 were from Great Britain. Adult (aged ≥18 years), treatment-naïve patients with histologically confirmed CD30+ Stage III or IV HL were eligible for inclusion, and randomisation was stratified according to geographic region (Americas; Asia; Europe) and IPS risk factors (0–1; 2–3; 4–7). Patients were randomised 1:1 to A+AVD (intervention; n=664) and ABVD (comparator; n=670) (Section B.2.3.2).[34, 112]

The ECHELON-1 protocol permitted the use of G-CSF for the treatment or prevention of neutropenia (Section B.2.3.2; Table 4), as recommended by the SmPC for all adult patients with previously untreated HL receiving brentuximab vedotin in combination therapy.[43] After enrolment of 70% of study participants, the independent data and safety monitoring committee (IDMC) recommended that all patients randomised to A+AVD receive prophylactic G-CSF support, due to the higher incidence of febrile neutropenia observed in the A+AVD arm.[34, 126] Alternative frontline medication (AFM) was permitted in patients with DS=5 at the time of their Cycle 2 PET assessment (Figure 4).[34, 112]

ECHELON-1 has extensive follow-up and multiple interim analyses have been reported. The first data cutoff was 20 April 2017, by which date all patients had completed the treatment period. The data cutoff for the 3-year update was 15 October 2018, 14 September 2020 for the 5-year update, and 01 June 2021 for the 6-year update.[31, 128, 129] The latest data cutoff was 11 March 2023, with over 7 years of follow-up.[123]

The outcome measures included in the economic model, as specified in the scope, include PFS, OS, AEs of treatments, and HRQoL. Other outcomes presented in this submission include the primary endpoint, modified PFS, not included in the economic model, and objective response rate (ORR) and complete remission (CR) rate, which are presented in Appendix N.1.3. All outcomes were prespecified.[34, 112]

Figure 4: ECHELON-1 trial design



*The results of the PET scan conducted at the end of the second treatment cycle (PET2) were primarily for disease assessment. However, an optional switch to alternative frontline therapy was permitted at the treating physician's discretion for patients with a Deauville score of 5. †In patients with Deauville score 5, the option was given to either continue with four cycles of study drugs (A+AVD or ABVD), or switch to the physician's choice of treatment.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; C2D25; cycle 2, day 25; CD30, CD30, cell membrane receptor 30; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HL, Hodgkin lymphoma; IRF, independent review facility; PET, positron emission tomography; PFS, progression-free survival; WHO, World Health Organization.
Source: Connors *et al* (2018);[112] Takeda ECHELON-1 CSR (2018).[34]

B.2.3.2 Trial methodology

Table 4 provides a summary of ECHELON-1 trial methodology.

Table 4: Summary of ECHELON-1 trial methodology

Locations	International study 218 sites in 21 countries over three continents (United Kingdom, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Hong Kong, Hungary, Italy, Japan, Norway, Poland, Republic of Korea, Russian Federation, South Africa, Spain, Taiwan, Turkey, United States); 23 sites were located in Great Britain.
Trial objective	ECHELON-1 was designed to compare A+AVD with ABVD as frontline therapy in patients with previously untreated CD30+ Stage III or IV HL
Trial design	Multicentre, randomised, open-label, Phase III trial. Patients were randomised 1:1 to A+AVD and ABVD using an interactive voice/web response system (IXRS) which automated randomisation and dispensation, eliminating the risk of allocation bias. Stratification factors included IPS risk factors (0–1; 2−3; 4–7) and region (Americas; Asia; Europe).
Duration of study	Median PFS follow-up: 89.2 months (95% CI: 86.4–90.1) Median OS follow-up: 89.3 months (95% CI: 87.0–90.2)
Participant eligibility criteria	**Key inclusion criteria** • Male or female patients aged ≥18 years • Treatment-naïve patients with Ann Arbor Stage III or IV HL • Histologically confirmed CD30+ HL (WHO classification)* • ECOG performance status ≤2 • Radiographically documented measurable disease per the International Working Group RECIL criteria
	Key exclusion criteria • Nodular lymphocyte predominant HL • Any sensory or motor PN • Diagnosed/treated for another malignancy within 3 years before first dose OR previously diagnosed with another malignancy with any evidence of residual disease†
Trial drugs (ITT population)	**Intervention (A+AVD; n=664):** Doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 were administered by IV infusion on Days 1 and 15 of each 28-day cycle for six cycles. Brentuximab vedotin was administered after AVD. Brentuximab vedotin 1.2 mg/kg was administered as an IV infusion over approximately 30 minutes starting within approximately 1 hour after completion of dacarbazine administration on Days 1 and 15 of each 28-day cycle for six cycles.‡
	Comparator (ABVD; n=670): Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 were administered by IV infusion on Days 1 and 15 of each 28-day cycle for six cycles.

Protocol amendment	**Use of G-CSF prophylaxis recommendation:** Use of G-CSF according to institutional guidelines was allowed per protocol for the management of patients in the A+AVD treatment arm who developed neutropenia. After enrolment of approximately 70% of the study population, the IDMC recommended that patients randomised to the A+AVD treatment arm be given prophylactic growth factor support beginning with Cycle 1. For the purpose of assessing the impact of the G-CSF use on safety, the sponsor defined G-CSF primary prophylaxis as G-CSF given by Day 5 of study treatment. By this definition, 83 patients in the A+AVD treatment arm and 43 patients in the ABVD treatment arm received G-CSF primary prophylaxis. Receipt of G-CSF at any time after Day 5 of Cycle 1 was defined as G-CSF secondary prophylaxis.
Concomitant medication	**Permitted concomitant medication:** • Alternative frontline medication (AFM): patients, including those with a Deauville score of 5 at the time of Cycle 2 PET assessment, were permitted though not required to switch to a physician's choice of alternative therapy for the remainder of frontline therapy. • The use of topical, inhalational ophthalmic steroids was permitted. • Patients were allowed to receive concomitant hormonal therapy provided they had been on a stable dosage for ≥1 month before enrolment. • The use of platelet and/or red blood cell supportive growth factors or transfusions was allowed when applicable. **Prohibited concomitant medication:** • Any investigational agent other than brentuximab vedotin. • Any frontline anticancer treatment for remission induction other than AVD or ABVD, unless based on what is stated above. • The concomitant use of brentuximab vedotin and bleomycin.
Primary outcomes	Modified PFS per IRF assessment using the Revised Response Criteria for Malignant Lymphoma. Modified PFS was defined as the time from the date of randomisation to the date of the first of documentation of progressive disease, death due to any cause, or for patients who were confirmed non-complete responders per IRF, receipt of subsequent anticancer therapy for HL after completion of frontline therapy. Modified PFS was a prespecified outcome.
Other outcomes used in the model/specified in scope	**Key secondary endpoint: overall survival (OS)** OS was to be analysed sequentially if the analysis of modified PFS primary endpoint was statistically significant. **Other endpoints used in the model: PFS per INV** The analysis of PFS included death and objective disease progression as events, as per the Revised Response Criteria for Malignant Lymphoma. PFS was defined as the time from randomisation to the time of first documentation of disease progression or death due to any cause, whichever occurred first. UK-based clinical experts confirmed that PFS is the most relevant endpoint for patients with previously untreated HL.[36] **Other outcomes specified in the scope (presented in Appendix N.1.3):** • Overall response rate (ORR) was defined as the proportion of patients who achieved complete remission or partial response at the end of treatment with randomised regimen (A+AVD or ABVD), as determined by an IRF (absence of a complete response was defined as Deauville score ≥3).

	• Complete remission rate per IRF was defined as the proportion of patients who achieved complete remission at the end of frontline therapy with the randomised regimen (A+AVD or ABVD).
Other outcomes of interest	• Patient-reported outcomes measured per the FACIT-Dyspnea 10, FACT/GOG-NTx neurotoxicity subscale, and EORTC QLQ-C30, and patient-reported health-related quality of life measured per the EQ-5D-3L questionnaire • Adverse reactions
Follow-up for outcome assessment	Post-treatment follow-up for all patients consisted of a physical exam, disease assessment, and radiological assessment if indicated[§], performed every 3 months until 36 months after EOT and then every 6 months until the first of disease progression or study closure (5 years after last patient enrolled). Information regarding the initiation of another lymphoma treatment was also collected. For patients who had progressive disease, survival/disease status and information regarding the initiation of an alternative lymphoma treatment was obtained by phone call. To support fertility assessment, any pregnancy occurring in patients or their partners from the date of first dose until the date of study closure was reported. Patients who stopped treatment for any reason other than progressive disease continued to have modified PFS/PFS follow-up visits until the occurrence of progressive disease; the patient withdrew consent for further follow-up; or, after completion of frontline therapy, the start of anticancer therapy. In the original study protocol, patients were to be followed for survival until 5 years from the date of the last patient randomised, or death, whichever occurred first. In a 2018 protocol amendment, this was extended to 10 years from the randomisation date of the last patient for assessment of the long-term safety outcomes. Information on the initiation of another anticancer therapy was also collected.
Pre-planned subgroups	Modified PFS was determined for pre-specified subgroup analysis defined by: • Age: <60 vs. ≥60 years; <65 vs. ≥65 years; <45 vs. ≥45 years • Region: Americas, Asia, Europe, North America • Number of IPS risk factors at baseline: 0–1; 2–3; 4–7 • Cancer stage at baseline: Stage III; Stage IV • Baseline B symptoms: Present; absent • Cycle 2 PET results: positive (DS >3); negative (DS ≤3) • Cycle 2 PET DS score: <5; 5 • Receipt of alternative frontline medication: Yes; no • Extranodal sites at baseline: 0, 1, >1.

Multiple other endpoints were collected during the clinical trial but are not presented in this submission for brevity (refer to protocol for details).
*Nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or CD30+ HL, not otherwise specified. [†]Patients with nonmelanoma skin cancer or carcinoma in situ of any type were not excluded if they had undergone complete resection. [‡]The actual dose was based on patients' weight according to the institutional standard and doses were required to be adjusted for patients who experienced a ≥10% change in weight from baseline. [§]Radiological assessments were required every 12 weeks (±1 week) until 12 months of post-treatment follow-up and then every 6 months (±2 weeks) until study closure.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AFM, alternative frontline medication; AVD, doxorubicin, vinblastine, dacarbazine; CD30, CD30, cell membrane receptor 30; CI, confidence interval; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Quality of life Questionnaire; EOT, end of treatment; EQ-5D-3L, European Quality of Life 5-Dimension 3-Level version; FACIT, Functional Assessment of Chronic Illness Therapy; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group –

Neurotoxicity; G-CSF, granulocyte colony stimulating factor; HL, Hodgkin lymphoma; IDMC, independent data monitoring committee; INV, investigator; IPS, international prognostic score; IRF, independent review facility; ITT, intention to treat; IV, intravenous; n, number; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PN, peripheral neuropathy; RECIL, response evaluation criteria in lymphoma; UK, United Kingdom; vs., versus; WHO, World Health Organization.
Source: Connors *et al* (2018);[112] Takeda ECHELON-1 CSR (2018).[34]

B.2.3.2.1 Modified PFS and PFS

The primary endpoint in ECHELON-1 was modified PFS, defined as the time from the date of randomisation to the date of the first of documentation of progressive disease, death due to any cause, or for patients who were confirmed non-complete responders per independent review facility (IRF), receipt of subsequent anticancer therapy for HL after completion of frontline therapy. This endpoint was chosen to encompass three possible outcomes that each represent a failure of the primary chemotherapy to eliminate HL:

- Documented progression at any time after initiation of primary chemotherapy
- Death from any cause
- Detection of a response that was less than complete at the end of primary chemotherapy (DS ≥3), followed by the delivery of subsequent anticancer therapy

For the third criterion to be met, patients had to have had a response that was less than complete at the end of primary chemotherapy (DS ≥3) and have received subsequent treatment; neither patients with false positive end-of-treatment PET scans who did not receive additional therapy nor those who received subsequent therapy in the absence of evidence of residual disease were considered to have had a modified progression event. This criterion ensured stringent assessment of occurrences of treatment failure that were unlikely to be captured by PFS. Thus, modified PFS was designed to capture all events that reflect a failure of frontline chemotherapy in advanced HL.[112]

PFS was a prespecified exploratory endpoint in ECHELON-1, and is used in the cost-effectiveness analysis instead of modified PFS since it is a more widely recognised and accepted endpoint for assessment of cancer treatments, and in particular, within the HL clinical community and the associated literature.[17, 19, 40, 42, 77, 118, 130] In ECHELON-1, PFS data are available from the latest 7-year follow-up period, compared with modified PFS data which are only available at the first interim analysis (at a median follow-up of 24.6 months).[112, 123] UK-based clinical experts noted the treatment benefit observed with PFS was consistent with that observed with the primary endpoint, modified PFS, and were in agreement that PFS was the most relevant endpoint for assessing efficacy, and is the most relevant in routine UK clinical practice.[36] Once the patients' scanning intervals lengthen as is appropriate during follow-up, it is the clinical symptoms of HL (e.g. enlarged lymph nodes, fever, night sweats, etc) that are likely to cause rapid presentation to the clinic. PFS is used in the cost-effectiveness analysis as it is the most relevant endpoint for UK clinical practice for assessment both on treatment and during long-term follow-up, providing 7 years of follow-up.

B.2.3.3 Baseline demographic and disease characteristics

Baseline characteristics for patients in ECHELON-1 are presented in Table 5. All data presented hereafter are based on the ITT population, unless otherwise specified.

Baseline demographic characteristics were well balanced between the treatment arms. Mean age was 38.8 (SD: 15.8; range: 18–82) and 40.2 (SD: 16.1; range: 18–83) years in the A+AVD and ABVD arms, respectively. There were 57% and 59% males in the A+AVD and ABVD arms, respectively. The majority of patients were white (84% and 83% in the A+AVD and ABVD arms, respectively).[31]

Disease characteristics were also well balanced between the treatment arms, including ECOG performance status, Ann Arbor stage at diagnosis, IPS, extranodal involvement at diagnosis and the proportion of patients with B symptoms (Table 5).[31]

UK-based clinical expert advisors concluded that the patient population included in ECHELON-1 is reflective of the patients they would see in routine clinical practice.[36, 131] Moreover, the proportion of patients with Stage III vs. Stage IV disease is reflective of what is observed in UK clinical practice, aligning with Cancer Research UK (CRUK) data for HL where 325 and 497 patients were diagnosed with Stage III and Stage IV disease, respectively, in England in 2021 (representing 39.5% and 60.5% of advanced HL for Stage III and Stage IV disease, respectively).[131]

Table 5: Baseline demographic and disease characteristics

Baseline characteristic	A+AVD (n=664)	ABVD (n=670)
Sex – n (%)		
Female	286 (43)	272 (41)
Male	378 (57)	398 (59)
Mean age – years (SD; range)	38.8 (15.8; 18–82)	40.2 (16.1; 18–83)
Age group (years) – n (%)		
<60	580 (87)	568 (85)
≥60	84 (13)	102 (15)
Ann Arbor stage at initial diagnosis – n (%)		
Stage II*	1 (<1)	0 (0)
Stage III	237 (36)	246 (37)
Stage IV	425 (64)	421 (63)
Unknown/missing	1 (<1)	3 (<1)
Ethnicity – n (%)		
Hispanic or Latino	51 (8)	55 (8)
Not Hispanic or Latino	571 (86)	577 (86)
Not reported	42 (6)	38 (6)
Race – n (%)		
White	560 (84)	554 (83)
Asian	56 (8)	57 (9)
Black or African American	20 (3)	25 (4)
Other	18 (3)	17 (3)
Not reported	10 (2)	17 (3)
Region – n (%)		
Americas	261 (38)	262 (39)
Europe	333 (50)	336 (50)
Asia	70 (11)	72 (11)

Baseline characteristic	A+AVD (n=664)	ABVD (n=670)
IPS – n (%)†		
0–1	142 (21)	141 (21)
2–3	355 (53)	357 (53)
4–7	167 (25)	172 (26)
ECOG performance status – n (%)‡		
0	376 (57)	378 (57)
1	260 (39)	263 (39)
2	28 (4)	27 (4)
Unknown/missing	0 (0)	2 (<1)
Extranodal involvement at diagnosis – n (%)		
Yes	411 (62)	416 (62)
1 extranodal site	217 (33)	223 (33)
>1 extranodal site	194 (29)	193 (29)
No	217 (33)	228 (34)
Unknown/missing	36(5)	26 (4)
Patients with B symptoms – n (%)	400 (60)	381 (57)

Data presented are based on the ITT population.
*The patient in this category was captured as a protocol violation. The patient was enrolled in error after an original scan outside the timeline per protocol determined a diagnosis of Stage III HL; the patient was withdrawn from the study after receiving one dose of study drug. †The IPS ranges from 0 to 7, with higher scores indicating increased risk of treatment failure: low-risk, 0 to 1; intermediate-risk, 2 to 3; high-risk, 4 to 7. ‡Values for the ECOG performance status range from 0 to 5, with higher scores indicating greater disability.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score; SD, standard deviation.
Source: Ansell *et al* (2022).[31]

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

B.2.4.1 Analysis sets

Six populations were included in the analysis sets, as described in Table 6.

Table 6: Analysis sets

Analysis set	Definition	A+AVD n (%)	ABVD n (%)
Intent-to-treat (ITT)	Included all patients randomised to treatment. Patients were analysed according to the treatment arm to which they were randomised. Used for analyses of all efficacy endpoints unless otherwise specified	664 (100)	670 (100)

Analysis set	Definition	A+AVD n (%)	ABVD n (%)
Per-protocol population (PP)	Included all randomised patients who met eligibility criteria and did not have major protocol violation determined by project clinician. All decisions to exclude patients from the PP population were made before clinical DBL. The PP population was used to complement the analysis of the ITT population for the primary efficacy endpoint (modified PFS) only. All patients were analysed according to the actual treatment received	650 (98)	652 (97)
Response-evaluable population	Subset of the ITT population with a confirmed diagnosis of HL and measurable disease at baseline, who received ≥1 dose of any study drug, and had ≥1 post-baseline response assessment. Used for the analyses of CR rate, ORR, and DOR	643 (97)	642 (96)
Safety population	Included all enrolled patients who received ≥1 dose of any study drug. Patients were analysed according to the actual treatment received. Used for all safety analyses	662 (100)	659 (98)
Pharmacokinetics (PK) population	Included enrolled patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. Used for population PK analyses	661 (100)	59 (9)*
Pharmacodynamics (PD) population	Included enrolled patients with sufficient dosing and pharmacodynamics data to reliably measure pharmacodynamics parameters. Used for pharmacodynamics analyses	660 (99)	645 (96)

*Sparse PK measurements were available for A+AVD patients for the determination of serum concentrations of the ADC and antibody, and plasma concentrations of MMAE. In addition, intensive PK measurements (iPK) were made in a subset of patients for each A+AVD (n=59) and ABVD (n=59) arms to measure serum concentrations of ADC and antibody, and plasma concentrations of MMAE and each component of AVD (i.e., doxorubicin, vinblastine and dacarbazine). Only the iPK population is applicable for the ABVD arm.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ADC, antibody–drug conjugate; CR, complete remission; DBL, database lock; DOR, duration of response; HL, Hodgkin lymphoma; ITT, intent-to-treat; MMAE, monomethyl auristatin E; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PP, per protocol.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.4.2 Statistical analyses

Statistical analyses methods are summarised in Table 7.

Table 7: Summary of statistical analyses

Hypothesis objective	• The primary null hypothesis was that there was no difference in modified PFS between the two treatments of A+AVD and ABVD. The alternative hypothesis was that A+AVD improves modified PFS. • The key secondary null hypothesis was that there was no difference in OS between A+AVD and ABVD. The alternative hypothesis was that A+AVD improves OS. • Hypotheses for the secondary endpoints were also tested.

Statistical analysis	**Randomisation** The randomisation scheme was generated by Takeda. Prior to dosing, a randomisation number was assigned to each patient and patients were randomised 1:1 using an interactive voice/web response system (IXRS). **Primary endpoint: modified PFS** Final analysis of modified PFS was performed after 263 modified PFS events (IRF). A total of 260 modified PFS events provided 90% power to detect an HR of 0.67 at a one-sided significance level of 0.025 using a log-rank test. The stratified log-rank test was used to compare modified PFS between treatment arms. Stratification factors included the number of IPS risk factors at baseline, and region. The HR along with the 2-sided 95% CI was estimated using the stratified Cox regression model with treatment as the explanatory variable. A stratified Cox regression model was used to further evaluate the effect of treatment on modified PFS after adjusting for prognostic factors (baseline, age, race, ECOG PS, stage, and presence of B symptoms) and PET2 results, with better efficacy for A+AVD vs. ABVD defined as HR <1. Sensitivity analysis was performed for modified PFS, by treating "treatment discontinuation for undocumented disease progression after the last adequate assessment" and "modified PFS event after more than one missed visit" as events whose date of progression was recorded as "date of last adequate assessment" and "date of modified PFS event", respectively. In the second sensitivity analysis, modified PFS based on the investigators' determinations of disease progression was analysed in the same manner as the primary analysis. In addition, modified PFS per INV assessment was censored at the last known alive date for those who do not have events. Patients with modified PFS events per INV assessment after more than one missed visit were censored at the date of last adequate assessment. In the third sensitivity analysis, if confirmed non-complete remission constitutes the modified PFS event, the modified PFS event date was the date of receipt of first dose of second-line therapy. Additional sensitivity analyses for modified PFS were performed based on the alterations of the handling of missing assessment and censoring (Table 8), on the basis of one alteration at a time, not on combined alterations unless otherwise specified. The primary analysis of modified PFS was performed for the following subgroups*: age (<60 vs. ≥60 years; <65 vs. ≥65 years; <45 vs. ≥45 years), region (Americas; North American; Europe; Asia), number of IPS factors (0–1; 2–3; 4–7), baseline cancer stage (Stage III; Stage IV), baseline B symptoms (present; absent), cycle 2 PET (positive [DS >3]; negative [DS ≤3]); Cycle 2 PET DS (<5; 5); receipt of alternative frontline therapy (yes; no); baseline extranodal sites (0; 1; >1); ECOG performance status (0; 1; 2); and gender (male; female). Two additional exploratory analyses were also performed: one for modified PFS with definition of frontline therapy restricted to no switch-in therapy; the other for PFS, which is defined as the earlier of 1) documented progressive disease or 2) death due to any cause. The statistical methods were similar to those used for modified PFS. In addition, PFS per INV assessments were censored at the last known alive date for those who do not have events. Patients with PFS events per INV assessment after more than one missed visit were censored at the date of last adequate assessment. **Key secondary endpoint: OS** OS was tested at a 1-sided 0.025 level when the test of modified PFS was statistically significant. The stratified log-rank test was used to

	compare OS between treatment arms. Stratification was as for modified PFS. The hazard ratio along with the 2-sided 95% CI were estimated using a stratified Cox regression model. Besides treatment and the stratification factors, the following prognostic factors were included in the model simultaneously: age, race (white; non-white), baseline ECOG score, baseline cancer stage, baseline B symptoms, and PET results from Cycle 2. Subgroup analyses were performed using subgroups defined for modified PFS analyses. **Other secondary endpoints:** **Patient-reported outcomes (PROs):** the global health status/QoL scale of EORTC QLQ-C30, shortness of breath scale of FACIT-Dyspnea 10, the sensory scale of FACT/GOG-NTX and EQ-5D-3L instruments were used. For EORTC QLQ-C30, FACIT-Dyspnea 10 and EQ-5D-3L, descriptive statistics of actual value and change from baseline of all subscale and total/summary scores, using mixed-effects models with repeated measures at each time point, are presented over time by treatment arm. A sensitivity analysis was performed to evaluate the impact on the analysis results from missing data imputation. Conditional on the patterns of missing data multiple imputation methods, including a pattern-mixture model, were considered. Any deaths that occur before the end of treatment were imputed by a value zero and were considered missing otherwise. For EQ-5D-3L, scores were summarised in descriptive statistics for the treatment arms. **Exploratory endpoints:** • **PFS:** PFS was defined as the time from randomisation to the time of first documentation of disease progression or death due to any cause, whichever occurred first. Analysis was performed for PFS per IRF and INV assessments using the same censoring guidelines as those used for the primary analysis: PFS observations were censored at the date of the last adequate assessment for patients who did not have an event at the last known alive date and patients with PFS events after more than one missed visit. Observations for patients with no baseline or postbaseline PFS assessments were censored at their randomisation date. Exploratory analyses for PFS were performed, using the statistical methods described for the primary analysis for modified PFS. • **Incidence of pregnancy:** Formal statistical comparison of pregnancy between arms was not conducted. Descriptive statistics of the number of pregnancies that occurred during follow-up are presented by treatment arm. • **Second malignancies:** Formal statistical comparison of second malignancy differences between arms was not conducted. Descriptive statistics of the incidence of second malignancies are presented by treatment arm.
Sample size, power calculation	The primary endpoint of the study was modified PFS, and the study was powered on the assumption of a 2-year modified PFS rate of 81% for patients in the A+AVD treatment arm and 73% for patients in the ABVD treatment arm, assuming an emergent plateau in the PFS event rate after 2 years. A total of 260 modified PFS events provided 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 using a log-rank test. Approximately 1,240 patients were to be randomised to achieve with 95% probability 260 modified PFS events in approximately 60 months assuming 36 months of patient accrual, a 5% annual dropout rate, and 24 months of modified PFS follow-up after randomisation of the last patient.

	The key secondary alpha-controlled endpoint, OS, was tested at a 1-sided 0.025 level once the test of modified PFS was statistically significant, by using the O'Brien-Fleming method with a Lan-DeMets alpha spending function.
Data management, patient withdrawals	Data that were potentially spurious or erroneous were examined under standard data management operating procedures. In general, missing data were treated as missing and no data imputation was applied, unless otherwise specified.
Statistical analysis timepoints	The final analysis of modified PFS was performed when 263 modified PFS events occurred. The data cutoff for this analysis was 20 April 2017. There were three formal interim analyses in the study, including one futility analysis of the CR rate and two interim analyses for OS: • The first formal interim analysis was a futility analysis. The CR rate at the end of frontline therapy was analysed when the first approximately 355 patients had completed the regimen to which they were randomised (i.e. received the planned study drug regimen with no more than two missed doses of A+AVD or ABVD) or had discontinued treatment prior to completion. • For OS, the first formal interim analysis was performed at the time of the final modified PFS analysis when 263 modified PFS events occurred. The data cutoff date for this analysis was 20 April 2017, at which time 67 deaths had been reported in the ITT population. The second OS interim analysis was planned after observing 103 deaths. The data cutoff date for this analysis was 01 June 2021, at which time 103 deaths had been reported in the ITT population. The final OS analysis was scheduled after observing 112 deaths or 10 years from the randomisation of the last patient, whichever occurred first. The data cutoff date for this analysis was 11 March 2023 at which time 115 deaths had been reported in the safety population. An additional analysis for PFS per investigator in the ITT population was conducted. The data cutoff date for this analysis was 15 October 2018.

*A number of additional subgroup analyses were added to the prespecified analyses in June 2016, approximately 1 year before clinical database lock, without knowledge of the treatment effect in efficacy data. These included modified PFS per IRF and investigator by age dichotomised around 45 and 65 years, ECOG performance status (0; 1; 2), and gender (male; female).
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; CR, complete remission; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; EQ-5D-3L, European Quality of Life 5-Dimension 3-Level version; FACIT, Functional Assessment of Chronic Illness Therapy; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity; HR, hazard ratio; INV, investigator; IPS, International Prognostic Score; IRF, independent review facility; ITT, intention to treat; OS, overall survival; PET2, positron emission tomography after Cycle 2; PFS, progression-free survival; PRO, patient-reported outcome; PS, performance status; QoL, quality of life.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.4.2.1 ECHELON-1 key endpoints and censoring rules

All trial endpoints presented in this appraisal, their definitions, and censoring rules are presented in Table 8.

Table 8: Summary of key endpoints

Endpoint/ assessment	Details	Timing of assessments and follow-up	Censoring rules
Primary endpoint			
Modified PFS per IRF	Modified PFS was defined as the time from the date of randomisation to the date of the first of (1) documentation of progressive disease; (2) death due to any cause; (3) for patients who are confirmed non-complete responders by IRF, receipt of anticancer therapy or radiotherapy for HL after completion of frontline therapy – these patients' modified PFS event date will be the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a DS score of ≥3.	Tumour biopsy, CT and PET scans, and B symptom assessment were conducted at screening and EOT. A CT and PET scan were also conducted at Cycle 2 (D25). B symptoms were also assessed once per cycle (D1) and during post-treatment follow-up. Disease status and B symptoms were assessed during post-treatment follow, every 3 months for 36 months and then every 3 months (± 14D) until study closure.	• No baseline and/or no post-baseline assessment, no subsequent anticancer therapy after frontline therapy, no death: censored to date of randomisation. • No documented modified PFS event: censored to date of last adequate assessment* • Lost to follow-up, withdrawal of informed consent before any documented modified PFS event: censored to date of last adequate assessment* • Treatment discontinuation for undocumented disease progression after last adequate assessment: censored to date of last adequate assessment* • Modified PFS event after more than one missed visit: censored to date of last adequate assessment*
Key secondary endpoint			
OS	OS was defined as the time from the date of randomisation to the date of death.	During post-treatment follow-up, survival was assessed every 3 months for 36 months and then every 6 months (± 14D) until study closure.	Patients without documented death at the time of analysis were censored at the date on which they were last known to be alive.

Endpoint/ assessment	Details	Timing of assessments and follow-up	Censoring rules
Secondary endpoints			
Quality of life endpoints (patient reported outcomes)	PRO assessments were based on the EORTC QLQ-C30, FACIT-Dyspnea 10, FACT/GOG-NTX neurotoxicity subscale, and EQ-5D-3L.	PROs were assessed at screening, and at D1 and D15 of all cycles, and at EOT. FACIT-Dyspnea 10 and FACT/GOG-NTX were collected until end of treatment. EQ-5D-3L was collected for 3 years post last dose of 1L therapy ending at posttreatment visit 12 until progressive disease (whichever first). EORTC QLQ-C30 was originally collected at all patient visits, including visits during posttreatment follow-up, until the final visit by the patient. Following a protocol amendment (16 July 2018), EORTC QLQ-C30 was collected for 3 years post last dose of 1L therapy ending at posttreatment visit 12 until progressive disease (whichever first).	The data were categorised into 3-month intervals indexing from study Day 1. For a given patient, if there were multiple measurements within a given 3-month interval, the worst score was used.
Exploratory endpoints			
PFS per INV	PFS was defined as the time from randomisation to the time of first documentation of disease progression or death due to any cause, whichever occurred first.	Tumour biopsy, CT and PET scans, and B symptom assessment were conducted at screening and EOT. A CT and PET scan were also conducted at Cycle 2 (D25). B symptoms were also assessed once per cycle (D1) and during posttreatment follow-up.	PFS per INV assessment was censored at the last known alive date for those who do not have events. Patients with PFS events per INV assessment after more than one missed visit were censored at the date of last adequate assessment.

Endpoint/ assessment	Details	Timing of assessments and follow-up	Censoring rules
		Disease status and B symptoms were assessed during post-treatment follow, every 3 months for 36 months and then every 6 months (± 14D) until study closure.	
Incidence of pregnancies (patients or partners of patients)	Any pregnancy that occurred in patients or their partners from the date of the first dose of any of the study drugs to the date of study closure after a positive serum pregnancy test.	A serum pregnancy test was performed for women of childbearing potential during screening and again at Cycle 1, Day 1 (baseline). A urine pregnancy test was required if the serum pregnancy test was not done within 4 days of the first dose of study drug. Dates and outcomes of all pregnancies were recorded from first dose of study drugs through end of study.	NA
Safety endpoints			
TEAEs	A TEAE was defined as any AE that occurred after administration of the first dose of any study drug through 30 days after the last dose of frontline therapy.	Recorded from first dose of study drugs through 30 days after the last dose of frontline therapy. Treatment-related AEs were followed until the sooner of resolution or study closure.	For the number of patients with AEs, patients reporting the same event more than once will have that event counted only once within each system organ class, high-level term, and preferred term. The assessment of relatedness was attributed to any of the study drugs in the combination regiment.

Multiple other endpoints were collected during the clinical trial but are not presented in this submission for brevity (refer to protocol for details).
*Adequate assessment was defined as sufficient data to evaluate a patient's disease status.
Abbreviations: 1L, first line; AE, adverse event; CR, complete remission; CT, computed tomography; D, day; DS, Deauville score; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; EOT, end of treatment; EQ-5D-3L, European Quality of Life 5-Dimension 3-Level version; FACIT, Functional Assessment of Chronic Illness Therapy; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity; HL, Hodgkin lymphoma; INV, investigator; IRF, independent review facility; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PRO, patient-reported outcome; TEAE, treatment-emergent adverse event.
Source: Connors *et al* (2018);[112] Takeda ECHELON-1 CSR (2018).[34]

B.2.4.3 Patient flow

Appendix D.2 presents the participant flow for ECHELON-1. Of the 1,585 patients who were screened, 1,334 patients were randomised to either A+AVD or ABVD treatment, and comprise the ITT analysis set: 664 and 670 to the A+AVD and ABVD arms, respectively.[34]

In the A+AVD arm, 628 patients (95%) completed study treatment per protocol and 593 patients (89%) completed the maximum number of cycles. In total, 14 patients (2%) were treated with both A+AVD and an alternative front-line therapy, having switched from A+AVD (12 patients switched due to AEs, one patient switched due to a PET2 DS of 5, one patient switched due to 'other reasons', and 20 patients (3%) had progressive disease or died before completion of front-line therapy. Of the 71 patients who did not complete the maximum number of cycles, the most common reasons for not doing so were AEs (n=28), progressive disease (n=17), 'other reasons' (n=15), and patient withdrawal (n=7).[34, 128]

In the ABVD arm, 634 patients (95%) completed the study treatment per protocol, and 608 patients (91%) completed the maximum number of cycles. In total, nine patients (1%) switched to an alternative front-line therapy (one patient due to AEs, four patients due to PET2 DS of 5, and four patients due to 'other reasons'), and 12 patients (2%) had progressive disease or died before completion of front-line therapy. Of the 62 patients who did not complete the maximum number of cycles, the most common reasons were AEs (n=22), withdrawal by patient (n=15), 'other reasons' (n=12), and progressive disease (n=9).

Table 9: Patient disposition

n (%)	A+AVD (n=664)	ABVD (n=670)
Patients completing study treatment per protocol*	628 (95)	634 (95)
Completed frontline therapy†	608 (92)	622 (93)
Randomised regimen only	594 (89)	613 (91)
Randomised regimen and AFM	14 (2)	9 (1)
Experienced progressive disease or died before completion of frontline therapy	20 (3)	12 (2)
Primary reason off study treatment		
Total	664 (100)	670 (100)
Adverse event	28 (4)	22 (3)
Completed maximum number of cycles per protocol	593 (89)	608 (91)
Lost to follow-up	2 (<1)	2 (<1)
Progressive disease	17 (3)	9 (1)
Protocol violation	1 (<1)	0
Unsatisfactory therapeutic response	1 (<1)	2 (<1)
Withdrawal by subject	7 (1)	15 (2)
Other	15 (2)	15 (2)
Patients who have participated in PFS follow-up	572 (86)	544 (81)
Patients who have participated in OS follow-up	[redacted]	[redacted]
Death	[redacted]	[redacted]
On-study death‡	9 (1)	13 (2)
Death during PTFU**	[redacted]	[redacted]

n (%)	A+AVD (n=664)	ABVD (n=670)
Reason for end of (discontinuation from) study	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]

All percentages are based on the number of patients in the ITT population.
*Patients were considered to have completed study treatment per protocol if they completed frontline therapy or experienced progressive disease per INV or died before completion of frontline therapy.
†Completion of frontline therapy was defined as receipt of planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD or conclusion of one alternative anticancer regimen for HL subsequent to A+AVD or ABVD discontinuation after the Cycle 2 PET assessment.
‡On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.
**PTFU deaths were defined as deaths that occurred after 30 days of the last dose of frontline therapy.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin , bleomycin, vinblastine, dacarbazine; AFM, alternative frontline medication; HL, Hodgkin lymphoma; INV, investigator; ITT, intent-to-treat; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PTFU, post-treatment follow-up.
Sources: Strauss *et al* (2021);[128] Takeda ECHELON-1 CSR (2018);[34] Takeda ECHELON-1 CSR (2024).[123]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of ECHELON-1 was conducted using the NICE checklist (based on Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care [University of York Centre for Reviews and Dissemination]) and is described further in Appendix D.[132] This assessment concluded that ECHELON-1 was methodologically robust and had low risk of bias overall, with an appropriate randomisation scheme, well-balanced patient characteristics between the patient arms, no unexpected imbalances in dropouts between groups, and good quality assurance for the trial (Appendix D).

A discussion around the strengths and limitations of ECHELON-1 is provided in Section B.2.12.2.

B.2.6 Clinical effectiveness results of the relevant trials

All data presented in this section are from ECHELON-1. Table 10 summarises data cutoffs (discussed in Section B.2.4.2; Table 7) presented in this submission, with their associated median follow-ups and relevant submission sections. Data on overall response rates and complete remission rates are presented in Appendix N.1.3. Data from the 3-year and 5-year updates are not presented in this submission, because these have been superseded by more recent data from longer follow-ups (6-year and 7-year follow-ups).

Table 10: Summary of trial data cuts relevant for this appraisal

	April 2017		**October 2018**	**June 2021**	**March 2023**	
Data cutoff	20 April 2017		15 October 2018	01 June 2021	11 March 2023	
Median follow-up (PFS and OS), months	24.6 (modified PFS per IRF) 24.7 (modified PFS per INV)		37.1	73.0	89.2 (PFS per INV) 89.3 (OS)	
Endpoints reported in submission	• Modified PFS per IRF • Modified PFS per INV • PET status after Cycle 2 • PROs • Treatment exposure • Safety and TEAEs during study treatment • Responses rates		• Safety (neutropenia and febrile neutropenia in subgroup treated with G-CSF; data reported as of April 2018; median follow-up: 30.6 months	• PFS per INV (6-year follow-up)	• PFS per INV (7-year follow-up) • OS • PFS and OS in prespecified subgroups • Incidence of live births • Safety and TEAEs during follow-up • Second malignancies	
Key publications	Takeda, ECHELON-1 CSR (2018)[34]		Straus *et al* (2020)[126]	Ansell *et al* (2022)[31]	Takeda, ECHELON-1 CSR (2024)[123]	
Included in section(s)	B.2.6.1.1 B.2.6.3 B.2.6.4 B.2.10.1 B.2.10.2 B.2.10.3.1	B.2.10.4.1 B.2.10.4.2 B.2.10.4.3 Appendix N.1.1 Appendix N.1.3 Appendix N.1.5	B.2.10.4.2	Appendix N.1.2	B.2.6.1.2 B.2.6.2 B.2.7.1 B.2.7.2	B.2.10.3.2 B.2.10.4.3 B.2.10.4.4 Appendix N.1.4

Abbreviations: G-CSF, granulocyte colony stimulating factor; INV, investigator; IRF, independent review facility; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PRO, patient-reported outcome; TEAE, treatment-emergent adverse event.

B.2.6.1 Modified PFS and PFS

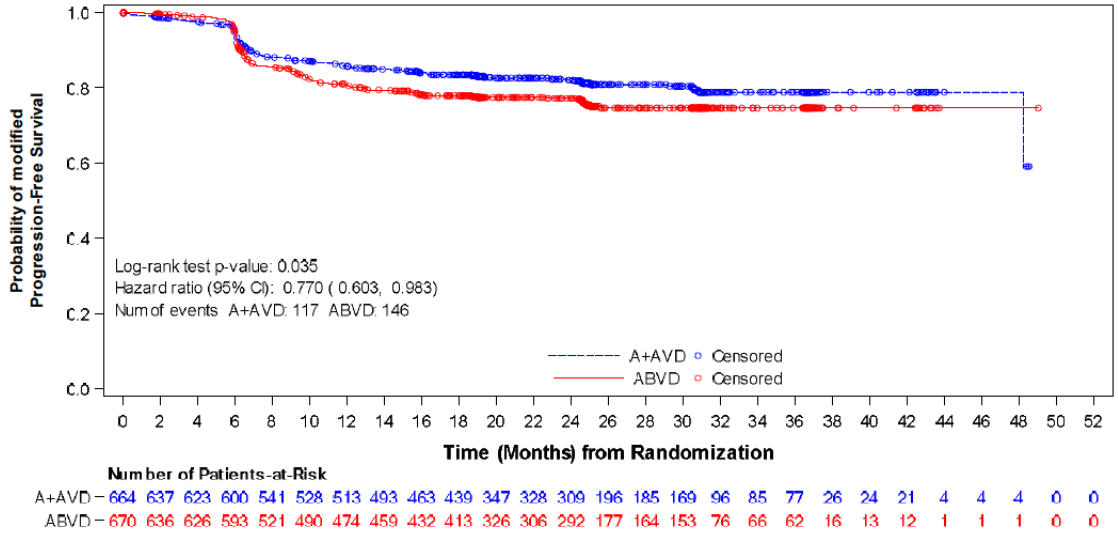
The primary endpoint in ECHELON-1 was modified PFS per IRF, defined as the time from the date of randomisation to the date of the first of documentation of progressive disease, death due to any cause, or for patients who were confirmed non-complete responders per IRF, receipt of subsequent anticancer therapy for HL after completion of frontline therapy. As discussed in Section B.2.3.2.1, this endpoint was designed to capture all events that reflect a failure of frontline chemotherapy in advanced HL, thus providing a stringent assessment of occurrences of treatment failure.[112] In addition, PFS was a prespecified exploratory endpoint in ECHELON-1.[34]

Modified PFS and PFS were assessed by both the IRF and the investigator (INV), a recognised practice within the domain of untreated lymphoma trials. However, in line with standard practice for a trial with such long follow-up, the IRF was disbanded 5 years after the trial initiation, by which point a sustained treatment benefit with A+AVD vs. ABVD had been independently confirmed.[34] Furthermore, there was a 91% concordance between IRF and INV determination of modified PFS (Section B.2.6.1.1), which highlights the robust use of modified PFS and PFS per investigator analysis at longer follow-up timepoints and reliability to use investigator assessments of PFS-based endpoints. Therefore, data presented from the latest data cutoff (11 March 2023) are based on the INV assessment.

B.2.6.1.1 Modified PFS | Primary endpoint | Data cutoff (DCO) 20 Apr 2017

After a median follow-up of 24.6 months (95% CI: 24.4–24.8), 117 modified PFS per IRF events (18%) were observed in the A+AVD treatment arm vs. 146 modified PFS events (22%) in the ABVD treatment arm. Median modified PFS per IRF was not estimable in either arm. The 2-year modified PFS rate was significantly higher in the A+AVD arm compared with the ABVD arm (82.1%; 95% CI: 78.8–85.0 vs. 77.2%; 95% CI: 73.7–80.4), with a stratified HR for progression, death, or treatment failure of 0.770 (95% CI: 0.603–0.983) corresponding to a 23% risk reduction with A+AVD compared with ABVD (p=0.035; Figure 5).[34, 112] Modified PFS per INV confirmed the findings of the modified PFS per IRF (Appendix N.1.1), with a 91% concordance between IRF and INV determination of an modified PFS event.[112]

Figure 5: Kaplan–Meier plot of modified PFS per IRF assessment (median follow-up 24.6 months)



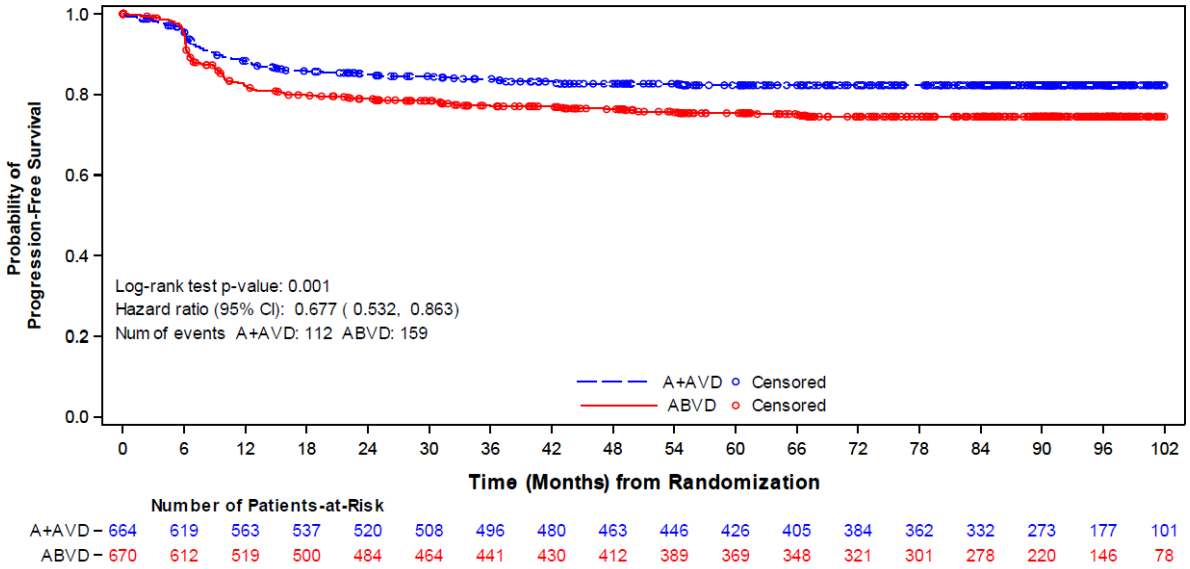
Hazard ratio (A+AVD/ABVD) and 95% CI were based on a stratified Cox's proportional hazard regression model with stratification factors region and number of IPS risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favours A+AVD arm.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; IPS, International Prognostic Score; IRF, independent review facility; PFS, progression-free survival.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.6.1.2 PFS per INV | DCO 11 Mar 2023

Due to the disbanding of the IRF 5 years after trial initiation, PFS assessed per INV represents the PFS data with the longest follow-up from ECHELON-1. At a median follow-up of 90.0 months (95% CI: 87.3–90.9) in the A+AVD arm and 86.4 months (95% CI: 84.4–89.6) for ABVD, 112 PFS events (17%) were observed in the A+AVD arm vs. 159 PFS events (24%) in the ABVD arm (Table 11), indicating a PFS benefit for A+AVD. Median PFS was not estimable (NE) in either group (95% CI: NE–NE in either group). A 32.3% reduction in risk of progression or death was observed with A+AVD compared with ABVD, in favour of A+AVD (HR: 0.677; 95% CI: 0.532–0.863; p=0.001; Table 11). Based on Kaplan–Meier estimates, the proportion of patients who are alive and progression-free at 102 months is 82.3% in the A+AVD arm and 74.5% in the ABVD arm (Figure 6).[123] There was a sustained plateau in the PFS Kaplan–Meier (Figure 6) from approximately 24 months, which aligns with clinical expert feedback that patients who have not relapsed by approximately 2 years are generally considered cured of their HL.[36, 123]

The PFS benefit for A+AVD vs. ABVD was sustained across multiple analysis timepoints (Appendix N.1.2), demonstrating a robust and durable improvement in PFS for A+AVD vs. ABVD up to at least 7 years.[31, 123]

Figure 6: Kaplan–Meier plot of PFS per INV | DCO 11 Mar 2023



Data presented are based on the ITT population.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin , bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; INV, investigator; ITT, intent-to-treat; PFS, progression-free survival.
Source: Takeda ECHELON-1 CSR (2024).[123]

Table 11: Analysis of PFS | DCO 11 Mar 2023

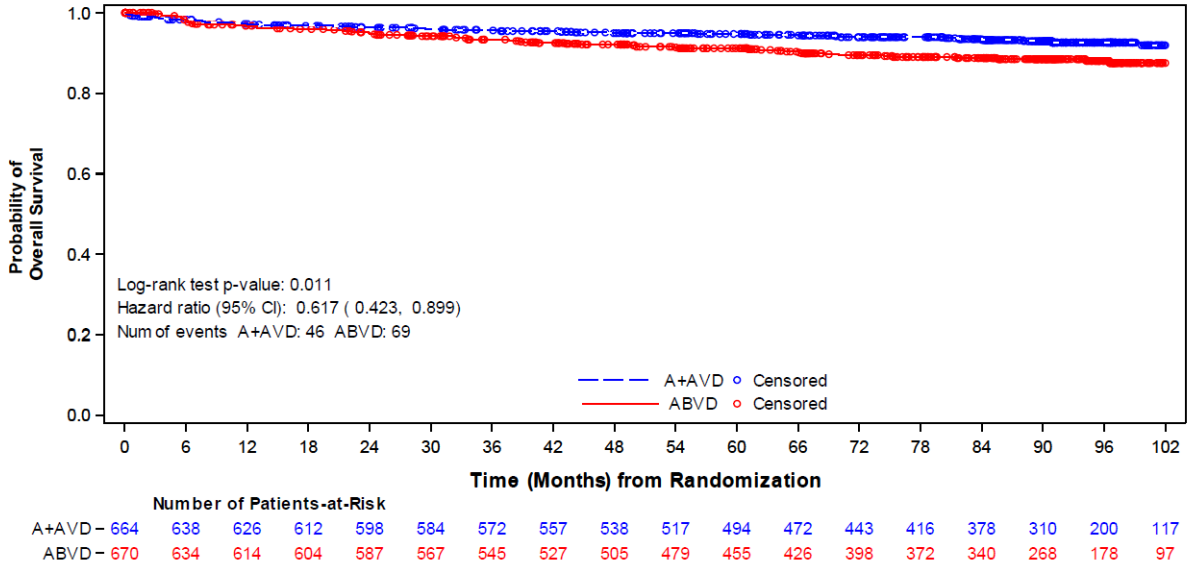
	A+AVD (n=664)	**ABVD (n=670)**
Median follow-up, months (95% CI)	90.0 (87.3–90.9)	86.4 (84.4–89.6)
Median PFS (95% CI)	NE (NE–NE)	NE (NE–NE)
PFS range	0–118.0	0–118.7
Number of events (%)	112 (17.0)	159 (24.0)
HR (95% CI), p-value	0.677 (0.53–0.86), p=0.001	
Number censored (%)	552 (83.0)	511 (76.0)
Progression-free survival at timepoints*, % (95% CI), n		
12 months	88.3 (85.6–90.6), n=563	82.1 (78.9–84.8), n=519
48 months	82.7 (79.5–85.4), n=463	76.3 (72.8–79.4), n=412
84 months	82.3 (79.1–85.0), n=332	74.5 (70.8–77.7), n=278
102 months	82.3 (79.1–85.0), n=101	74.5 (70.8–77.7), n=78

*Kaplan–Meier estimates.
Data presented are based on the ITT population
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; n, number, NE, not estimable.
Source: Takeda, ECHELON-1 CSR (2024);[123] Takeda (2023).[124]

B.2.6.2 OS | DCO 11 Mar 2023

At a median follow-up of 90.1 months (95% CI: 87.7–90.8) for A+AVD and 88.3 months (95% CI: 85.2–89.9) for ABVD), a total of 46 deaths (7%) occurred in the A+AVD arm and 69 (10%) in the ABVD arm (Table 12). The analysis of OS significantly favoured A+AVD, showing a 38.3% reduction in the risk of death in the A+AVD arm vs. the ABVD arm (HR: 0.617; 95% CI: 0.423–0.899; p=0.011). Based on Kaplan–Meier estimates, the proportion of patients who are alive at 102 months is 91.9% in the A+AVD arm and 87.5% in the ABVD arm (Table 12).[123] Therefore, the data from the 7-year follow-up in ECHELON-1 demonstrate a statistically significant improvement in OS with A+AVD vs. ABVD (Figure 7).

Figure 7: Kaplan–Meier plot of OS | DCO 11 Mar 2023



Data presented are based on the ITT population.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin , bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; ITT, intent-to-treat; OS, overall survival.
Source: Takeda ECHELON-1 CSR (2024).[123]

Table 12: Analysis of OS | DCO 11 Mar 2023

	A+AVD (n=664)	**ABVD (n=670)**
Median follow-up, months (95% CI)	90.1 (87.7–90.8)	88.3 (85.2–89.9)
Median OS (95% CI)	NE (115.1–NE)	NE (NE–NE)
OS range, months	0–118.0	0–118.7
Number of events (%)	46 (7.0)	69 (10.0)
HR (95% CI), p value	0.617 (0.42–0.9), p=0.011	
Number censored (%)	618 (93.0)	601 (90.0)
Survival at timepoints*, % (95% CI), n		
12 months	97.2 (95.7–98.3), n=626	96.7 (95.1–97.9), n=614
48 months	94.9 (92.9, 96.4), n=538	92.1 (89.7–94.0), n=505

	A+AVD (n=664)	ABVD (n=670)
84 months	93.5 (91.1–95.2), n=378	88.8 (85.8–91.1), n=340
102 months	91.9 (89.0–94.1), n=117	87.5 (84.2–90.2), n=97

*Kaplan–Meier estimates.
Data presented are based on the ITT population
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; n, number, NE, not estimable.
Source: Takeda, ECHELON-1 CSR (2024);[123] Takeda (2023).[125]

B.2.6.3 PET status after Cycle 2 | DCO 20 Apr 2017

After PET2 disease assessment, a numerically higher rate of PET2 negativity was observed in the A+AVD arm vs. the ABVD arm; however this is not statistically significant (relative risk: 1.028; 95% CI: 0.99–1.07).[34] In the A+AVD arm, 588 patients (89%) were PET2-negative, 47 (7%) were PET2-positive, and PET2 status was unknown or missing for 29 patients (4%). In the ABVD arm, 577 patients (86%) were PET2-negative, 58 (9%) were PET2-positive, and PET2 status was unknown or missing for 35 patients (5%).[31]

B.2.6.4 Patient-reported outcomes | DCO 20 Apr 2017

Patient-reported outcomes (PROs) were evaluated in the ITT population using the EORTC QLQ-C30, Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnea 10, the EQ-5D-3L questionnaire, and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity subscale (FACT/GOG-NTx). All assessments were collected at baseline (before study drug was administered) and during study treatment (Day 1 of each cycle) until end of treatment. QoL was assessed during post-treatment follow-up (PTFU) up to 36 months after the end of treatment by EORTC QLQ-C30 and EQ-5D-3L only.[31, 34]

During the on-treatment period, the differences between A+AVD vs. ABVD on some QoL subscales of EORTC QLQ-C30, EQ-5D, and FACIT-Dyspnea 10 were not clinically meaningful based on the minimally important difference (MID) commonly accepted for patients with advanced cancers (see below for details). During PTFU, QoL by EORTC QLQ-C30 or EQ-5D-3L returned to baseline levels or was found to be better than baseline. These data suggest that any QoL differences are likely driven by differences in AE experiences during the on-treatment period. This is consistent with the known side effects of brentuximab vedotin, which clinicians are familiar with managing in routine practice and typically resolve after the end of treatment (Section B.2.10.2).[34, 43] The fact that post-treatment QoL returned to better than baseline levels supports the positive impact of successful treatment on long-term patient QoL.

B.2.6.4.1 EORTC QLQ-C30

Mean EORTC QLQ-C30 scores for global health/QoL status trended lower in the A+AVD arm compared with the ABVD arm across treatment cycles and at the end of treatment (Figure 8). However, the differences in scores did not reach the MID of 10 published for patients with advanced cancers, indicating they were not clinically meaningful.[133] Additionally, after 6 months of follow-up, global health/QoL scores increased in both treatment arms and returned to levels higher than baseline and age-adjusted general

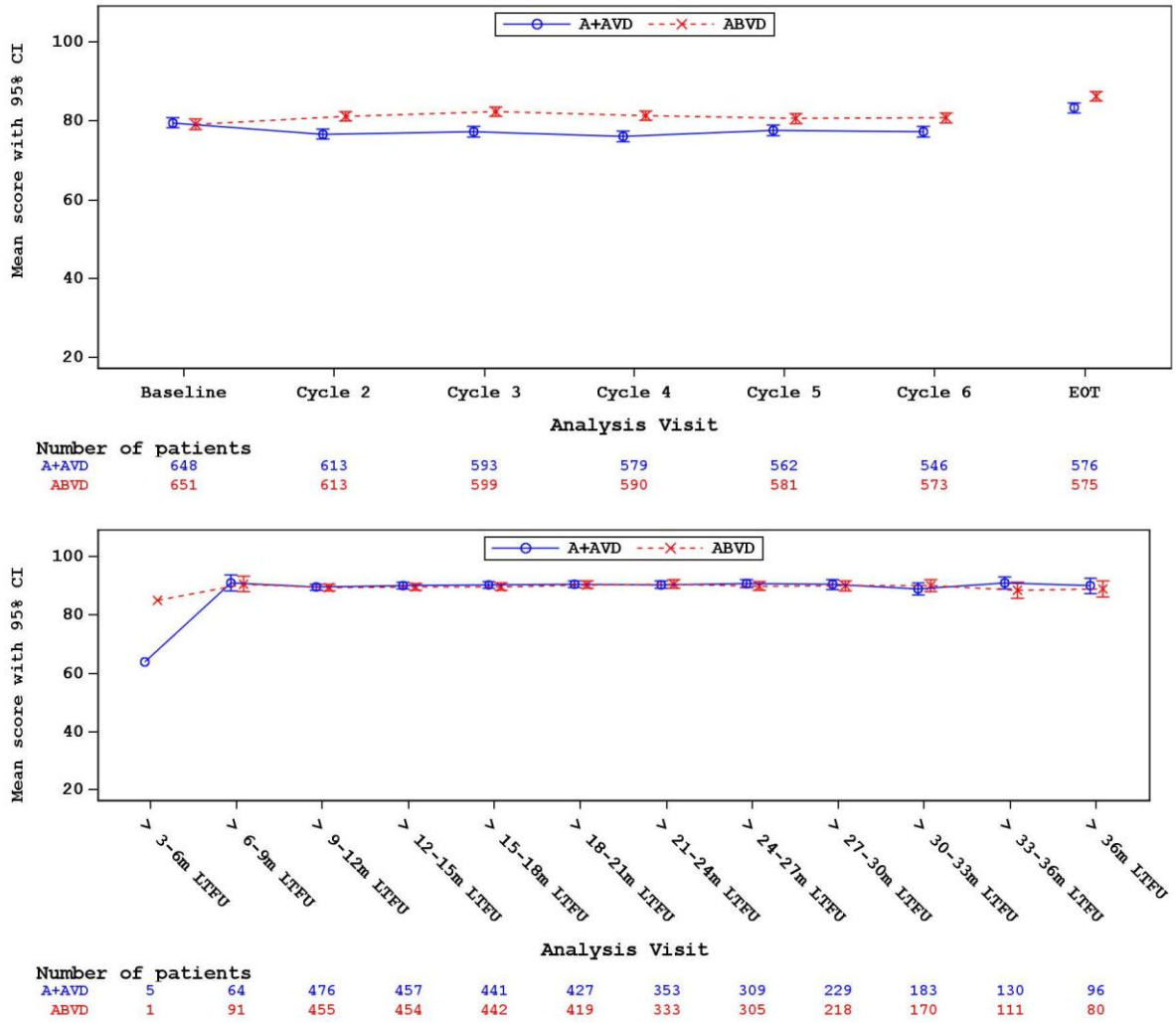
population norms[u].[134] No differences in scores were observed between A+AVD and ABVD during the follow-up period (Figure 8).[34]

Compared with both baseline and scores measured during treatment, mean EORTC QLQ-C30 subscale scores for QoL subscales (global health/QoL, cognitive function, emotional functioning, physical functioning, role functioning, social functioning) increased after 6–9 months after the end of treatment and remained stable up to 36 months, whereas no differences were observed between the two treatment arms (Appendix N.1.5.1). No meaningful differences were observed between A+AVD patients and ABVD patients for any of the subscale QoL scores or summary scores over the same period.[34]

For the mean subscale symptom scores (insomnia, nausea and vomiting, pain, and fatigue; Appendix N.1.5.1), which were generally higher for A+AVD patients than ABVD patients during first-line treatment, scores decreased from those reported during first-line treatment and no differences were observed between the two treatment arms from the end of treatment through to 36 months after end of treatment. At the end of follow-up, the change from baseline reflected a marked improvement during long-term follow-up for both treatment arms.[34]

[u] EORTC QLQ-C30 general population norms for population in the UK are based on the study by Nolte *et al* (2019),[134] which gathered data from 11 European countries, including the UK. The total sample number was 11,343 participants, 50.4% of which were male, 59.6% were <60 years old, and 1,026 (9.0%) were from the UK. The global health/QoL mean score on EORTC QLQ-C30 for the participants in the UK was 62.3 (SD, 23.7).[134]

Figure 8: Mean EORTC QLQ-C30 Summary score over time | DCO 20 Apr 2017



Data presented are based on the ITT population; data collection was continued for patients who discontinued the study treatment until the patient discontinued scheduled study visits; patients continuing on study treatment were excluded from long-term follow-up.
Baseline was defined as the value collected at the time closest to, but before, the start of study drug administration. Long-term follow-up visits indexed from Study Day 1. Patients on study treatment were excluded. The score range is 0-100. A high score for summary score represents a high QOL; a high score for a functional scale represents a high healthy level of functioning, a high score for the global health status /QOL represents a high QOL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; EOT, end of treatment; ITT, intent-to-treat; LTFU, long-term follow-up; QOL, quality of life.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.6.4.2 FACIT-Dyspnea 10

A trend of worsening dyspnoea was observed in both treatment arms across treatment cycles. In the absence of an established MID for FACIT-Dyspnea 10, a well-established guideline suggests an SD of 0.5 on baseline scores as a reasonable and scientifically supportable estimate of a medium effect size, and this value was used as a conservative approach to determine clinical meaningfulness.[135] As such, although the change from

baseline indicated differences between the two treatment arms at Cycles 3 and 5, these differences were not clinically meaningful (see Appendix N.1.5.2).[34]

B.2.6.4.3 FACT/GOG-NTX Neurotoxicity scale

Mean subscale scores were lower in the A+AVD arm compared with the ABVD arm over the course of the study and at end of treatment (see Appendix N.1.5.3). In the absence of a referenced MID for the FACT/GOG-NTX neurotoxicity subscale, a threshold of 3 points has been used in studies for this subscale, which corresponded to the MID value obtained for the FACIT-Fatigue scale. These differences in FACT/GOG-NTX neurotoxicity subscale scores at Cycles 4 (mean score change from baseline: −4.72), 5 (mean score change from baseline: −6.03), and 6 (mean score change from baseline: −7.74), were clinically meaningful and reflective of the higher proportion of patients in the A+AVD arm experiencing peripheral neuropathy (Section B.2.10.4.3).[34]

The combination of brentuximab vedotin plus vinblastine means the A+AVD regimen includes two components with potentially overlapping microtubule-targeting mechanisms of action.[136] As such, higher rates of peripheral neuropathy in the A+AVD arm compared with the ABVD arm are consistent with the safety profile of brentuximab vedotin.[38, 136] However, symptoms of peripheral neuropathy continued to improve or resolve over time after the end of treatment, and any events of worsening neuropathy could have been managed by dose delay (Sections B.2.10.4.3 and B.2.10.5).[34]

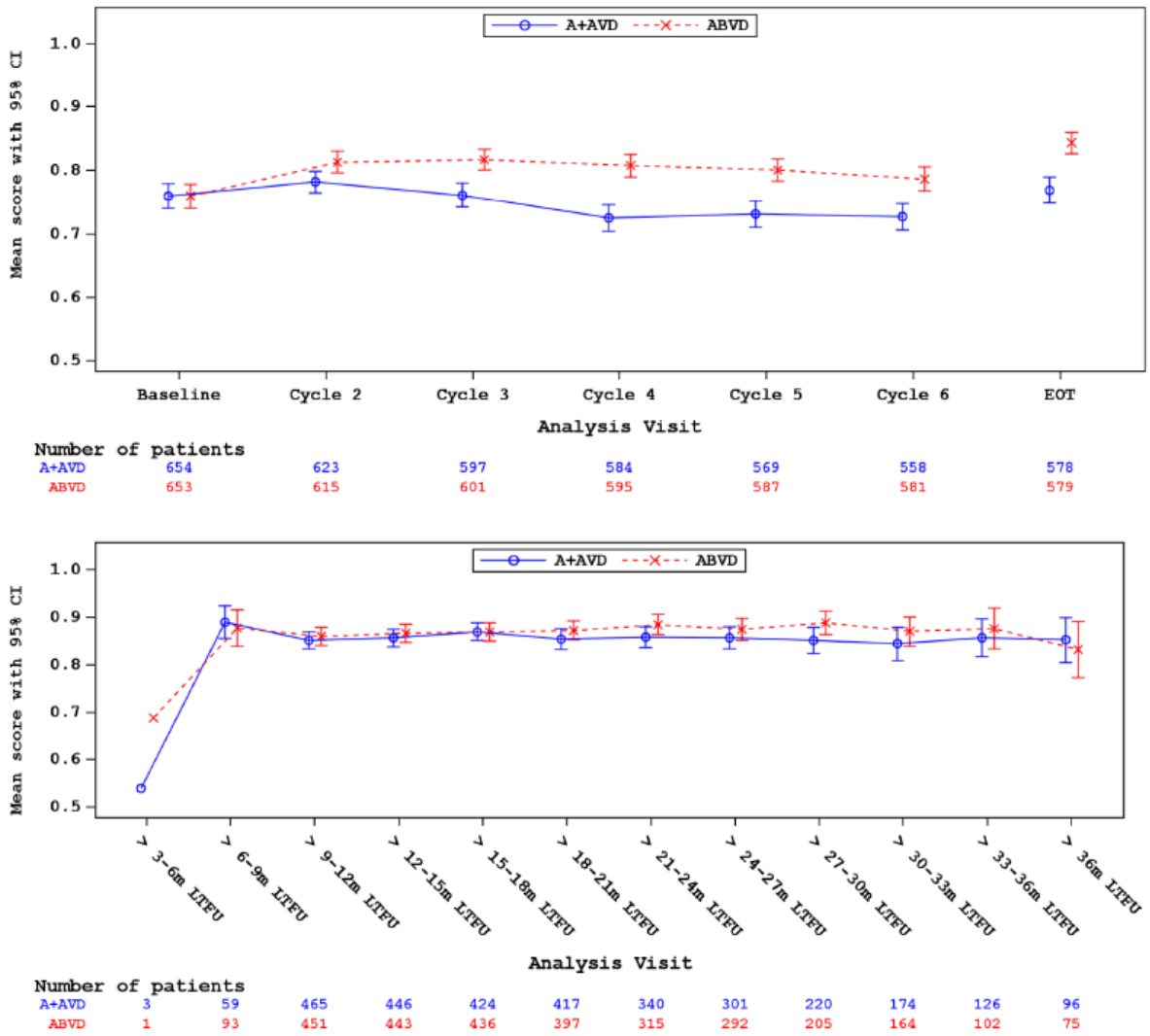
B.2.6.4.4 EQ-5D-3L

The EQ-5D-3L included data from both the EQ-5D descriptive system and the visual analogue scale (VAS). Additionally, EQ-5D time trade-off (EQ-5D TTO) indexed data were analysed using the UK-based value sets.[34]

The mean EQ-5D-3L (UK) TTO-indexed scores over time were higher for the ABVD arm during first-line treatment. Such differences were not clinically significant as they did not differ from the MID of 0.07 established for the UK TTO score.[137] During long-term follow-up, however, mean scores improved for both the A+AVD and ABVD arms, as they returned to higher levels than baseline, and were comparable across the two treatment arms from end of treatment through to 36 months after the end of treatment (Figure 9).[34] Of note, EQ-5D-3L index scores from 6–9 months to 36 months from end of treatment (mean: 0.88–0.91) are similar to population norms (mean: 0.92 across all EU5 countries and age groups, or approximately 0.89 for the UK general population aged 35–44 years)[v].[138]

[v] EQ-5D-3L general population norms based on Janssen *et al* (2021), which gathered data from five European countries, including the UK. The total sample number was 21,425 participants, of whom 45.8% were male and 78.4% were <65 years old. Of all participants, 6,319 were from the UK, of whom 44.4% were male. The total EQ-5D-3L index score of the overall population was 0.916.[138]

Figure 9: Mean EQ-5D-3L UK TTO score over time | DCO 20 Apr 2017



Data presented are based on the ITT population; patients on treatment were excluded.
Baseline was defined as the value collected at the time closest to, but before, the start of study drug administration. Long-term follow-up visits indexed from Study Day 1. The range of EQ-5D-3L UK TTO is 0-1; a higher score indicates a more preferred health status.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; EOT, end of treatment; European Quality of Life 5-Dimension 3-Level version; ITT, intent-to-treat; LTFU, long-term follow-up; TTO, time trade-off; UK, United Kingdom.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.6.5 Efficacy conclusions

ECHELON-1 was a randomised, controlled trial that enrolled 1,334 patients (including 154 patients from Great Britain) with over 7 years of follow-up.[31, 123] The trial comparator – ABVD – is a chemotherapy combination used extensively in UK clinical practice in patients with CD30+ Stage III or IV HL. Baseline characteristics were well balanced between treatment arms and UK-based clinical advisors confirmed that the

patients included are representative of those they would treat in routine UK clinical practice.[36, 128]

Survival outcomes in ECHELON-1 consistently favoured A+AVD compared with ABVD. For the stringent primary endpoint of modified PFS per IRF, A+AVD was associated with a significant 23% reduction in the risk of treatment failure, progression, or death at a follow-up of ~2 years (HR: 0.770; 95% CI: 0.603–0.983; p=0.035).[34, 112, 128] In addition, A+AVD was associated with a robust and durable improvement in PFS per INV vs. ABVD, with a 32.3% reduction in risk of progression or death at 7-year follow-up (PFS events occurred in 17% and 24% in the A+AVD and ABVD arms, respectively; HR: 0.677; 95% CI: 0.532–0.863; p=0.001), reinforcing the modified PFS results.[123, 128] Importantly, treatment with A+AVD resulted in a significant, 38.3% lower risk of death vs. ABVD (HR: 0.617; 95% CI: 0.423–0.899; p=0.011). The OS benefit with A+AVD at 7-year follow-up was sustained, and consistent with that observed at 6 years' follow-up in ECHELON-1, despite less frequent use of subsequent therapies, including stem cell transplants, in the A+AVD arm (Section B.3.5.4.1).[31, 123]

As described in Ansell *et al* (2022), historically, it has been difficult to show a survival benefit over SoC (e.g. ABVD) in the context of first-line therapy in previously untreated HL, partly because many patients with R/R HL can receive first relapse multiagent chemotherapy as well as receiving an ASCT, which is curative in approximately 50% of patients.[12, 28, 31] Notably, A+AVD is the first regimen to show an OS advantage compared with ABVD (PET-adapted or six cycles) in patients with previously untreated Stage III or IV HL. In ECHELON-1, the use of subsequent treatments was less frequent with A+AVD compared with ABVD, including fewer ASCT (Section B.3.5.4.1).[31] Hence, it has been suggested that the OS benefit observed in ECHELON-1 with A+AVD is unlikely to be due to under-treatment of disease or under-performance of salvage agents administered in patients in the ABVD arm. Factors suggested as potential reasons for the OS benefit with A+AVD are the additional mechanisms of action previously observed for brentuximab vedotin, including antibody-dependent cellular phagocytosis, bystander activity in the tumour microenvironment, induction of immunogenic cell death, and depletion of CD30-expressing regulatory T-cells.[31]

After PET2 disease assessment, a higher rate of PET2 negativity was observed in the A+AVD arm vs. the ABVD arm (89% vs. 86%, respectively).[34] Though not statistically significant, these results suggest there may be a benefit to initiating treatment with A+AVD compared with ABVD, especially considering that failure to achieve PET2 negativity is associated with poorer PFS and OS outcomes compared with patients who achieve PET2 negativity, even when treatment is intensified for PET2-positive patients in subsequent cycles, as seen in RATHL.[88]

Across both treatment arms, mean PRO scores (EORTC QLQ-C30 subscales and Global scores and EQ-5D-3L) improved to greater levels after treatment compared with baseline scores. Moreover, EQ-5D-3L and EORTC QLQ-C30 scores after treatment were similar to

age-adjusted population norms[w], suggesting that treatment may restore patient HRQoL and not cause long-term decrement.[134, 138]

In conclusion, ECHELON-1 demonstrates a survival advantage (PFS and OS) for A+AVD over ABVD in patients with previously untreated CD30+ Stage III or IV HL, with no long-term decrement in quality of life.[31, 123] Of particular importance is the significant OS benefit of A+AVD vs. ABVD, since ECHELON-1 is the first trial to show a significant OS advantage for any regimen compared head to head with ABVD (PET-adapted or six cycles) in patients with previously untreated Stage III or IV HL.[16]

B.2.7 Subgroup analysis

Subgroups were prespecified for the primary endpoint, modified PFS, and included age, region, number of IPS risk factors, cancer stage at baseline, baseline B symptoms, PET2 assessment, PET2 DS, receipt of AFM, and baseline extranodal sites. A number of additional subgroup analyses not described in the statistical analysis plan were added to the prespecified analyses in June 2016, approximately 1 year before the clinical database lock, prior to study investigators' awareness of the treatment effect for efficacy endpoints. These included age, ECOG performance status score, and gender. Prespecified subgroup analysis for OS was performed using the subgroups defined for modified PFS analyses, presented in Table 13. PFS was an exploratory endpoint and was likewise analysed using the subgroups prespecified for modified PFS.

Table 13: Subgroup definitions

Subgroup	Definition of subgroup
Age	<60 vs. ≥60 years; <65 vs. ≥65 years; <45 vs. ≥45 years
Region	Americas; Asia; Europe; North America
Number of IPS risk factors at baseline	0–1; 2–3; 4–7
Cancer stage at baseline	Stage III; Stage IV
Baseline B symptoms	Present; absent
Cycle 2 PET results	Positive (Deauville score of >3); negative (Deauville score of ≤3)
Cycle 2 PET Deauville score	<5; 5
Receipt of alternative frontline medication	Yes; No
Extranodal sites at baseline	0; 1; >1
ECOG performance status score	0; 1; 2
Gender	Male; Female

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPS, international prognostic score; PET, positron emission tomography.
Source: Takeda ECHELON-1 CSR (2018).[34]

[w]EQ-5D general population norms are based on Janssen *et al* (2021), which gathered data from five European countries, including the UK. The total sample number was 21,425 participants, of which 45.8% were male and 78.4% were <65 years old. From all participants, 6,319 were from the UK, of which 44.4% were male. The mean total EQ-5D-3L index score (TTO-based) of the overall EU5 population was 0.916 and the mean VAS score of the overall population was 78.3.[138]

EORTC QLQ-C30 general population norms for the UK are based on Nolte *et al* (2019), which covered 11 European countries, including the UK. The total sample number was 11,343 participants, 50.4% of which were male, 59.6% were <60 years old, and 1,026 (9.0%) were from the UK. The global health/QoL mean score for UK participants was 62.3 (SD, 23.7).[134]

B.2.7.1 PFS per INV | DCO 11 Mar 2023

Overall, PFS results across subgroups were consistent with the ITT population (HR: 0.677; 95% CI: 0.532–0.863), with the majority of subgroups showing a treatment benefit with A+AVD vs. ABVD (Figure 10). A treatment benefit with A+AVD was also observed in patients who received AFM (A+AVD, n= [%]; ABVD: n= [%]; HR: , 95% CI:), in patients who did not receive AFM (A+AVD, n= [%]; ABVD: n= [%]; HR: , 95% CI:), patients with DS=5 at Cycle 2 (A+AVD, n= [%]; ABVD: n= [%]; HR: , 95% CI:), and patients with DS<5 at Cycle 2 (A+AVD, n= [%]; ABVD: n= [%]; HR: , 95% CI:).[123, 139–142] No subgroup analysed had a lower bound 95% CI that crossed the threshold HR of 1 in favour of ABVD. In subgroups where the upper bound 95% CI crossed the HR of 1, the number of patients and associated number of PFS events were much lower than the ITT population, and therefore these data should be interpreted with caution (Figure 10).[123]

Figure 10: Forest plot of PFS per INV | Key subgroups | DCO 11 Mar 2023

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; ECOG, Eastern Cooperative Oncology Group; INV, investigator; IPFP, international prognostic factors project; PFS, progression-free survival.
Source: Takeda ECHELON-1 CSR (2024).[123]

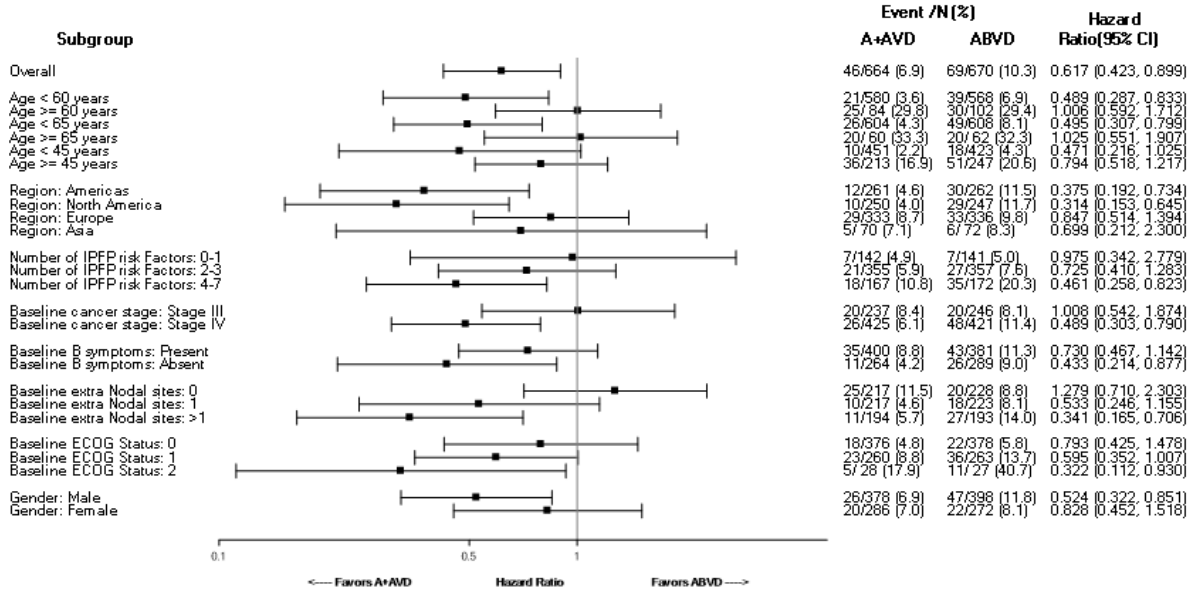
B.2.7.2 OS | DCO 11 Mar 2023

Overall, OS results across key subgroups were consistent with the ITT population (HR: 0.617; 95% CI: 0.423–0.899), with the majority of subgroups showing a treatment benefit for A+AVD compared with ABVD (Figure 11). A treatment benefit with A+AVD was also observed in patients who received AFM (A+AVD, n= [%]; ABVD: n= [%]; HR: , 95% CI:), in patients who did not receive AFM (A+AVD, n= [%]; ABVD: [%]; HR: , 95% CI:), patients with DS=5 at Cycle 2 (A+AVD, [%]; ABVD: n [%]; HR: , 95%

CI: [redacted]), and patients with DS<5 at Cycle 2 (A+AVD, n=[redacted] [[redacted]%]; ABVD: n=[redacted][[redacted]%]; HR: [redacted], 95% CI: [redacted]).[123, 143–146]

Similar to PFS (Section B.2.7.1), in subgroups where the upper bound 95% CI crossed the threshold HR of 1, the number of patients and associated number of OS events were much lower than the ITT population, and therefore these data should be interpreted with caution (Figure 11).[123, 140, 142] The low number of OS events overall in the setting of previously untreated HL poses an obstacle to observing a benefit within subgroups. The number of OS events in many of the subgroups is very small (e.g. only [redacted] OS events occurred in each arm of the IPS 0–1 subgroup) and it is thus extremely challenging to draw any statistical conclusions, other than those provided by the more robust ITT analysis (Section B.2.6.2).

Figure 11: Forest plot of OS | Key subgroups | Prespecified analysis | DCO 11 Mar 2023



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; DCO, data cutoff; IPFP, international prognostic factors project; OS, overall survival.
Source: Takeda ECHELON-1 CSR (2024).[123]

B.2.8 Meta-analysis

Not applicable.

B.2.9 Indirect and mixed treatment comparisons

Not applicable; head-to-head evidence comparing A+AVD with ABVD-based treatment, the relevant comparator for this appraisal, is provided by the ECHELON-1 trial (Sections B.2.1 to B.2.7).

As described in Section B.3.2.3.2, outcomes for patients receiving six cycles of ABVD (as per ECHELON-1) were assumed to be equivalent to the PET-adapted ABVD strategy followed in the RATHL trial for the purposes of economic modelling. To support this, unanchored, unadjusted, and adjusted indirect treatment comparisons (ITCs) of ABVD-based regimens were conducted, with methods and results presented in Appendix D and Section B.3.2.3.2.

B.2.10 Adverse reactions

The safety data presented are from the safety population of ECHELON-1, defined as patients who received ≥1 dose of any study drug in the frontline treatment regimen. The safety population consisted of 662 patients in the A+AVD treatment arm and 659 patients in the ABVD treatment arm. All TEAEs were collected from the 20 April 2017 DCO; additional data are provided from the latest DCO (11 March 2023), including deaths and drug-related serious AEs (SAEs) during the follow-up period, peripheral neuropathy, and second malignancies.

B.2.10.1 Treatment exposure | DCO 20 Apr 2017

The two treatment arms received a similar number of treatment cycles administered over a similar duration of treatment. A similar relative dose intensity (RDI) was reported for the two treatment arms.[34]

Patients in the A+AVD arm received a median of six treatment cycles (range: 1–6) over a median of 24.2 weeks (range: 2.0–35.0 weeks) for brentuximab vedotin, 24.5 weeks for doxorubicin and dacarbazine, and 24.4 weeks for vinblastine (range, 2.0–48.9 weeks for AVD). The median RDI was 99.5% (range: 16.7–114.3%) for brentuximab vedotin, 100% (range: 4.1–109.2%) for doxorubicin, 99.1% (range: 15.4–115.2%) for vinblastine, and 100% (range: 66.0–111.9%) for dacarbazine. Patients in the ABVD arm received a median of six treatment cycles (range: 1–6) over a median of 24.0 weeks for all four study drugs (range: 2.0–39.1 weeks for bleomycin; 2.0–45.4 weeks for AVD). A median RDI of 100% was reported for doxorubicin (range: 59.6–111.1%), median RDI of 99.8% for bleomycin (range: 8.1–119.4%), a median RDI of 99.3% for vinblastine (range: 9.3–116.2%), and a median RDI of 100% (range: 13.9–114.0%) for dacarbazine.[34] A similar proportion of patients completed all six cycles of treatment (A+AVD: n=593, 89.3%; ABVD: n=608, 90.7%).[31]

B.2.10.2 Treatment-emergent adverse events | DCO 20 Apr 2017

A similar proportion of AEs of any grade (99% vs. 98%) and drug-related TEAEs (97% vs. 94%) were reported for the A+AVD and ABVD treatment arms, respectively. There were more Grade ≥3 and serious AEs with A+AVD vs. ABVD (Grade ≥3: 83% vs. 66% and serious AEs: 43% vs. 27%). There were fewer AEs that resulted in study drug discontinuation with A+AVD vs. ABVD (88 vs. 105). In the ABVD arm, the highest number of dose modifications was reported for the bleomycin component (n=315), including dose discontinuation (n=106) and dose delays (n=211). An AE resulting in dose modification was reported in 64% of patients receiving A+AVD compared with 44% of patients receiving ABVD (Section B.2.10.2.2). There were nine (1%) on-study deaths reported in the A+AVD arm, of which eight were assessed by the investigator to be treatment-related. In the ABVD arm, 13 (2%) on-study deaths were reported, of which seven were assessed to be treatment-related (Table 14).[34]

Table 14: Summary of TEAEs | Safety population | DCO 20 Apr 2017

n (%)	A+AVD (n=662)	ABVD (n=659)
Any AE	653 (99.0)	646 (98.0)
Drug-related AE*	641 (97.0)	617 (94.0)

n (%)	A+AVD (n=662)	ABVD (n=659)
Grade ≥3 AE	549 (83.0)	434 (66.0)
Serious AE	284 (43.0)	178 (27.0)
Drug-related serious AE	240 (36.0)	125 (19.0)
AE resulting in study drug discontinuation*	88 (13.0)	105 (16.0)
AE resulting in dose modification	423 (64.0)	293 (44.0)
On-study deaths	9 (1.0)	13 (2.0)
Deaths due to treatment-related AEs	8 (1.0)	7 (1.0)

*ECHELON-1 was not locked after the original 20 Apr 2017 DCO, meaning on-treatment TEAEs were available to update as required. Subsequent to the DCO, the number and proportion of patients reporting drug-related AEs for A+AVD were revised to 646 patients (98.0%) and for ABVD to 623 patients (95.0%); likewise, AEs resulting in study drug discontinuation were observed in 87 patients (13.0%) in the A+AVD treatment arm and 104 patients (16.0%) in the ABVD arm. These are noted here for completeness.[123]
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: Takeda ECHELON-1 CSR (2018).[123]

B.2.10.2.1 Most-common TEAEs | DCO 20 Apr 2017

The most common TEAEs of any grade reported for ≥20% of patients in the A+AVD treatment arm were neutropenia (58%), nausea (53%), constipation (42%), vomiting (33%), fatigue (32%), peripheral sensory neuropathy (29%), diarrhoea and pyrexia (27% each), alopecia and neuropathy peripheral (26% each), decreased weight (22%), and abdominal pain, anaemia, and stomatitis (21% each). The most common TEAEs of any grade reported for ≥20% of patients in the ABVD treatment arm were nausea (56%), neutropenia (45%), constipation (37%), fatigue (32%), vomiting (28%) and pyrexia and alopecia (22% each; Table 15).[34]

At least one drug-related TEAE of any grade was reported for 641 patients (97%) in the A+AVD treatment arm and 617 patients (94%) in the ABVD treatment arm. The most common drug-related TEAEs reported for ≥20% of patients in the A+AVD treatment arm were neutropenia (55%), nausea (48%), constipation (33%), vomiting and peripheral sensory neuropathy (27% each), fatigue (26%), neuropathy peripheral (25%), and alopecia (24%). The most common drug-related TEAEs in the ABVD treatment arm were nausea (52%), neutropenia (41%), fatigue (27%), constipation (25%), vomiting (24%) and alopecia (20%; Table 15).[34]

Table 15: TEAEs reported by ≥20% of patients in either treatment arm by preferred term | Safety population | DCO 20 Apr 2017

n (%)	A+AVD (n=662)		ABVD (n=659)	
	Any	Drug related	Any	Drug related
≥1 TEAE	653 (99.0)	641 (97.0)	646 (98.0)	617 (94.0)
Neutropenia	382 (58.0)	366 (55.0)	295 (45.0)	270 (41.0)
Nausea	348 (53.0)	319 (48.0)	371 (56.0)	342 (52.0)
Constipation	279 (42.0)	216 (33.0)	241 (37.0)	168 (25.0)
Vomiting	216 (33.0)	182 (27.0)	183 (28.0)	156 (24.0)

n (%)	A+AVD (n=662)		ABVD (n=659)	
	Any	Drug related	Any	Drug related
Fatigue	211 (32.0)	169 (26.0)	211 (32.0)	178 (27.0)
Peripheral sensory neuropathy	189 (29.0)	180 (27.0)	111 (17.0)	107 (16.0)
Diarrhoea	181 (27.0)	120 (18.0)	121 (18.0)	61 (9.0)
Pyrexia	179 (27.0)	113 (17.0)	147 (22.0)	91 (14.0)
Neuropathy peripheral	174 (26.0)	163 (25.0)	85 (13.0)	73 (11.0)
Alopecia	173 (26.0)	159 (24.0)	146 (22.0)	135 (20.0)
Weight decreased	148 (22.0)	90 (14.0)	40 (6.0)	21 (3.0)
Abdominal pain	142 (21.0)	91 (14.0)	65 (10.0)	30 (5.0)
Anaemia	140 (21.0)	107 (16.0)	67 (10.0)	51 (8.0)
Stomatitis	138 (21.0)	118 (18.0)	104 (16.0)	93 (14.0)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.10.2.2 TEAEs resulting in changes to treatment | DCO 20 Apr 2017

An AE which resulted in premature study drug discontinuation was reported in 88 patients (13%) in the A+AVD arm and 105 patients (16%) in the ABVD arm. The most frequently reported TEAEs that resulted in premature study drug discontinuation for patients who received A+AVD were peripheral sensory neuropathy (3%), PN and peripheral motor neuropathy (PMN; 2% each). The most frequently reported TEAEs that resulted in premature study drug discontinuation for patients who received ABVD were dyspnoea (4%), pulmonary toxicity, cough, decreased carbon monoxide diffusing capacity (2% each) and pneumonitis (1%; Table 16; Appendix F, Appendix Table 43).[34]

A dose modification was defined as a dose reduction, dose delay or dose hold, or an infusion interruption. One or more TEAEs that resulted in a dose modification was reported for 423 patients (64%) in the A+AVD arm and 293 patients (44%) in the ABVD arm. The most frequently reported TEAEs that resulted in a dose modification for the patients who received A+AVD were neutropenia (22%), febrile neutropenia, peripheral sensory neuropathy and PN (9% each). The most frequently reported TEAEs that resulted in a dose modification for patients treated with ABVD were neutropenia (15%), febrile neutropenia (4%), and peripheral sensory neuropathy, decreased neutrophil count and pyrexia (3% each; Table 16; Appendix F, Appendix Table 44).[34]

A dose delay was the most frequently reported dose modification for patients in both treatment arms. A higher proportion of dose reductions (29% vs. 10%) and dose delays (48% vs. 33%) was reported for the A+AVD arm whereas a slightly higher proportion of dose interruptions was reported for the ABVD arm (3% vs. 5; Table 16). The most frequently reported TEAEs that resulted in a dose delay for patients who received A+AVD were neutropenia (21%), febrile neutropenia (8%), pyrexia (4%), and decreased neutrophil count (3%). The most frequently reported TEAEs that resulted in a dose delay for patients receiving ABVD were neutropenia (15%), and febrile neutropenia and decreased neutrophil count (3% each; Table 16).[34]

In patients in the A+AVD arm who received G-CSF primary prophylaxis (n=83; Section B.2.10.4.2) dose delays were less common compared with those who did not (35% vs. 49%). Furthermore, receipt of primary prophylaxis with G-CSF decreased the frequency of dose reductions (20% vs. 26%).[126]

Table 16: TEAEs associated with changes to treatment | Safety population | DCO 20 Apr 2017

n (%)	A+AVD (n=662)	ABVD (n=659)
Patients with ≥1 TEAE resulting in study drug or dose discontinuation	88 (13.0)	105 (16.0)
Most common TEAEs resulting in study drug or dose discontinuation		
Peripheral sensory neuropathy	23 (3.0)	6 (<1.0)
Neuropathy peripheral	16 (2.0)	3 (<1.0)
Peripheral motor neuropathy	10 (2.0)	1 (<1.0)
Dyspnoea	2 (<1.0)	25 (4.0)
Carbon monoxide diffusing capacity decreased	0	10 (2.0)
Cough	0	12 (2.0)
Pulmonary toxicity	0	12 (2.0)
Patients with ≥1 TEAE resulting in dose modification	423 (64.0)	293 (44.0)
Dose held	44 (7.0)	32 (5.0)
Dose interrupted	22 (3.0)	33 (5.0)
Dose reduced	191 (29.0)	65 (10.0)
Dose delayed	318 (48.0)	217 (33.0)
Most common TEAEs resulting in dose modification		
Neutropenia	145 (22.0)	102 (15.0)
Peripheral sensory neuropathy	62 (9.0)	17 (3.0)
Febrile neutropenia	60 (9.0)	25 (4.0)
Neuropathy peripheral	60 (9.0)	11 (2.0)
Pyrexia	30 (5.0)	17 (3.0)
Neutrophil count decreased	23 (3.0)	22 (3.0)
Patients with ≥1 TEAE resulting in dose delay	318 (48.0)	217 (33.0)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.10.3 Deaths and SAEs

B.2.10.3.1 On-study deaths and SAEs | DCO 20 Apr 2017

A total of nine on-study deaths were reported for the A+AVD treatment arm, none of which had switched to an AFM (Table 17). The investigator considered the death of eight patients to be treatment-related, and the majority of on-study deaths were associated with neutropenia and its complications, including neutropenic sepsis and septic shock (Table 17). Importantly, none of the A+AVD patients who died on study had received G-CSF primary prophylaxis.[34]

A total of 13 patients in the ABVD treatment arm died on study. This included one patient who had switched to an AFM. The investigator considered the death of seven patients to be

treatment-related, and the majority of on-study deaths in this treatment arm were associated with pulmonary toxicity (Table 17).[34]

At least one treatment-emergent SAE was reported for 284 patients (43%) in the A+AVD arm and 178 patients (27%) in the ABVD arm. At least one drug-related SAE was reported for 240 patients (36%) in the A+AVD arm and 125 patients (19%) in the ABVD arm.[34] The most frequently reported treatment-related and drug-related SAEs are summarised in Table 17.

Table 17: Summary of on-study deaths and SAEs | Safety population | DCO 20 Apr 2017

	A+AVD (n=662)	ABVD (n=659)
On-study deaths, n	9	13
Switched to AFM	0	1
Cause of death, n		
Myocardial infarction	2	0
Cardiorespiratory arrest	1	2
Haematophagic histiocytosis	1	0
Respiratory failure	1	0
Multiple organ dysfunction syndrome	1	0
Neutropenic sepsis	1	0
Septic shock	1	0
Pneumonia	0	3
Pneumocystis pneumonia	0	1
Pulmonary toxicity	0	1
Cardiopulmonary failure	0	1
Pneumonitis	0	1
Acute respiratory distress syndrome	0	1
Respiratory disorder	0	1
Cerebrovascular accident	0	1
Unknown	1	1
Treatment-related death per INV, n	8	7
Patients with ≥1 treatment-emergent SAE, n (%)	284 (3.0)	178 (27.0)
Febrile neutropenia	114 (17.0)	43 (7.0)
Pyrexia	44 (7.0)	28 (4.0)
Neutropenia	19 (3.0)	4 (<1.0)
Pneumonia	18 (3.0)	15 (2.0)
Pneumonitis	2 (<1.0)	12 (2.0)
Patients with ≥1 drug-related SAE, n (%)	240 (36.0)	125 (19.0)
Febrile neutropenia	110 (17.0)	38 (6.0)
Pyrexia	39 (6.0)	21 (3.0)
Neutropenia	19 (3.0)	4 (<1.0)
Pneumonitis	1 (<1.0)	10 (2.0)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AFM, alternative frontline medication; DCO, data cutoff; INV, investigator; SAE, serious adverse event.
Source: Takeda ECHELON-1 CSR (2018).[34]

B.2.10.3.2 Deaths and drug-related SAEs during post-treatment follow-up | DCO 11 Mar 2023

During follow-up, a total of [redacted] deaths ([redacted]%) were reported for the A+AVD treatment arm, of which [redacted] ([redacted]%) were disease related, and [redacted] deaths ([redacted]%) were reported for the ABVD treatment arm, of which [redacted] ([redacted]%) were disease related. The majority of deaths were reported >30 days of the last dose of frontline therapy (A+AVD: n=[redacted] [[redacted]%]; ABVD: n=[redacted] [[redacted]%]). Of these, [redacted] deaths ([redacted]%) in the A+AVD arm and [redacted] ([redacted]%) in the ABVD arm were disease related (Appendix F, Appendix Table 45).[147]

At least one drug-related SAE was reported in [redacted] patients ([redacted]%) in the A+AVD treatment arm and [redacted] patients ([redacted]%) in the ABVD treatment arm. The most frequent drug-related SAE in both treatment arms was febrile neutropenia, reported by [redacted] patients ([redacted]%) in the A+AVD arm and [redacted] patients ([redacted]%) in the ABVD arm (Appendix F, Appendix Table 46).[148] This is consistent with the known safety profile of brentuximab vedotin and is well-managed in clinical practice.[13, 43]

B.2.10.4 Selected safety events of clinical interest

Safety events of clinical interest chosen based on clinical expert opinion and the known safety profile of brentuximab vedotin include:[13, 43, 70]

- Pulmonary toxicity (Section B.2.10.4.1)
- Neutropenia and febrile neutropenia (Section B.2.10.4.2)
- Peripheral neuropathy (Section B.2.10.4.3)
- Second malignancies (Section B.2.10.4.4)

Pulmonary toxicity is a potentially serious and long-lasting complication of treatment with bleomycin (a component of both ABVD and escBEACOPDac), while second malignancies can arise following treatments for HL (Section B.1.3.3.2).[5, 15, 32, 54, 55] Neutropenia and peripheral neuropathy have been previously reported with treatment with brentuximab vedotin, and it is recommended that patients are monitored for these AEs while treated with brentuximab vedotin.[43] Both neutropenia and peripheral neuropathy can be managed appropriately in clinical practice via administration of G-CSF prophylaxis (as mandated in the SmPC for A+AVD for this indication) and monitoring and adjusting the regimen as required, respectively.[13, 70]

B.2.10.4.1 Pulmonary toxicity | DCO 20 Apr 2017

Pulmonary toxicity events included all preferred terms in the Interstitial Lung Disease (ILD) Standardised Medical Dictionary for Regulatory Activities (MedDRA) query. The preferred terms identified were lung infiltration, pneumonitis, interstitial lung disease, acute respiratory distress syndrome (ARDS), organising pneumonia, pulmonary fibrosis, and pulmonary toxicity.[34]

During treatment, a higher incidence of pulmonary toxicity effects, including fatal events, was observed with ABVD vs. A+AVD.[31] The overall rate of pulmonary toxicity was lower in the A+AVD arm (n=12; 2%) than in the ABVD arm (n=44; 7%).[34, 129] Five (<1%) patients in the A+AVD arm and 21 (3%) patients in the ABVD arm had Grade ≥3 pulmonary toxicity. Three patients had a fatal (Grade 5) pulmonary toxicity event in the ABVD arm but no Grade 5 pulmonary toxicity was reported in the A+AVD arm.[34, 129]

The ILD events of any grade reported for the A+AVD patients were lung infiltration and pneumonitis, reported for six patients each, and interstitial lung disease, reported for one patient (<1% each). Grade 4 lung infiltration and Grade 3 pneumonitis were reported for two patients treated with A+AVD each (<1%). Lung infiltration and pneumonitis were reported as an SAE for two patients treated with A+AVD patients each, and interstitial lung disease was reported as an SAE for one patient treated with A+AVD (<1% each).[34]

For ABVD, pneumonitis was reported for 18 patients (3%), pulmonary toxicity for 16 patients (2%), and interstitial lung disease for six patients (<1%). Grade 3 or higher pneumonitis was reported for nine patients and Grade 3 or higher pulmonary toxicity for seven patients (1% each). Grade 5 pneumonitis, ARDS, and pulmonary toxicity were reported for one patient each. Pneumonitis was reported as an SAE for 12 patients (2%) and pulmonary toxicity was reported as an SAE for five patients (<1%). Pulmonary toxicities were monitored but no formal statistical comparison between arms was conducted.[34]

B.2.10.4.2 Neutropenia and febrile neutropenia

ITT population | DCO 20 Apr 2017

Treatment-emergent neutropenia was reported for 454 patients (69%) in the A+AVD arm compared with 361 patients (55%) in the ABVD arm. Grade ≥4 neutropenia and an SAE of neutropenia was reported for 313 (47%) and 22 (3%) patients in the A+AVD arm respectively, vs. 178 (27%) and five (<1%) patients in the ABVD arm, respectively. Treatment-emergent febrile neutropenia of any grade was reported for 128 patients (19%) in the A+AVD arm and 52 patients (8%) in the ABVD arm. Treatment-emergent febrile neutropenia showed a sequential decreased frequency and severity from Cycle 1 through Cycle 6 for both treatment arms. The incidence of Grade 4 febrile neutropenia ranged from 3% during Cycle 1 to <1% during Cycle 6 for the A+AVD arm. In the ABVD arm, the range was from 1% during Cycle 1 to <1% during Cycle 6 (except for Cycle 3 during which no Grade 4 febrile neutropenia was reported for the ABVD arm).[34]

Patients who received G-CSF primary prophylaxis | Apr 2018

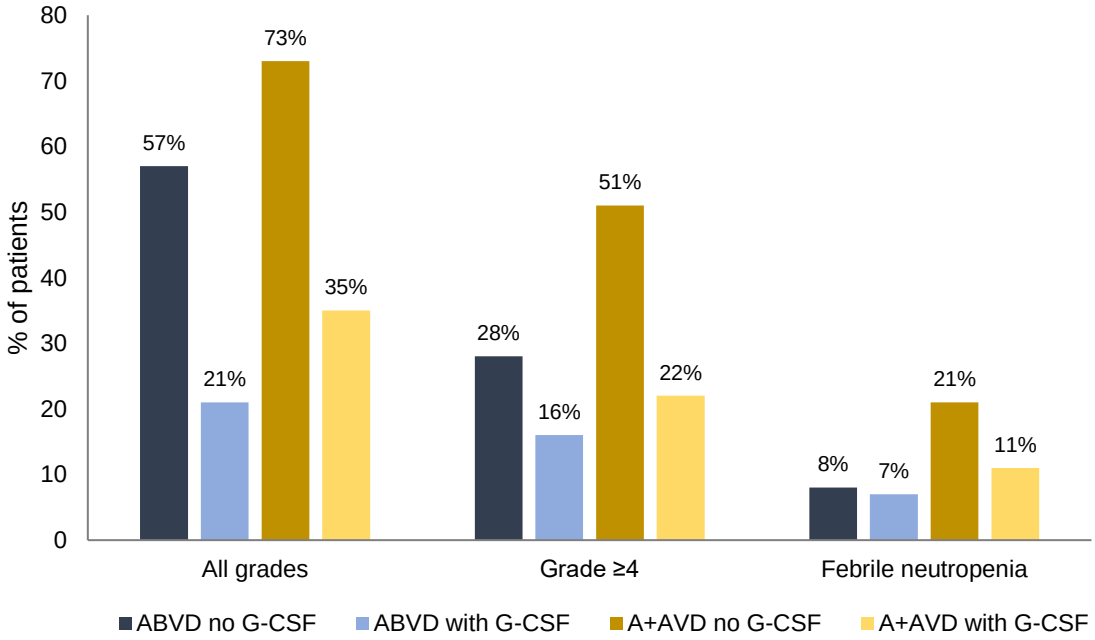
In ECHELON-1, the use of G-CSF according to institutional guidelines was allowed per protocol for the management of patients in the A+AVD treatment arm who developed neutropenia. G-CSF prophylaxis per protocol was also used in patients treated with ABVD, at the clinician's discretion. After enrolment of approximately 70% of the study population, the IDMC recommended that patients randomised to the A+AVD treatment arm be given prophylactic growth factor support beginning with Cycle 1, consistent with subsequent (and current) SmPC recommendations on using G-CSF prophylaxis for patients treated with brentuximab vedotin.[43]. For the purpose of assessing the impact of the G-CSF use on the safety profile, G-CSF primary prophylaxis was defined as G-CSF given by Day 5 of study treatment. By this definition, a total of 83 patients (13%) in the A+AVD treatment arm and 43 patients (6.5%) in the ABVD treatment arm received G-CSF primary prophylaxis. A further 453 patients received G-CSF at any time after Day 5, which was defined as secondary prophylaxis.[126]

As of April 2018, in the A+AVD arm, for patients who received G-CSF primary prophylaxis, the incidence of neutropenia of any grade was lower compared with those who did not (35% vs. 73%, respectively) and the incidence of febrile neutropenia at any time during treatment was likewise reduced (11% vs. 21%, respectively; Figure 12). In the A+AVD arm, seven of

nine deaths that occurred within 30 days after the last dose of the study drug were associated with neutropenia. Of note, none of these patients had received primary prophylaxis with G-CSF before the onset of neutropenia, with the exception of one patient who entered the trial with pre-existing neutropenia.[126]

This difference between patients treated with G-CSF primary prophylaxis in the A+AVD arm vs. those who were not was consistent for higher grades of neutropenia. Grade ≥3 neutropenia was reported by 29% of patients treated with G-CSF compared with 70% who did not receive G-CSF in the A+AVD arm. Grade ≥4 neutropenia was reported by 22% of patients treated with G-CSF compared with 51% who were not. In contrast, across the 659 patients in the ABVD arm, the rate of neutropenia for those who did not receive G-CSF was 55%. Grade ≥3 neutropenia was reported by 19% of patients in the ABVD arm who received G-CSF primary prophylaxis compared with 50% who did not, and Grade≥4 neutropenia was reported by 16% of patients who received G-CSF primary prophylaxis compared with 28% who did not (Figure 12).[34, 126]

Figure 12: Incidence of neutropenia with and without G-CSF primary prophylaxis | April 2018 | Safety population (A+AVD, n=662; ABVD, N=659)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; G-CSF, granulocyte-colony stimulating factor.
Sources: Straus *et al* (2020);[126] Takeda UK Clinical Study Report.[34]:

B.2.10.4.3 Peripheral neuropathy | DCO 20 Apr 2017 and 11 Mar 2023

At the end of treatment (DCO 20 April 2017), at least one PN[x] event of any grade occurred in 443 patients (67%) receiving A+AVD and 286 patients (43%) receiving ABVD. Grade 2 PN and Grade ≥3 PN occurred in 130 patients (20%) and 70 patients (11%) who received A+AVD respectively, and 57 (9%) and 11 (2%) patients who received ABVD, respectively.

[x]PN was determined on the basis of a standardised MedDRA query.

Among patients with PN, a trial drug was discontinued in 44 patients (10% of those with PN) in the A+AVD arm and 11 patients (4% of those with PN) in the ABVD arm.[34]

PN events resolved rapidly within a year in both arms and most remaining PN events were resolved by the latest DCO. As of March 2023, of the 443 patients in the A+AVD arm who reported PN during the treatment period, 381 (86%) had either complete resolution (n=[redacted]; [redacted]%) or amelioration (n=[redacted]; [redacted]%) of symptoms. In the ABVD arm, of the [redacted] patients who reported PN on treatment, 249 patients (87%) had either complete resolution (n=[redacted]; [redacted]%) or amelioration (n=[redacted]; [redacted]%). In the A+AVD arm, median time to resolution was [redacted] weeks (range: [redacted] weeks) and median time to improvement was [redacted] weeks (range: [redacted] weeks). In the ABVD arm, median time to resolution was [redacted] weeks (range: [redacted] weeks) and median time to improvement was [redacted] weeks (range: [redacted]weeks).[123]

PN is a known AE associated with the use of brentuximab vedotin and can be managed appropriately in clinical practice through monitoring and adjusting the regimen as required.[13, 43]

B.2.10.4.4 Second malignancies | DCO 11 Mar 2023

Second malignancies included malignancies other than CD30+ HL that occurred at any time before study closure or malignancies that occurred more than 30 days after the last dose of frontline therapy that were deemed an SAE and related to study drugs. A second malignancy was reported in 33 patients (5%) who received A+AVD and 39 patients (6%) who received ABVD.[123]

[redacted] second malignancy was reported as the cause of death in [redacted] in the A+AVD treatment arm (oesophageal cancer). [redacted] second malignancies were reported as the cause of death in patients in the ABVD treatment arm[123] No formal statistical comparison of second malignancies between the two treatment arms was conducted.

The risk of second malignancies is a critical consideration for patients with HL due to its potential effects on long-term survival.[5, 31] As such, the fact that numerically fewer second malignancies were reported in the A+AVD treatment arm indicates a potential treatment benefit with A+AVD compared with ABVD in Stage III or IV HL.[31]

B.2.10.5 Safety conclusions

During the treatment period in ECHELON-1, six cycles of A+AVD was a well-tolerated regimen with a manageable safety profile. The safety profile of A+AVD was generally consistent with expectations from the wide previous experience of brentuximab vedotin as monotherapy and in combination chemotherapy, with no new safety areas of interest identified.[13, 43, 149, 150] UK-based clinical experts highlighted that they considered the safety profile of A+AVD to be acceptable.[70]

In general, there was a similar rate of drug-related AEs with A+AVD and ABVD (97% vs. 94%, respectively). The most common TEAEs reported for both A+AVD and ABVD arms were neutropenia (58% vs. 45%, respectively), nausea (53% vs. 56%, respectively), and constipation (42% vs. 37%, respectively). There were fewer AEs resulting in premature drug discontinuation in the A+AVD arm compared with the ABVD arm (13% vs. 16%, respectively), despite the fact that A+AVD was associated with a higher rate of Grade ≥3 AEs (83% vs. 66%, respectively). Moreover, despite a higher incidence of treatment-

emergent SAEs (43% vs. 27%) and drug-related SAEs (36% vs. 19%) in the A+AVD arm compared with the ABVD arm, fewer on-study deaths were recorded in the A+AVD arm vs. the ABVD arm (nine vs. 13 patients). Of note, none of the patients in the A+AVD arm who died on study due to AEs had received G-CSF primary prophylaxis.[34, 123, 126]

A+AVD was associated with a higher rate of neutropenia than ABVD; however, following protocol modification (Section B.2.3.1), primary prophylaxis with G-CSF was subsequently offered to patients and used in 13% of the A+AVD arm. Use of G-CSF prophylaxis was associated with a 38%-point lower incidence of neutropenia, a 29%-point reduction in Grade ≥4 neutropenia, and a 10%-point reduction in febrile neutropenia in patients treated with A+AVD. The SmPC for brentuximab vedotin recommends G-CSF prophylaxis from the first dose of treatment with A+AVD, meaning all patients treated with A+AVD in England and Wales would be expected to receive G-CSF prophylaxis, and the incidence and severity of neutropenia is therefore expected to be lower in clinical practice than observed in ECHELON-1.[43] [34, 36] Safety findings from ECHELON-1 are therefore considered to be conservative. Given seven deaths that occurred within 30 days after the last dose of study drug were associated with neutropenia in the A+AVD arm, the OS improvement observed in ECHELON-1 for A+AVD vs. ABVD may therefore also be conservative.

The combination of brentuximab vedotin plus vinblastine means the A+AVD regimen includes two components with overlapping microtubule-targeting mechanisms of action, which is considered to result in the higher rates of neuropathy reported in the A+AVD arm than in the ABVD arm (67% vs. 43%).[38, 136] However, symptoms of PN continued to improve or resolve over time after the end of treatment (A+AVD: 86%; ABVD: 87%) at 7 years' follow-up.[123] Management of new or worsening neuropathy, outlined in the brentuximab vedotin SmPC, states that Grade 2 events should be managed by reducing the dose to 0.9 mg/kg to a maximum of 90 mg every 2 weeks and Grade 3 events should be managed by delaying the dose, then reducing to 0.9 mg/kg to a maximum 90 mg every 2 weeks; clinicians should discontinue treatment if Grade 4 events occur.[43] In ECHELON-1, one patient (0.2%) experienced a Grade 4 neuropathy event.[123] Clinical advisors considered PN could be managed in routine clinical practice through monitoring and adjusting the regimen, as required, and also noted that the PN events in ECHELON-1 showed a marked reduction in all grades by 7 years, which matched their expectations.[13, 36]

During treatment, a lower incidence of bleomycin-related pulmonary toxicity, including fatal events, was observed with A+AVD compared with ABVD (2% vs. 7%, respectively).[31, 127] No fatal pulmonary toxicity events were reported in the A+AVD arm, whereas three patients had a fatal pulmonary toxicity event in the ABVD arm. For many clinicians this is likely to be of particular importance, since bleomycin-related toxicities can be a particular concern to clinicians when selecting a treatment for previously untreated HL patients.[70] Given that bleomycin-induced changes to lung function are only partially reversible at 5 years, avoidance of bleomycin via treatment with A+AVD instead of ABVD could avoid long-term lung damage in HL survivors and is one of the key considerations in the treatment of patients with untreated Stage III or IV HL.[21]

Finally, a numerically lower incidence of second malignancies was observed with A+AVD compared with ABVD (33 vs. 39 patients, respectively). [redacted] second malignancy was reported as the cause of death in a patient in the A+AVD arm, compared with [redacted] deaths due to second malignancies in the ABVD arm.[31] No clear mechanistic explanation has been

identified to explain the possible trend towards a reduced risk of second malignancies in the A+AVD arm vs. ABVD.[31] Two possible – though non-exhaustive – reasons could be the omission of bleomycin or reduction in subsequent treatments in the A+AVD arm, but there is insufficient evidence to conclusively support either reason.[123] However, because second malignancies are likely to inflict a substantial disease and patient burden in patients who undergo potentially aggressive treatments, these findings may reassure patients and clinicians that A+AVD is associated with a numerically lower rate of second malignancies than ABVD.[5]

B.2.11 Ongoing studies

No ongoing studies of brentuximab vedotin are of relevance to this submission.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from ECHELON-1

ECHELON-1, a randomised study with 1,344 patients, demonstrated improved PFS and OS for A+AVD vs. ABVD in untreated CD30+ Stage III or IV HL based on a median follow-up of over 7 years.[16, 31, 123] A+AVD was associated with a robust and durable 32.3% improvement in PFS per INV vs. ABVD, with PFS events occurring in 17% and 24% of patients, respectively (HR: 0.677; 95% CI: 0.532–0.863; p=0.001).[123] The findings for PFS per INV were reinforced by findings for the stringent primary endpoint of modified PFS per IRF (median follow-up: 24.6 months).[34] Importantly, the absence of disease progression represents a clinically meaningful endpoint for these patients, indicating that patients who have achieved cure from HL have the potential for improved quality of life and the avoidance of subsequent treatments with their associated toxicities and burden (Sections B.1.3.3.2, B.1.3.3.3, and B.1.3.3.4).[12, 67, 98]

Of particular importance, the reduced rate of disease progression with A+AVD translated into an OS benefit in ECHELON-1, something that is unprecedented in recent clinical trials of untreated Stage III or IV HL.[15, 17, 18, 31, 78] A+AVD was associated with a statistically significant 38.3% reduction in risk of death vs. ABVD, with OS events in 7% and 10% of patients, respectively (HR: 0.617; 95% CI: 0.423–0.899; p=0.011).[123] As described in Section B.2.6.5 and in Ansell *et al* (2022), this OS benefit is particularly noteworthy due to the historic difficulty in showing an OS advantage over SoC therapies with new first-line treatments for HL.[31]

A numerically higher rate of PET2 negativity was observed in the A+AVD arm vs. the ABVD arm (588 vs.577 patients, respectively), which is indicative of an early treatment benefit with A+AVD vs. ABVD.[34] Considering that failure to achieve PET2 negativity was significantly associated with inferior PFS and OS in the RATHL study compared with patients who achieved PET2 negativity, and despite treatment escalation in patients who were PET2 positive, there is an anticipated benefit to achieving early disease control with first-line treatments.[88]

In both treatment arms, mean scores for EORTC QLQ-C30 subscales and the EQ-5D-3L VAS indicated an HRQoL reduction vs. baseline during treatment that was marginally greater with A+AVD than ABVD; however, the difference was not considered clinically meaningful. After treatment, the difference from baseline in both treatment arms showed an

improvement in HRQoL that was sustained and similar between arms.[34] Additionally, scores after treatment were similar to population norms.[134, 138] These results suggest a long-term improvement in HRQoL resulting from A+AVD treatment that is similar to ABVD, and that treatment may restore patient HRQoL to similar levels as people without HL.

The safety profile of A+AVD in ECHELON-1 was considered acceptable by clinical experts, as it aligned with expectations from the wide clinical experience of using brentuximab vedotin in multiple other indications, and no new safety signals were identified.[13, 43, 149, 150] Peripheral sensory or motor neuropathy can be managed in a clinical setting via dose reductions, pauses, or discontinuations according to severity, as outlined in the SmPC.[43] In ECHELON-1, rates of peripheral neuropathy were higher in the A+AVD arm than the ABVD arm; however, most had either completely resolved or ameliorated by the latest data cutoff.[31, 123]

A particular benefit of A+AVD over ABVD is that it is a bleomycin-free regimen and therefore does not expose patients to bleomycin-related pulmonary toxicity. As expected, pulmonary toxicity was lower in the A+AVD arm than with ABVD treatment (reported by 2% and 7% of patients, respectively).[21, 34] Pulmonary toxicities due to bleomycin occur with the current SoC treatment and can be severe and long lasting; they are a key treatment consideration for clinicians.[15, 21, 32, 54, 55, 70] Given that pulmonary toxicities are only partially reversible 5 years from the end of treatment, with long-term complications in HL survivors, complete avoidance of bleomycin via the A+AVD regimen could reduce the incidence of long-term pulmonary toxicity in HL survivors.[21]

Although there was a higher rate of neutropenia in the A+AVD arm compared with ABVD, initiation of G-CSF primary prophylaxis in the A+AVD arm reduced the incidence of Grade ≥3 neutropenia to 29% – substantially less than that reported across the ABVD arm (48%) – and reduced the incidence of febrile neutropenia to 11% (compared with 8% across the ABVD arm). Additionally, in patients treated with A+AVD, use of G-CSF prophylaxis was associated with a 38%-point lower incidence of neutropenia, a 29%-point reduction in Grade ≥4 neutropenia, and a 10%-point reduction in febrile neutropenia compared with those who did not use G-CSF prophylaxis.[126] The SmPC for brentuximab vedotin recommends G-CSF prophylaxis for all previously untreated patients with CD30+ HL treated with A+AVD, and rates of neutropenia in clinical practice are therefore expected to be lower than observed for the overall safety population, and similar to those reported by patients administered G-CSF prophylaxis in ECHELON-1.[43, 126] Of note, although the incidence of treatment-emergent SAEs was higher in the A+AVD arm than the ABVD arm (43% and 27%, respectively), the incidence was 33% in patients in the A+AVD arm who had received G-CSF primary prophylaxis.[126] Taking into consideration that seven deaths which occurred within 30 days from the last dose of study drug were associated with neutropenia in the A+AVD arm, the safety results for A+AVD for the ECHELON-1 ITT population are likely to be conservative in relation to neutropenia. Finally, second malignancies following treatment for HL is the largest cause of mortality in long-term survivors of HL.[5, 24, 26] Even though second malignancies were not statistically compared between treatment arms in ECHELON-1, it is reassuring that the number of second malignancies reported in the A+AVD arm was lower than in the ABVD arm (33 vs. 39 patients, respectively).[123]

B.2.12.2 Strengths and limitations of the clinical evidence base

ECHELON-1 was a randomised, controlled study in adult patients with untreated CD30+ Stage III or IV HL with substantial follow-up of over 7 years (median follow-up for PFS per INV: 90.0 months [95% CI: 87.3–90.9] in the A+AVD arm and 86.4 months [95% CI: 84.4–89.6] in the ABVD arm). Additionally, ECHELON-1 enrolled a large number of patients (N=1,334), including 154 patients from Great Britain.[34, 36, 123] Clinical experts agreed that the patients enrolled in ECHELON-1 were reflective of those seen in UK clinical practice and noted the robust number of patients from Great Britain (N=154).[36]

ECHELON-1 provides the clinical evidence base to inform the relevant comparator in this appraisal: an ABVD-based treatment (Section B.3.2.3.2).[15] Similar efficacy is assumed between six cycles of ABVD (i.e. the ABVD regimen in ECHELON-1) and PET-adapted ABVD treatment (i.e. the RATHL approach), since the de-escalated ABVD/AVD regimen demonstrated similar, non-inferior 3-year PFS vs. six cycles of ABVD in the RATHL study (Section B.1.3.4.3 and Appendix D).[31, 77, 151] Furthermore, only a minority of patients in ECHELON-1 (7% and 9% in the A+AVD and ABVD treatment arms, respectively) were PET2 positive and therefore could potentially be candidates for treatment escalation.[31] The unadjusted ITC supported that six cycles of ABVD per ECHELON-1, which is also recommended by the ESMO guidelines, and ABVD per RATHL, provide similar efficacy (Section B.3.2.3.2). These analyses are further supported by clinical expert opinion elicited at the 2024 access advisory board (Section B.1.3.4), which agreed that efficacy outcomes for patients receiving six cycles of ABVD (as per ECHELON-1) are expected to be equivalent to the PET-adapted ABVD strategy followed in the RATHL trial.[28, 36, 88]

ECHELON-1 was an open-label trial, where investigators and patients knew the individual treatment assignments; this is common practice where treatments have different AE profiles with substantially different management requirements, in order to maximise patient safety.[112] As such, it is possible that PROs in patients from both arms may have been influenced by patients' knowledge of their treatment assignment. However, despite the open-label nature of the trial, both patients and investigators were blinded to aggregate efficacy data throughout the study. An open-label design ensures that treating physicians are aware of potential adverse effects of the treatment administered, and is common across clinical trials in untreated HL.[82, 121, 152–155] Notably, a number of recent practice-changing clinical trials in HL have been open-label, including trials such as RATHL and HD18 in patients with untreated advanced HL.[121, 155] The open-label design of ECHELON-1 is thus consistent with that of other key trials that have shaped the first-line management of HL in the UK.[82, 121]

The primary endpoint in ECHELON-1 was modified PFS per IRF, which is not a commonly used primary endpoint across clinical trials, yet provides a stringent measure of treatment failure by capturing events of additional treatment use which would not impact standard PFS.[112] In addition to the statistically significant modified PFS treatment benefit with A+AVD vs. ABVD, ECHELON-1 demonstrated a robust and sustained treatment benefit for PFS per INV. While PFS per INV was an exploratory endpoint and not alpha-controlled, its rigour and clinical relevance are equivalently high to that of modified PFS per IRF during the long-term follow-up of ECHELON-1.[34] Clinical advisors also agreed that the PFS results mirrored the treatment benefit observed for the primary endpoint, modified PFS.[36] The primary endpoint of modified PFS encompasses all elements of PFS per INV; further, PFS per INV is generalisable to routine clinical practice both during treatment and long-term follow-up of

patients with CD30+ HL in remission.[112] Once patients' scanning intervals lengthen in follow-up, it is the clinical symptoms of HL (e.g. enlarged lymph nodes, fever, night sweats, weight loss) that are likely to cause rapid presentation to the clinic.[15, 28] PFS per INV was assessed at a long, 7-year follow-up and was monitored to the standards of the primary endpoint, since its components were collected as part of modified PFS.[112] Crucially, the absence of disease progression as assessed by INV represents a truly clinically meaningful endpoint for patients with CD30+ Stage III or IV HL, representing survival free of disease with the potential for improved quality of life and avoidance of further HL therapy and its associated toxicity and burden (Sections B.1.3.3.2, B.1.3.3.3, and B.1.3.3.4).[12, 67, 98] Consequently, PFS per INV provides robust and clinically relevant evidence for the treatment benefit of A+AVD vs. ABVD.

B.2.12.3 Summary

Advanced-stage HL is unusual among cancers in that first line treatments have the ability to cure the disease.[6] However, despite 5-year OS of 70–80% in Stage III or IV disease, 20−30% of patients who are not cured by first-line therapy require burdensome subsequent treatments with a decreasing chance of achieving cure at each subsequent line.[10, 22, 23, 46, 156–158] There therefore remains an unmet need for a well-tolerated first-line treatment that can improve survival outcomes in Stage III or IV HL, especially for patients who would otherwise be suitable for an ABVD-based regimen.[16]

A+AVD offers a bleomycin-free regimen which has shown improved PFS and OS vs. ABVD and increases the proportion of patients with previously untreated HL who are considered cured. The avoidance of bleomycin and its associated pulmonary toxicity has the potential to reduce the side effect burden and long-term effects associated with treatment.[5, 15, 54, 70, 84] Moreover, the patient and healthcare system burden of subsequent treatments is reduced due to the increased proportion of patients cured in the A+AVD arm vs. the ABVD arm. This is reinforced by the subsequent therapy data collected in ECHELON-1, which showed more frequent use of chemotherapy, ASCT, alloSCT, bendamustine, and brentuximab vedotin in the ABVD arm (Section B.3.5.4.1). In addition to providing treatment benefit without additional HRQoL burden, A+AVD is not expected to create any meaningful additional administration burden as all four components of each multiagent regimen are administered on the same day as IV infusion (Section B.3.5.1.2).

A+AVD represents the first regimen to show an OS advantage compared with ABVD (PET-adapted or six cycles) in patients with previously untreated Stage III or IV HL, while also providing improved PFS and an acceptable tolerability profile. These data support the use of A+AVD as a preferred first-line treatment option for patients who would otherwise be suitable for treatment with ABVD.[13, 16, 31, 123]

B.3 Cost effectiveness

A cost-utility analysis with a lifetime (60 years) time horizon was conducted to evaluate the cost-effectiveness of A+AVD vs. ABVD in the anticipated indication of adults with previously untreated CD30+ Stage III or IV HL, in England and Wales.

- The economic model was an area under the curve (AUC) partitioned survival analysis (PartSA) model, comprised of three mutually exclusive health states: progression free, post-progression and dead.
- Efficacy inputs (PFS, OS, TEAEs, duration of therapy), HRQoL and subsequent therapies were informed by the ITT patient-level data from ECHELON-1.
- Mixture cure models (MCMs) were fitted to PFS and one-knot spline models fitted to OS for A+AVD and ABVD-based treatment from ECHELON-1, which included standardised mortality rate (SMR)-adjusted background mortality applied as a competing risk.
- Resource use aligns with relevant summary of product characteristics (SmPCs), clinical guidelines, and UK clinical expert feedback.
- Costs were obtained from the latest available source where available i.e. the electronic marketing information tool (eMIT) accessed February 2024, British National Formulary (BNF) accessed February 2024, NHS Reference Costs 2021/22, and the Personal Social Services Research Unit (PSSRU) 2022. Costs collected from other sources were inflated to 2021/22 using inflation indices in the PSSRU.
- Beyond the cure timepoint of 24 months after treatment discontinuation, cured patients were assumed to accrue no monitoring and follow-up care costs and experience utility aligned with the general population.
- A confidential discount of [redacted]% was applied to the unit cost of brentuximab vedotin.

In the base case, at the PAS price, A+AVD accrues [redacted] additional QALYs at an additional cost of £[redacted] compared to ABVD. The ICER is £[redacted] and the net health benefit (NHB) is [redacted] based on a willingness-to-pay (WTP) threshold of £30,000 per QALY gained.

- The probabilistic ICER is £[redacted], and the probabilistic analyses indicate that A+AVD has a [redacted]% and [redacted]% chance of being cost-effective at WTPs of £20,000 and £30,000, respectively.
- Scenario analyses explored assumptions around SMRs, discount rates, baseline characteristics, PFS and OS extrapolation, subsequent therapy distribution, G-CSF use and relative dose intensity.

B.3.1 Published cost-effectiveness studies

An SLR was conducted, with searches run 1st August 2022 and updated on 8th January 2024, to identify economic evaluations in adult patients with previously untreated CD30+ Stage III or IV HL from the published literature, including HTA reports. A detailed description of the search methodology, a PRISMA flow diagram, and results are presented in Appendix G.

In total, 11 studies across 11 publications were identified in the original and updated SLRs. Table 18 presents the study characteristics for the eleven identified studies. Six were

conducted from a Canadian perspective, three from a US perspective, one from an Indian perspective and one did not report the perspective taken (although the currency used was GBP). All studies which specified more detail indicated a payer or healthcare perspective; no studies were identified considering a societal perspective.

Table 18: Economic evaluations in patients with advanced HL | Study characteristics

Author, year	Summary of model	Patient population (average age in years)	Intervention, comparator	QALYs (intervention, comparator)	Total costs (currency) (intervention, comparator)	ICER (per QALY gained)
Delea *et al* (2019)[159]	Semi-Markov model with seven health states based on disease progression and whether patients receive ASCT. Model developed with a lifetime time horizon from a US healthcare payer perspective and based on the ECHELON-1 trial. Two analyses were run: one based on investigator-assessed modified PFS and a second on the modified PFS for the North American population of the ECHELON-1 trial.[53] The ECHELON-1 trial reports a median follow-up of 24.6 months.	Patients who are treatment-naïve with Stage III or IV classical HL with characteristics similar to those enrolled in the ECHELON-1 trial. Mean age (SD): 39.5 (0.58)	• A+AVD • ABVD (six cycles)	**Overall population:** • A+AVD: 15.07 QALYs • ABVD: 14.31 QALYs • Incremental: 0.76 QALYs **North American population:** • A+AVD: 15.58 QALYs • ABVD: 14.27 QALYs • Incremental: 1.31 QALYs	**Overall Population:** • A+AVD: $351,456 USD • ABVD: $220,750 US • Incremental: $130,706 USD **North American Population:** • A+AVD: $314,723 USD • ABVD: $224,014 USD • Incremental: $90,709 USD	**Overall Population** • A+AVD vs. ABVD: $172,074 USD (per QALY) **North American population** • A+AVD vs. ABVD: $69, 442 USD (per QALY)

Author, year	Summary of model	Patient population (average age in years)	Intervention, comparator	QALYs (intervention, comparator)	Total costs (currency) (intervention, comparator)	ICER (per QALY gained)
Goenka *et al* (2023)[160]	Markov model with eight health states that were treatment-specific. The transition of the cohort between the health states was simulated every six months for a time horizon of 5 years and is based on the Indian health system perspective. The model was based on several trials such as HD2000, EORTC, RATHL, and AHL2011 trials.	Patients with advanced Hodgkin lymphoma (aHL). Average age: 35 years	• SoC is ABVD (six cycles) • RAT-1 consists of response adapted treatment beginning with two cycles of ABVD chemotherapy and escalates to escalated BEACOPP chemotherapy in patients with a positive interim PET-2 scan. • RAT-2 consists of an de-escalation approach beginning with two cycles of escalated BEACOPP and then de-escalates to ABVD or another two courses of escalated BEACOPP in patients with a negative interim PET-2 scan.	• SoC: 3.001 QALYs • RAT 1: 3.222 QALYs • RAT 2: 3.226 QALYs • Incremental (RAT 1 vs. SoC): 0.221 QALYs • Incremental (RAT 2 vs. SoC): 0.225 QALYs	• SoC: ₹422,819 INR • RAT 1: ₹272,402 INR • RAT 2: ₹229,230 INR • Incremental (RAT 1 vs. SoC): ₹150,417 INR • Incremental (RAT 2 vs. SoC): ₹193,589 INR	• RAT 1 vs. SoC: -₹680,060 INR (per QALY) • RAT 2 vs. SoC: -₹859,836 INR (per QALY)

Author, year	Summary of model	Patient population (average age in years)	Intervention, comparator	QALYs (intervention, comparator)	Total costs (currency) (intervention, comparator)	ICER (per QALY gained)
Huntington *et al* (2018)[161]	Markov model with four health states that were treatment-specific (including salvage therapies). Model developed with a lifetime time horizon from a US payer perspective, and based on the ECHELON-1 trial.[53] The ECHELON-1 trial reports a median follow-up of 24.6 months.	Individuals were Stage III or IV HL, newly diagnosed. Cohort age: 36 years	• A+AVD • ABVD (six cycles)	• A+AVD: 19.86 QALYs • ABVD: 19.30 QALYs • Incremental: 0.56 QALYs	• A+AVD: $361,137 USD • ABVD: $184,291 USD • Incremental: $176,846 USD	• A+AVD vs. ABVD: $317,254 USD (per QALY) [95% CI $159,408 to $903,061 USD]
Huntington *et al* (2018)[162]	Markov decision-analytic model (no further details provided)	Patients receiving first-line therapy with Stage III/IV HL (age NR)	• A+AVD • ABVD (six cycles)	• Incremental (A+AVD vs. ABVD): 0.48 QALYs	• A+AVD: $334,863 USD • ABVD: $193,780 USD • Incremental: NR	A+AVD vs. ABVD: $292,266 USD (per QALY)
Norum *et al* (1996)[163]	Cost-utility analysis using direct data collection – no economic model. A median follow-up of 52 months is reported.	Patients who are newly diagnosed with stage I to IV HL Median age: 38	• Treatment • No Treatment	NR for Stage III or IV population. For whole HL population: • Treatment vs. no treatment, no health benefit discount: 15.3 QALYs • 5% health benefit discount: 10.4 QALYs • 10% health benefit discount: 7.3 QALYs	• Stage III: £13,489 GBP • Stage IV: £29,837 GBP	NR for Stage III or IV population. For whole HL population: • Treatment vs. no treatment, no discount:

Author, year	Summary of model	Patient population (average age in years)	Intervention, comparator	QALYs (intervention, comparator)	Total costs (currency) (intervention, comparator)	ICER (per QALY gained)
						£795 (per QALY) • 5% discount: £1,175 (per QALY) • 10% discount: £1,651
Prica *et al* (2019)[164]	Markov decision analytic model, with a 20-year time horizon from a Canadian public health payer's perspective	Patients who are transplant-eligible, with newly diagnosed advanced-stage HL (age NR)	• ABVD (six cycles) • BEACOPP+HD18 • PET-adapted ABVD (RATHL) • A+AVD • AHL-2011	• ABVD: 12.1 QALYs • BEACOPP+HD18: 12.8 QALYs • RATHL: 13.2 QALYs • ECHELON-1 (A+AVD): 12.7 QALYs • AHL-2011: 13.4 QALYs	• ABVD: $94,152 CAD • BEACOPP+HD18: $72,203 CAD • RATHL: $59,247 CAD • ECHELON-1 (A+AVD): $165,294 CAD • AHL-2011: $58,136 CAD	NR
Raymakers *et al* (2018)[165]	Time-dependent Markov model with a 15 year time horizon (no further details provided)	Patients with advanced-stage HL requiring front-line therapy (age NR)	• A+AVD • ABVD (six cycles)	• Incremental QALY (A+AVD vs. ABVD): 0.30	• Incremental cost (A+AVD vs. ABVD): $87,000 CAD	A+AVD vs. ABVD: $280,000 CAD per QALY
Raymakers *et al* (2020)[166]	Markov model with six health states. The model had a 15 year time horizon, from the Canadian	Patients with advanced-stage HL requiring front-line	• A+AVD • ABVD (six cycles)	• A+AVD: 9.62 (95% CI 7.29–11.0) QALYs • ABVD: 9.16 (95% CI 6.98–10.49) QALYs • Incremental QALY: 0.46 QALYs	• A+AVD: $411, 190 CAD (95%CI $300,490–$554,715)	A+AVD vs. ABVD: $418,122 CAD per QALY

Author, year	Summary of model	Patient population (average age in years)	Intervention, comparator	QALYs (intervention, comparator)	Total costs (currency) (intervention, comparator)	ICER (per QALY gained)
	healthcare payer perspective and based on the ECHELON-1 trial	therapy (age NR)			• ABVD: $218,854 CAD (95%CI $156,367–$310,743) • Incremental cost: $192,336 CAD	
Vijenthira *et al* (2020)[167]	Markov decision-analytic model, with five health states that were treatment specific. The model had a 20-year time horizon from a Canadian public health payers perspective and was based on the HD2000, EORTC, HD15, HD18, RATHL, ECHELON-1, and AHL-2011 trials.	Patients who are transplant-eligible, with newly diagnosed advanced-stage HL. The cohort age was 35 years.	• AHL-2011 • PET-adapted ABVD (RATHL) • escBEACOPP • A+AVD • ABVD (six cycles)	• AHL-2011: 13.2 QALYs • RATHL: 12.7 QALYs • escBEACOPP: 12.4 QALYs • A+AVD: 12.3 QALYs • ABVD: 11.7 QALYs	**Direct Costs:** • AHL-2011: $53,129 CAD (95% CI $31,914-$94,446) • RATHL: $64,172 CAD (95% CI $40,903–$105,084) • escBEACOPP: $76,777 CAD (95% CI $47,614–$120,972) • A+AVD: $240,856 CAD (95% CI $194,122–$296,271) • ABVD: $94,801 CAD (95% CI $63,402–$141,379)	Because PET-adapted de-escalation (AHL-2011) was a dominant therapy, the authors did not present incremental data
Vijenthira *et al* (2018)[168]	Markov decision-analytic model with a 20-year lifetime horizon from the Canadian healthcare payer perspective.	Patients who are transplant-eligible with newly diagnosed advanced-stage HL.	• BEACOPP • ABVD (limited information on comparator)	• BEACOPP:11.4 QALYs • ABVD:10.4 QALYs • QALY survival benefit with BEACOPP: 1 QALY	**Direct costs:** • BEACOPP: $81,296 • ABVD: $98,081 • Net Benefit: $16,785	NR. Paper provides cost per QALY estimate but no incremental data

Author, year	Summary of model	Patient population (average age in years)	Intervention, comparator	QALYs (intervention, comparator)	Total costs (currency) (intervention, comparator)	ICER (per QALY gained)
pCODR Expert Review Committee (2020)[169]	Markov model with five health states and a 65-year lifetime horizon from the Canadian public health care payer perspective and based on the ECHELON-1 trial. The ECHELON-1 trial reports a median follow-up of 24.6 months.	Patients with advanced-stage HL requiring front-line therapy	• A+AVD • ABVD (six cycles)	• Incremental QALY (A+AVD vs. ABVD): 0.96	**Base Case Results:** • Incremental costs (A+AVD vs. ABVD): $59,981 CAD	**Original Submission**: • A+AVD vs. ABVD: $62,258 CAD per QALY **CADTH Reanalysis Results**: • A+AVD vs. ABVD: • $134,059 per QALY

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, procarbazine; CAD, Canadian Dollars; CADTH, Canadian Agency for Drugs and Technologies in Health; esc, escalated; HL, Hodgkin lymphoma; ICER, incremental cost-effectiveness ratio; NR, not reported; PET, positron emission tomography; QALY, quality adjusted life year; RAT-1, response Adapted Treatment beginning with two cycles of ABVD chemotherapy and then escalates to escalated BEACOPP chemotherapy in patients with a positive interim PET2 scan; RAT-2, de-escalation approach beginning with two cycles of escalated BEACOPP and then de-escalates to ABVD or another two courses of escalated BEACOPP in patients with a negative interim PET2 scan; RATHL, Risk-Adapted Therapy in Hodgkin Lymphoma; US, United States; USD, United States Dollars.

Eight of the 11 identified studies compared A+AVD with ABVD-based regimens; with five citing ECHELON-1 as the primary data source. Six of the eight studies comparing A+AVD with ABVD modelled ABVD (six cycles) as per ECHELON-1, whereas Prica *et al* (2019) and Vijenthira *et al* (2020) modelled ABVD (six cycles) as per ECHELON-1 and PET-adapted ABVD as per the RATHL approach.[164, 167] Of the five studies citing ECHELON-1 as the primary data source, two appeared to have access to the patient-level data and three studies used digitised data from the Connor *et al* (2018) publication. All five studies were based on the first data cut from ECHELON-1 with a median follow-up of 24.6 months. Three of these five considered a lifetime horizon; Delea *et al* (2019) and Huntington *et al* (2018) used the ITT population from ECHELON-1 and the Canadian Agency for Drugs and Technologies in Health (CADTH) submission for A+AVD used the Stage IV subgroup data.[159, 161, 162, 169]

Total QALYs accrued by A+AVD in the two ITT populations ranged from 15.07 to 19.86 and the total QALYs accrued by ABVD ranged from 14.31 to 19.30. The incremental QALYs across the two studies using the ITT ECHELON-1 data and a lifetime horizon ranged from 0.56 to 0.76 for A+AVD vs. ABVD. The incremental QALYs of 0.56 come from a study using digitised data from the Connors *et al* (2018) publication. Whereas the incremental QALYs of 0.76 come from a study using the patient-level data from ECHELON-1.

As well as key differences in model settings e.g. perspective, time horizon, and discount rate, the identified studies differed with respect to model structure, approach to estimating transition probabilities, and approach to incorporating excess mortality. Appendix G provides more detail; a summary is provided below.

Whilst the model structure presented in this submission has fewer health states than those published in the literature, this submission is based on the final analysis from ECHELON-1 with a median follow-up of 89.2 months for PFS and 89.3 months for OS. As most events occur within the first 24 months of ECHELON-1, the data reflects outcomes relating to later health states. This was corroborated by clinical experts at the January 2024 advisory board, who confirmed that the entire disease pathway for these patients, including those with progressed disease, is within 7 years i.e. reflected by the follow-up from ECHELON-1 (Section B.2.6). The published literature uses data from earlier data cuts with shorter follow-up, including the primary data cut from ECHELON-1.

Another difference is that PFS outcomes in this submission are informed by 7-year PFS INV from ECHELON-1. All published studies reporting on cost-effectiveness analyses using the ECHELON-1 data use modified PFS. Feedback from UK clinical experts indicates that this endpoint is not used in UK clinical practice (Sections B.2.3.2.1 and B.2.6.1), and therefore the approach adopted in this submission is deemed to be more meaningful and relevant to inform decision-making in the UK setting.

Four of the 11 studies included excess mortality in addition to background mortality (Delea *et al* [2019], pCODR Expert Review Committee [2020], Vijenthira *et al* [2018], and Vijenthira *et al* [2020]); all four used differential rates for A+AVD and ABVD acknowledging differing mortality due to treatment toxicities and second malignancies.[159, 167–169] In two papers, this difference was calculated using additional pulmonary toxicity with ABVD (Delea *et al* [2019] and pCODR Expert Review Committee [2020]) and in the other two papers this difference was calculated using different second malignancy rates (Vijenthira *et al* [2018] and Vijenthira *et al* [2020]).[159, 167–169] The application of differential standardised mortality rates (SMRs) to adjusted background mortality aligns with the approach undertaken in this submission

(Section B.3.3.2.1). Six studies either did not include excess mortality in addition to background mortality or provided insufficient information to determine the approach.

B.3.2 Economic analysis

Eleven economic evaluations were identified by the SLR, including five that used ECHELON-1 as the primary data source (Section B.3.1). Identified studies differed with respect to model structure and derivation of key inputs. Importantly, when comparing to the decision problem relevant to this submission, the identified studies were informed by data with short follow-up and included endpoints not relevant to the UK clinical setting (e.g. modified PFS). No studies from a UK perspective were identified.

Therefore, whilst the approaches to modelling detailed in the identified studies have been considered, a *de novo* cost-effectiveness model (CEM) was developed to inform this appraisal.

B.3.2.1 Patient population

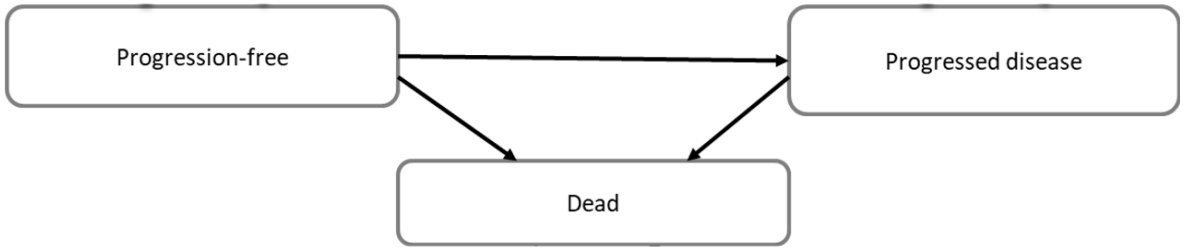
In line with the NICE final scope and anticipated marketing authorisation (Appendix C), the population considered in the CEM is adult patients with previously untreated CD30+ Stage III or IV HL.[35]

B.3.2.2 Model structure

The CEM was developed in Microsoft Excel (Version 2310; 2023) and used an area under the curve (AUC), partitioned survival analysis (PartSA) approach. The model comprised three mutually exclusive health states (Figure 13):

1. progression-free,
2. progressed disease/relapsed and/or refractory setting, and
3. death.

Figure 13: Model structure



The model structure reflects the progressive nature of HL. This structure is common in economic evaluations of oncology medicines, is consistent with the clinical pathway of care described in Section B.1.3.4, captures the outcomes listed in the final scope, and has been implemented in all previous NICE submissions in frontline lymphoma, including diffuse large B-cell lymphoma (DLBCL; TA874) and systemic anaplastic large cell lymphoma (sALCL; TA641).[40, 170] Additionally, this model structure has been implemented in all previous NICE

submissions for brentuximab vedotin, including untreated sALCL (TA641), R/R sALCL (TA478), CD30+ HL (TA524) and CD30+ cutaneous T-cell lymphoma (CTCL; TA577).[39–42]

Health state occupancy is informed directly by extrapolated PFS and OS curves from ECHELON-1. The area under the PFS curve informs the proportion of patients in the 'pre-progression' health state over time. The area under the OS curve informs the proportion of patients who are alive. The proportion of patients who are alive with progressed disease, and hence reside in the 'progressed disease/relapsed and/or refractory setting' health state, is calculated as the area between the PFS and OS curves. Costs and QALYs are accrued according to the proportion of patients in the progression-free and progressed disease health states over time.

PFS and OS are modelled independently (i.e. using independent parametric functions), hence it is possible for the PFS curve to lie above the OS curve, yielding negative numbers of patients in the 'progressed' health state. Therefore, the extrapolated PFS curve is capped by the OS curve to ensure PFS events cannot occur to patients who have died.

B.3.2.2.1 Cured patients

As described in Section B.1.3, the goal of first-line HL treatment is cure, with 70–80% of patients with Stage III or IV disease cured by first-line treatment, corroborated by clinical experts at the November 2023 and January 2024 UK advisory boards (Section B.1.3.4).[6, 12, 14] This is reflected in the plateau observed in the PFS Kaplan–Meier data. Therefore, it was considered critical to ensure the impact of cure is captured by the economic model.

A cure timepoint of 24 months after the end of treatment was assumed for A+AVD and ABVD. This was deemed to be appropriate as 24 months: (1) aligns with the events observed in the ECHELON-1 PFS Kaplan–Meier (Section B.3.3); (2) aligns with clinical advisor feedback at the January 2024 advisory board and subsequent UK clinical expert opinion and; (3) aligns with the BSH guidelines which state that patients are usually followed up for two years after first-line treatment.[15] A 24-month cure timepoint may be conservative, as the plateau is evident in the PFS ECHELON-1 data as early as 12 months; however, scenario analyses were conducted to explore the impact of this timepoint on cost-effectiveness.

After the cure timepoint, patients who are cured accrue no additional monitoring or follow-up costs (Section B.3.5.2). This assumption is based on UK clinical feedback, which indicated that if patients had not relapsed within 24 months after treatment discontinuation, clinicians would consider them cured and would discharge them, with no further follow up; this is further supported by the BSH guidelines previously described.

In addition, patients who are cured are assumed to experience utility aligned with the general population (Section B.3.4.6). This assumption is supported by UK clinical expert feedback and the HRQoL data collected in ECHELON-1; after 24 months following treatment discontinuation, observed utilities align with general population utility values reported in Hernandez-Alava *et al* (2022).[171] As the observed HRQoL data for patients who are pre-progression and off treatment closely align with the general population utility values, this assumption has a minimal impact, which is further supported by the cure timepoint scenarios previously described.

Of the two published frontline lymphoma NICE appraisals, TA641 assumed no additional costs after 3 years and TA874 assumed no additional costs and general population utility after 2 years.[1,8] The approach of assuming zero or substantially reduced costs and general population utility for patients who are cured is also consistent with later line lymphoma NICE appraisals.[172, 173]

In addition, standard parametric modelling assumes that all patients will experience an event of interest (i.e. progression or death), but this assumption does not hold for curable cancers. Therefore, in the base case, PFS was extrapolated using mixture cure models (MCMs) (Section B.3.3.2.2). This approach has previously been used in PartSA models in NICE appraisals for frontline lymphoma (DLBCL; TA874) and in later line lymphoma appraisals where cure is the relevant clinical outcome (large B-cell lymphoma [TA872] and mantle cell lymphoma [TA677]).[170, 172, 173] One other frontline lymphoma NICE appraisal has been published (sALCL; TA641); this appraisal used background mortality to reflect a cure, but did not use MCMs.[40] However, the Committee agreed that the standard parametric extrapolations were uncertain and that alternative models, such as spline or MCMs, could have been explored.

MCMs were also explored for OS (Appendix O). However, whilst the deterministic extrapolations provided a good fit to the observed data, clinically plausible cure rates and long-term predictions based on feedback from UK clinical experts, the extrapolations predicted in the probabilistic analyses estimated cure rates and outcomes that were clinically implausible and did not align with the observed data from ECHELON-1, UK clinical expert feedback, or the literature. This was anticipated to be driven by the low numbers of events observed in the ECHELON-1 OS data which are expected in this patient population, which resulted in wide confidence intervals associated with the parameters informing the MCM extrapolations. Therefore, in the base case, the complex hazard and survival functions observed for OS were extrapolated using one-knot splines (Section B.3.3.2.3), which capture the change in the hazards for patients who are cured, without assumptions about the proportion of cured vs. non-cured subgroups directly. Other approaches to extrapolate PFS and OS were explored in scenario analyses.

As described in Section B.3.3.2.1, background mortality was applied as a competing risk to ensure that modelled patients do not have a lower risk of death compared with the general population. Importantly, as discussed in Section B.1.3.3.2, current treatment strategies in previously untreated HL are associated with burdensome side effects, including long-term treatment-related toxicities (particularly pulmonary toxicity associated with bleomycin-containing regimens) and second malignancies, that are associated with a long-term increased risk of death, even in patients who are considered cured from their HL.[5, 21, 86] Moreover, for patients who relapse on first-line therapy, subsequent treatment options (including stem-cell transplantation) are associated with substantial toxicity, and patients experience ongoing disease burden and poorer survival outcomes at each subsequent line.[24–27] Therefore, SMRs were applied to reflect the increased risk of death in the A+AVD and ABVD treatment arms vs. the general population.

The use of SMRs is supported by approaches used in two published frontline lymphoma NICE appraisals (Table 19): TA641 applied an SMR (1.19) to background mortality to reflect the increased risk of death in patients who are cured, and TA874 explored an SMR (1.10)

adjustment as a scenario analysis, with unadjusted background mortality in the base case.[40, 170] The approach of exploring adjustments of background mortality to reflect an increased risk for patients who are cured is also consistent with later line lymphoma NICE appraisals (Table 19).[172, 173]

Table 19: Comparison of background mortality approach across NICE lymphoma appraisals

NICE appraisal	Disease setting	Base case	Scenario
TA874[170]	Untreated DLBCL	Unadjusted background mortality from UK lifetables i.e. an SMR of 1.00	Equivalent to an SMR of 1.10
TA641[40]	Untreated sALCL	Adjusted background mortality from UK lifetables and equivalent to an SMR of 1.05	Equivalent to SMRs of 1.075 and 1.10
TA872[172]	Later line DLBCL	Unadjusted background mortality from UK lifetables i.e. an SMR of 1.00	SMR of 1.09
TA677[173]	Later line MCL	Adjusted background mortality from UK lifetables and equivalent to an SMR of 1.09	NA
TA567[174]	Later line DLBCL	Unadjusted background mortality from UK lifetables i.e. an SMR of 1.00 from 2 years.	Applied up to 5 years.

Abbreviations: DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; NA, not applicable; NICE, National Institute for Health and Care Excellence; sALCL, systemic anaplastic large cell lymphoma; SMR, standardised mortality rate.

In the absence of data reporting SMRs for A+AVD and ABVD-based treatment in this population, clinical opinion was sought from UK clinical experts.[36] Feedback indicated that the risk of death after the cure time point was between 5% and 10% higher than the general population. UK clinical experts further highlighted that excess mortality in frontline HL is expected to be lower than in the frontline lymphomas considered in TA641 and TA874 (sALCL and DLBCL, respectively) as long-term survivorship is more of a widely recognised goal in HL compared to other lymphomas. Additionally, it was emphasised that the SMRs should be lower in frontline vs. relapsed lymphomas where treatment toxicities have cumulated across multiple lines of therapy.[36]

Furthermore, UK clinical experts advised that the excess mortality risk is expected to differ between A+AVD and ABVD-based treatment. It was advised that the risk of death after A+AVD is expected to be lower than after ABVD as ABVD is associated with more long-term pulmonary-related toxicities, a higher number of patients progressing and receiving a subsequent SCT, and a numerically greater number of second malignancies vs. A+AVD. Based on this, it was considered appropriate to assume that A+AVD is associated with a lower SMR than ABVD. The approach of assuming differential SMRs for A+AVD and ABVD aligns with four studies (Delea *et al* [2019], pCODR Expert Review Committee [2020], Vijenthira *et al* [2018], and Vijenthira *et al* [2020]) identified in the economic SLR (Section B.3.1).[159, 167–169]

To reflect the increased risk of mortality vs. the general population after being cured with A+AVD and ABVD-based treatment, and to accurately reflect expert clinical opinion, the

base case assumed differential SMRs of 1.05 and 1.10, respectively. Given the uncertainty associated with this assumption, alternative scenarios were explored.

B.3.2.2.2 Model settings

The analysis adopted a 7-day cycle length to allow for different dosing schedules across the chemotherapy regimens and, in doing so, ensure drug cycles are accurately costed. A half-cycle correction was applied using the life table method to account for uncertainty in the timing of transitions within the cycle period, where the time in each cycle was estimated by taking the average of the number of people at the start and end of the cycle. A scenario analysis was conducted which explores the impact of excluding the half-cycle correction.

In accordance with the NICE methods and process guide, a lifetime horizon (60 years) was adopted. The lifetime horizon is imperative to reflect the differential long-term outcomes experienced by patients treated with A+AVD, i.e. the high likelihood of cure, and the relatively young population (starting age of 39.5 years). After 60 years, 99.96% of patients are predicted to have died in the A+AVD arm. Alternative time horizons (50 and 70 years) were explored in scenario analyses.

The analysis was conducted from the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales, and costs and health outcomes were discounted at an annual rate of 3.5%.[175] Alternative discount rates (0.0% and 1.5%) were explored in scenario analyses. A non-reference-case discount rate of 1.5% may be relevant in this disease setting as A+AVD satisfies the three criteria described in the NICE methods and process guide: (1) A+AVD is for people who would otherwise die; as demonstrated by the OS benefit in ECHELON-1, a higher proportion of patients survive following treatment with A+AVD compared to ABVD, (2) A+AVD is likely to restore a large proportion of patients to full or near-full health, and (3) the benefits from A+AVD are likely to be sustained over a lifetime. Additionally, treatment costs are fixed, predictable, and are accrued in the first six treatment cycles.

There are no published NICE appraisals considering previously untreated CD30+ Stage III or IV HL. Therefore, key features of this analysis were compared with the only two previous NICE appraisals for frontline lymphomas (Table 20).

Table 20: Economic analysis features

Factor	Previous appraisals of frontline lymphoma		Current appraisal	
	TA641 sALCL[40]	TA874 DLBCL[170]	Chosen values	Justification
Model structure	PartSA	PartSA	PartSA	The model structure reflects the progressive nature of HL. This structure is common in economic evaluations of oncology medicines, is consistent with the clinical pathway of care described in Section B.1.3.4, captures the outcomes listed in the final scope, and has been implemented in all previous NICE submissions in frontline lymphoma.[40, 170] Additionally, this model structure has been implemented in all previous NICE submissions for brentuximab vedotin.[39–42]
Cycle length	21 days	7 days	7 days	A 7-day cycle length is sufficiently granular to allow for different dosing schedules across the chemotherapy regimens and, in doing so, ensure drug cycles are accurately costed.
Time horizon	45 years (lifetime)	60 years (lifetime)	60 years (lifetime)	A lifetime horizon was selected, as per the NICE reference case to capture all relevant differences in costs and outcomes.[175] A lifetime horizon of 60 years is assumed. Scenario analyses explored 50 and 70 years.
PFS and OS extrapolation	Standard parametric curves were used, with adjusted background mortality taking over at varying timepoints. The Committee agreed that the standard parametric extrapolations were uncertain and that alternative models, such as spline or MCMs, should have been explored by the Company.	The company and EAG both used a MCM to extrapolate PFS and OS. For OS, the Kaplan–Meier data were used until 30 months, followed by an MCM model.	MCMs to extrapolate PFS and one-knot splines to extrapolate OS.	Cure is the goal of treatment for adult patients with previously untreated CD30+ Stage III or IV HL. Therefore, PFS was extrapolated using MCMs in the base case. Independent MCMs were explored for OS (Appendix O). However, the extrapolations predicted in the probabilistic analyses estimated cure rates and outcomes that were clinically implausible. Therefore, in the base case, the complex hazard and survival functions observed for OS were extrapolated using one-knot splines (Section B.3.3.2.3) which capture a change in the hazards for patients who are cured, without assumptions about the number of heterogenous

Factor	Previous appraisals of frontline lymphoma		Current appraisal	
	TA641 sALCL[40]	TA874 DLBCL[170]	Chosen values	Justification
				subgroups directly. Alternative models were also explored for both PFS and OS (Appendix O). This approach is supported by the ECHELON-1 Kaplan–Meier curves, the literature, case precedence across NICE appraisals, and clinical expert feedback at the November 2023 and January 2024 UK advisory boards.[6, 8, 12, 14, 40, 170, 172, 173] Alternative approaches were explored in scenario analyses.
Excess mortality	An SMR of 1.19 was applied to general population mortality (reflecting a 5% reduction in life expectancy) based on clinician feedback indicating a range of 3%-10%. The EAG preferred the midpoint from clinician feedback i.e. 6.5%.	The cured population is assumed to have the same risk of death as the age- and sex-matched general population after 2 years. A scenario analysis explored a hazard ratio of 1.1 to reflect excess mortality.	SMRs of 1.05 and 1.10 are applied to the background mortality in the A+AVD and ABVD arms, respectively – based on UK clinical expert feedback.	See Section B.3.2.2.1.
Assumptions for modelling cure	Patients who were alive for 3 years (i.e. in the progression-free and progressed disease health states) were assumed to accrue no additional costs.	The cured population is assumed to accrue no additional costs and have the same utility values as the age- and gender-matched UK population from 2 years.	A cure timepoint of 24 months after end of treatment is assumed, after which patients who are cured accrue no additional monitoring or follow-up costs and are associated with utility aligned with the general population.	A cure timepoint of 24 months: (1) aligns with the events observed in the ECHELON-1 PFS Kaplan–Meier data (Section B.3.3), and (2) aligns with clinical advisor feedback at the January 2024 advisory board and subsequent UK clinical feedback. A 24-month cure time point may be conservative, as the plateau is evident in the PFS ECHELON-1 data as early as 12 months. Scenario analyses explore the impact of cure timepoints of 36 and 60 months following treatment discontinuation.

Factor	Previous appraisals of frontline lymphoma		Current appraisal	
	TA641 sALCL[40]	TA874 DLBCL[170]	Chosen values	Justification
Treatment waning effect	No	No	No	Treatment waning is not relevant in this setting where patients are cured after 24 months. The data available from the ECHELON-1 trial are mature (median follow-up of 89.2 months for PFS and 89.3 months for OS), with treatment only lasting a maximum of six cycles. This follow-up well exceeds the cure timepoint.
Source of utilities	EQ-5D-3L collected in ECHELON-2 and literature for progressed disease.[176]	Values based on GOYA trial.[177]	EQ-5D-3L collected in ECHELON-1.	Uses EQ-5D-3L data collected from the RCT assessing the intervention in the population in the decision problem, as per the NICE reference case.[175]
Source of costs	eMIT, BNF, NHS Reference Costs, and previous NICE appraisals (TA478, TA567, and TA577) for SCT costs.[41, 42, 174, 178–180]	Based on TA306 for SOC and intervention. Unit costs from NHS reference costs, PSSRU and BNF.[181, 182]	eMIT, BNF, NHS Reference Costs, published literature for second malignancy costs, previous NICE appraisals (TA462, TA478, and TA524) for subsequent therapy costs.[39, 116]	As per the NICE reference case.

Abbreviations: BNF, British National Formulary; CEM, cost-effectiveness model; DLBCL, diffuse large B cell lymphoma; eMIT, electronic marketing information tool; HL, Hodgkin's lymphoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplant; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention considered in this analysis is A+AVD, administered intravenously on days 1 and 15 of each 28-day treatment cycle for up to six cycles. The regimen consists of 1.2 mg of brentuximab vedotin per kilogram of body weight (mg/kg), 25 mg of doxorubicin per square meter of body-surface area (BSA; mg/m^2), 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine. A+AVD may be discontinued due to an AE, progressive disease, unsatisfactory therapeutic response, or withdrawal by the patient.

This dosing regimen aligns with ECHELON-1, the anticipated marketing authorisation for A+AVD in adult patients with previously untreated CD30+ Stage III or IV HL, and the current SmPC for brentuximab vedotin.[43]

B.3.2.3.2 Comparator

As described in Section B.1.3.4.3, it is anticipated that A+AVD will be used in patients who would otherwise be suitable for ABVD. In current UK clinical practice, patients suitable for ABVD-based treatment either receive ABVD for six cycles (i.e. as per the ABVD arm in ECHELON-1) or as per the PET-adapted RATHL approach. Clinicians at the advisory boards conducted by Takeda agreed with the proposed positioning of A+AVD and stated that it is in line with their expected use of it within the treatment pathway for previously untreated HL, based on ECHELON-1. Therefore, in line with UK clinical feedback, ABVD-based treatment is the relevant comparator for A+AVD for adult patients with previously untreated CD30+ Stage III or IV HL.[15, 35]

As described in Section B.1.3.4, in UK clinical practice, and as per the BSH guidelines, a PET-adapted approach for ABVD comprises two cycles of ABVD followed by either escalation or de-escalation of treatment based on findings of an interim PET scan (PET2): PET2-negative patients are de-escalated to treatment with AVD (four cycles) and PET2-positive patients are escalated to receive treatment with escBEACOPDac (four cycles).[15, 88] However, importantly, not all UK centres use a PET-adapted approach, with some preferentially treating patients with six cycles of ABVD, as per the comparator arm in ECHELON-1.[36] Therefore, ABVD-based treatment in the analysis comprises a weighted average of ABVD treatment for six cycles (i.e. as per the ABVD arm in ECHELON-1) and ABVD treatment via the PET-adapted approach. The distribution of patients receiving six cycles vs. PET-adaptation was informed by UK clinical expert feedback, which highlighted that approximately 10% and 90% of patients in the UK receive each approach, respectively. This distribution is explored in scenario analyses where 0% and 100%, and 5% and 95% distributions are explored.

Importantly, PFS and OS for ABVD-based treatment is assumed to be equivalent irrespective of approach. Specifically, the efficacy of the ABVD arm in ECHELON-1 was considered to be equivalent to ABVD administered via the PET-adapted approach. This assumption was considered reasonable based on the following:

- As described in Section B.2.12.2, the de-escalated ABVD/AVD regimen demonstrated similar, non-inferior 3-year PFS vs. six cycles of ABVD in the RATHL study

- Only a minority of patients in ECHELON-1 (7% and 9% in the A+AVD and ABVD treatment arms, respectively) were PET2 positive and therefore could potentially be candidates for treatment escalation. Importantly, in the RATHL trial, the minority of patients who were PET-positive after 2 initial cycles of ABVD were escalated to escBEACOPP; however, because this part of the trial was not randomised, it is unknown whether such escalation leads to better outcomes than continuing therapy with either ABVD or AVD

- The unadjusted ITC and unanchored matched adjusted indirect comparison conducted (summarised below) supported that six cycles of ABVD as per ECHELON-1, which is also recommended by the ESMO guidelines (Appendix M), and PET-adapted ABVD as per RATHL, are comparable with respect to efficacy

- Following a review of the clinical trial data and the unadjusted and adjusted indirect comparisons, and clinical expert opinion at the 2024 access advisory board confirmed that reported outcomes for patients receiving six cycles of ABVD in the ECHELON-1 trial were considered equivalent to outcomes of the PET-adapted ABVD strategy in the RATHL trial, and that efficacy observed in UK clinical practice is considered similar for ABVD-based treatment regardless of approach used.[36]

As discussed in B.1.3.4 and B.2.1, the RATHL study is the only trial identified by the SLR which assessed the PET-adapted RATHL approach in a UK setting in a population of interest (the Stage III and IV subgroup data from the RATHL trial is of most relevance to this decision problem). Of note, the RATHL trial's PET-adaptation design included escalation to treatment with BEACOPP-14 or escBEACOPP following a positive interim PET scan after two cycles of ABVD, as opposed to escBEACOPDac which is now used in UK clinical practice. Despite this difference, feedback from clinicians at the December 2023 advisory board (Section B.1.3.4) highlighted that whilst there are differences in safety between these regimens, efficacy is expected to be similar between BEACOPP-14, escBEACOPP and escBEACOPDac.[13] Therefore, UK clinicians considered RATHL outcomes reflective of UK clinical practice and appropriate for comparison with the ECHELON-1 data.

To explore the comparative efficacy of ABVD-based treatments, the following analyses were conducted:

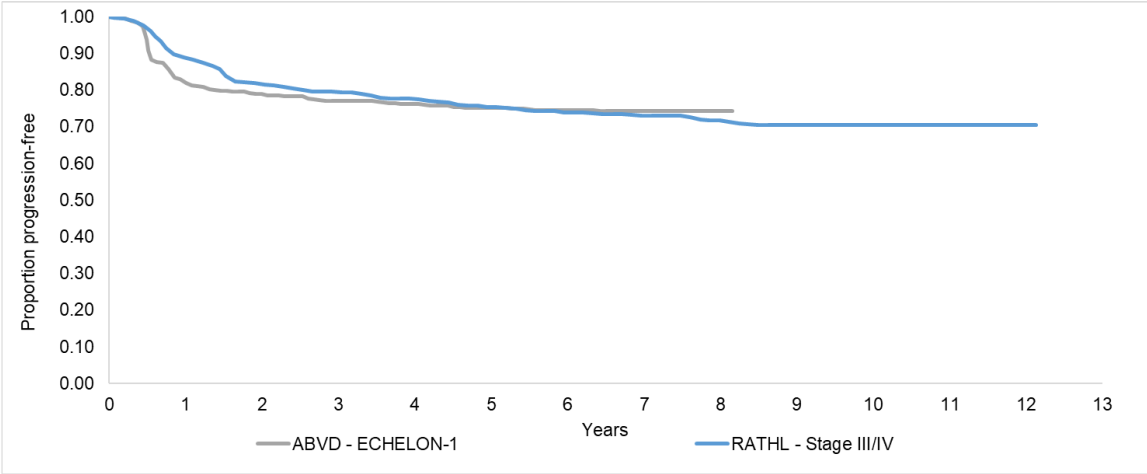
1) an unadjusted, unanchored comparison of ABVD (six cycles) from ECHELON-1 and PET-adapted ABVD from the Stage III or IV subgroup of the RATHL study and

2) an unanchored matched adjusted indirect comparison (MAIC) of ABVD (six cycles) from ECHELON-1 and PET-adapted ABVD from the Stage III or IV subgroup of the RATHL study.

An unanchored, unadjusted comparison of PFS and OS for ABVD-based treatment from the ECHELON-1 trial (ABVD [six cycles]) vs. the Stage III or IV subgroup of the RATHL study (PET-adapted ABVD) is presented in Figure 14 and Figure 15, respectively. For both PFS and OS, results were similar across ECHELON-1 and RATHL trials in patients who were treated with an ABVD-based regimen. Median follow-up for ABVD in ECHELON-1 was 86.4 months (range: 84.4–89.6 months) and 88.3 months (range: 85.2–89.9) for PFS and OS, respectively, vs. 7.3 years (IQR: 5.3–8.7) in the RATHL study. Based on the Kaplan–Meier curves, the 7-year PFS rate for ABVD in ECHELON-1 vs. RATHL was 74.5% (95% CI:

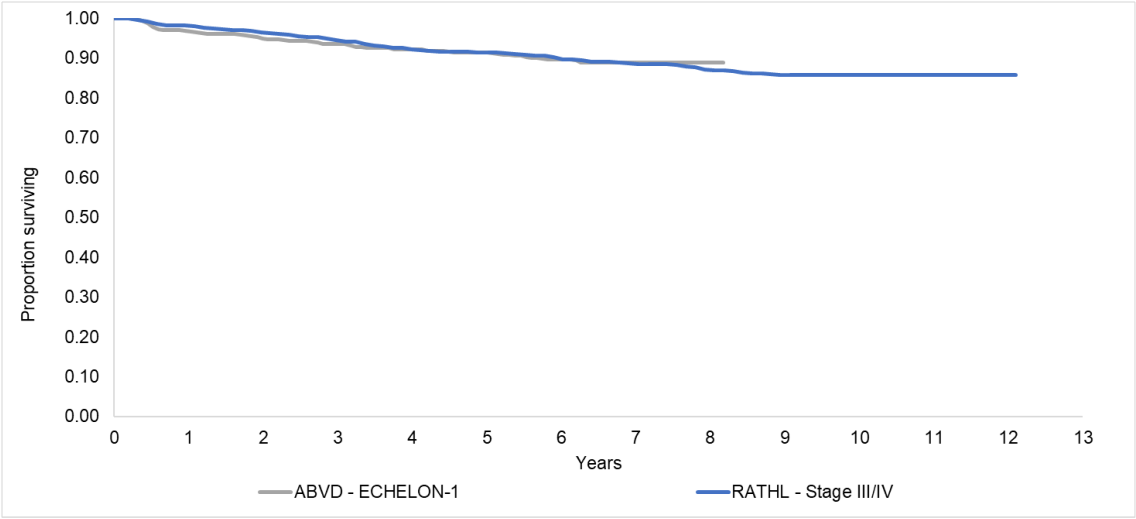
70.8–77.7%; Section B.2.6.1.2) vs. 73.4% (95% CI: 69.7–76.8%), respectively. The 5-year PFS rates for ABVD in ECHELON-1 were 75.3% (95% CI: 71.8–78.5%) %) and [redacted]% (95% CI: [redacted]%) for ABVD in RATHL. The 7-year OS for ABVD in ECHELON-1 was 87.5% (95% CI: 84.2–90.2%; Section B.2.6.2) and ABVD in RATHL was 88.7% (95% CI: 85.7–91.0%), whereas the 5-year OS rates were 91.2% (95% CI: 88.6–93.2%) and [redacted]% (95% CI: [redacted]%), respectively.[88, 123]

Figure 14: PFS Kaplan–Meier overlay between ABVD – ECHELON-1 ITT (median follow-up: 7.2 years) and all eligible population – RATHL, Stage III or IV subgroup (median follow-up: 7.3 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PFS, progression-free survival; RATHL, Response-Adjusted Therapy for Advanced Hodgkin Lymphoma
Source: Luminari *et al* (2023);[88] Takeda, ECHELON-1 CSR (2024).[123]

Figure 15: OS Kaplan–Meier overlay between ABVD – ECHELON-1 ITT (median follow-up: 7.2 years) and all eligible population – RATHL, Stage III or IV subgroup (median follow-up: 7.3 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival; RATHL, Response-Adjusted Therapy for Advanced Hodgkin Lymphoma
Source: Luminari *et al* (2023);[88] Takeda, ECHELON-1 CSR (2024).[123]

Overall, the unanchored, unadjusted comparison supports the assumption of equivalent efficacy between ABVD (six cycles) used in ECHELON-1 and PET-adapted ABVD used in the RATHL trial. This is consistent with conclusions from the RATHL study which demonstrated similar, non-inferior 3-year PFS vs. six cycles of ABVD.[88]

For completeness, results from unanchored MAICs are presented in Appendix D.1.7. An unanchored MAIC was conducted due to the lack of a common comparator arm, as per NICE technical support document (TSD) 18.[183] Although there are limitations associated with the results of the MAICs, the results from the MAIC support the assumption of equal efficacy. However, the results should be interpreted with caution.

Although efficacy is considered equivalent across ABVD-based treatment, the analysis accounts for expected differences in costs (acquisition, administration, and concomitant medication; Section B.3.5.1) and tolerability (Section B.3.3.3) between approaches. Total costs were calculated based on the weighted average of ABVD treatment for six cycles and ABVD treatment via the PET-adapted approach (10% vs 90%), as previously described.

The ABVD (six cycles) dose comprises 25 mg/m^2 of doxorubicin, 10 U/m^2 of bleomycin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine – ABVD is administered as an intravenous (IV) infusion on days 1 and 15 of each 28-day treatment cycle for up to six cycles as per the regimen received in ECHELON-1. Dosing for the PET-adapted ABVD approach was informed by NHS protocols and validated by UK clinical experts (Section B.3.5.1.1).[36, 184–196]

B.3.3 Clinical parameters and variables

Data based on the ITT population of ECHELON-1 were used to inform clinical efficacy for A+AVD and ABVD-based treatment. Data from the final data-cut off were used (11 March 2023; median follow-up 89.2 months for PFS and 89.3 months for OS) unless otherwise specified. As described in Section B.3.2.3.2, the analysis accounts for expected differences in costs (acquisition, administration, and concomitant medication; Section B.3.5.1) and tolerability (Section B.3.3.3) between ABVD (six cycles) and PET-adapted ABVD.

B.3.3.1 Baseline characteristics

Modelled baseline characteristics were sourced from ECHELON-1 in the base case (Table 21). Mean starting age and gender distribution were used to estimate general population mortality and utility values. Body weight and body surface area (BSA) were used to estimate dosing and acquisition costs. A scenario analysis explores the use of baseline age and gender from the Stage III or IV subgroup in the RATHL study; only a median age was available.

Table 21: Baseline characteristics

Population characteristics	Value (SD, 95% CI)	
	ECHELON-1	RATHL
Age (years)	39.53 (0.44, 38.68–40.39)	[redacted]
Proportion male	58.17% (0.01, 55.51–60.81%)	[redacted]
Body weight (kg)	75.06 (0.53, 74.03–76.09)	NA

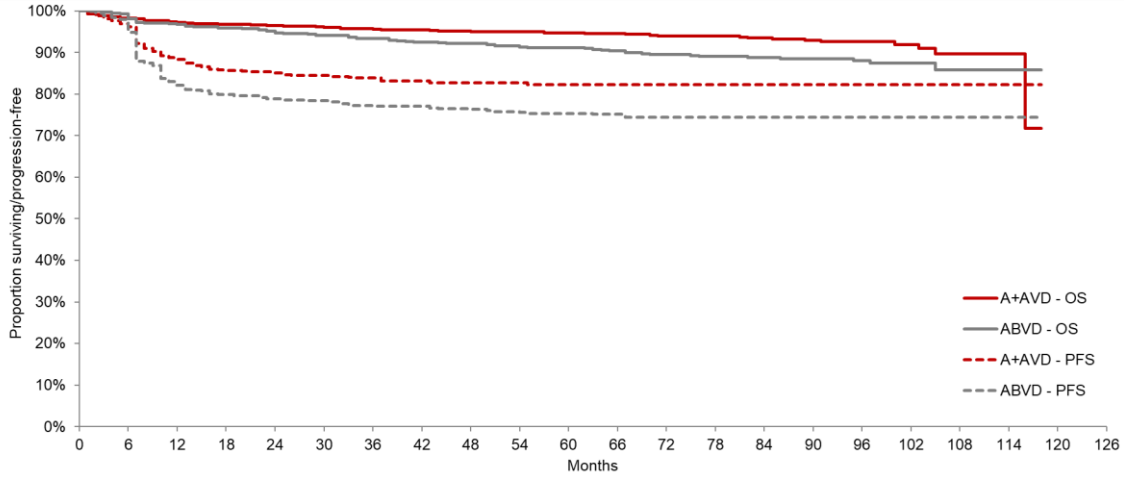
Population characteristics	Value (SD, 95% CI)	
	ECHELON-1	RATHL
BSA (m^2)	1.88 (0.01, 1.87–1.89)	NA

Abbreviations: BSA, body surface area; CI, confidence interval; kg, kilogram; NA, not available; SD, standard deviation.

B.3.3.2 Survival extrapolations

As described in Section B.3.2.2, PFS and OS for A+AVD and ABVD were informed by the ECHELON-1 final data cut. Observed PFS and OS Kaplan–Meier curves are presented in Figure 16.

Figure 16: PFS and OS Kaplan–Meier curves | ECHELON-1



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival; PFS, progression-free survival.

Extrapolation of PFS and OS is described in Section B.3.3.2.2 and B.3.3.2.3, respectively. Analyses were performed in accordance with the NICE Decision Support Unit (DSU) TSDs 14 and 21.[197, 198]

Independent MCMs and independent one-knot splines were used to extrapolate PFS and OS, respectively, in the base case. Independent models were selected based on log-cumulative hazard plots, Schoenfeld residuals, hazard plots, and UK clinical feedback (Sections B.3.3.2.2 and B.3.3.2.3 for PFS and OS, respectively). The NICE TSD 21 describes a variety of survival modelling approaches that can be used when hazard functions are complex, including MCMs or flexible parametric models e.g. splines, which may be useful when an assumption of cure is reasonable. In patients with previously untreated CD30+ Stage III or IV HL, approximately 70–80% of patients are cured with current treatments; cure is a well-recognised goal of treatment in this setting (Section B.1.3.3.1).[6, 22, 23] This is observed in the Kaplan–Meier curves from ECHELON-1 for PFS for A+AVD and ABVD, where there is a plateau from approximately 12–18 months, and the observed hazard plots that trend to zero (Section B.3.3.2.2). Therefore, more flexible parametric models that can better capture the shapes of complex hazard functions were explored.

Palmer *et al* (2023) build on the recommendations reported in the NICE TSD 21 and suggest an algorithm to help determine whether flexible models are required and, if so, which

methods are appropriate to explore.[199] This algorithm consists of four key questions, described in Table 22, which were considered to inform the base case parametric modelling approach, and the responses to the questions posed in Palmer *et al* (2023) support the use of independent MCMs for PFS and independent splines for OS. For completeness, Appendix O describes other approaches explored in scenario analyses, including independent one-knot splines for PFS, independent MCMs for OS, independent standard parametric curves, and dependent curves for all approaches. In addition to the rationale described in Table 22, assessment of visual fit of the standard parametric curves to the observed data, and assessment of the hazards in the observed data, further discredits the plausibility of using standard parametric curves for extrapolation.

Table 22: Rationale supporting flexible cure modelling | Palmer *et al* (2023)[199]

Question from Palmer *et al* (2023)	Response relevant to this submission
Does the trial under investigation have two or more arms? If yes, assess whether the proportional hazards assumption is likely to hold taking into consideration external data as well as the following tests on the observed data: (1) log-cumulative hazard plots, (2) scaled-Schoenfeld residual plots, and the (3) Grambsch-Therneau tests	• ECHELON-1 compares A+AVD with ABVD i.e. two treatment arms. • The proportional hazards assumption was explored through the log-cumulative hazard plots, the scaled-Schoenfeld residual plots and the Grambsch-Therneau tests in Section B.3.3.2.2 and B.3.3.2.3 for PFS and OS, respectively. Proportional hazards is shown to be violated for both PFS and OS. • Therefore, independent parametric modelling was pursued in the base case.
Is flexible survival modelling required and adequately justified? To support this elicit expert beliefs and consider data maturity and evidence of turning points in the observed hazard plot and potential for future turning points based on external evidence, clinical plausibility, hazard plots, and mechanism of action. Using these insights evaluate the possibility of a cure based on the evidence of a plateau in OS, whether a cure is clinically plausible for the target population based on external evidence, evidence of a plateau in acceptable intermediate endpoints for OS, and the mechanism of action of the drug.	As described in Section B.1.3.4, cure is a well-recognised goal of treatment in this setting. This is documented in the literature and was corroborated by clinical experts at the January 2024 UK market access advisory board. Median follow-up from the final data cut from ECHELON-1 is 89.2 and the plateau is observed from 12–18 months. Additionally, the hazard functions trend to zero for PFS.
Is the assumption of a meaningful cure fraction for the intervention and/or comparator plausible and supported with robust evidence? If yes, consider fitting MCMs. Additionally, explore non-cure models such as spline models, landmark models, piecewise models, or parametric mixture models. Using insights from external evidence and expert beliefs select plausible models based on external evidence, clinical plausibility, log-cumulative hazard plots, and AIC/BIC goodness-of-fit statistics.	The literature indicates that approximately 70–80% of patients with previously untreated CD30+ Stage III or IV HL are cured with current first-line treatments, which is supported by UK clinicians.[22, 23] Therefore, independent MCM modelling is pursued in the base case for PFS. Independent MCMs were explored for OS (Appendix O). However, the OS extrapolations predicted in the probabilistic analyses estimated cure rates and outcomes that were clinically implausible. Therefore, in the base case, the complex hazard and survival functions observed for OS were extrapolated using one-knot splines (Section B.3.3.2.3), which capture a change in the hazards for patients who are cured, without assumptions about the number of heterogenous subgroups directly. Alternative models were

Question from Palmer *et al* (2023)	Response relevant to this submission
	also explored for both PFS and OS (Appendix O). The base case curve selection was informed by within-trial (internal validation) i.e. assessment of proportional hazards and accelerated failure time assumptions, observed hazard plots, visual comparison of the predicted curves with the observed data, and AIC/BIC goodness-of-fit statistics, and external validation i.e. external evidence and clinical plausibility – aligning with the recommendations in the NICE TSD 14, NICE TSD 21, and Palmer *et al* (2023). Throughout this process, plausible alternatives have also been identified and explored in scenario analyses.
Are the results of the cost-effectiveness analysis sensitive to the choice of extrapolation model? If yes, present results from all plausible models and if no, present results based on the base case and include other plausible models as sensitivity analyses.	Visual assessment and landmark analyses highlight similar predictions across all plausible extrapolation models. Therefore, choice of extrapolation model has a limited impact on cost-effectiveness results. However, for completeness, scenarios are presented considering these plausible approaches (Section B.3.11.3).

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; HL, Hodgkin lymphoma; MCM, mixture cure model; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TSD, Technical Support Document.

MCMs assume a proportion of patients are cured and so are not at risk of the event, where the residual uncured proportion are at risk of the event and have a survival function which tends to zero. The MCMs were fitted in R and R Studio (2023.06.1) using the *flexsurvcure* function, and are described as follows:

$$S(t) = \pi + (1 - \pi)S_u(t)$$

Where π is the proportion of cured patients, (1 – π) is the proportion of uncured patients and $S_u(t)$ is the survival function of the uncured patients. Background mortality is applied within the CEM, based on the national UK lifetables 2020–2022.[200] The model incorporates SMRs to adjust background mortality and reflect the increased risk of death over the model time horizon, an SMR of 1.05 is applied in the A+AVD arm and 1.10 in the ABVD arm (Sections B.3.2.2.1 and B.3.3.2.1).

One-knot splines provide a flexible approach to modelling the complex hazard and survival functions. These models make no assumptions about the number of heterogenous subgroups directly, unlike the MCMs which look specifically at cured and non-cured groups. The complexity of the function depends on the number and location of joining points of the function, with these joining points known as “knots”. One-, two-, and three-knot splines were explored in the survival analyses. However, the observed hazard plots indicate only one change in the hazard function; therefore, one-knot splines were used in the base case which is supported by the limited differences observed from the more complicated models. This aligns with the literature referenced in the NICE TSD 21 indicating that predicted survival functions within the range of the follow-up have been shown to be very insensitive to the

number and location of the knots, provided that there are a sufficient number to capture the underlying shape.[198] The one-knot splines were fitted in R and R Studio (2023.06.1) using the *flexsurvspline* function, and are described as follows:

$$\log[\mathrm{H}(\mathrm{t})] = \log[-\log[\mathrm{S}(\mathrm{t})]] = \mathrm{s}(\log(\mathrm{t})|\gamma, \mathrm{k0})$$

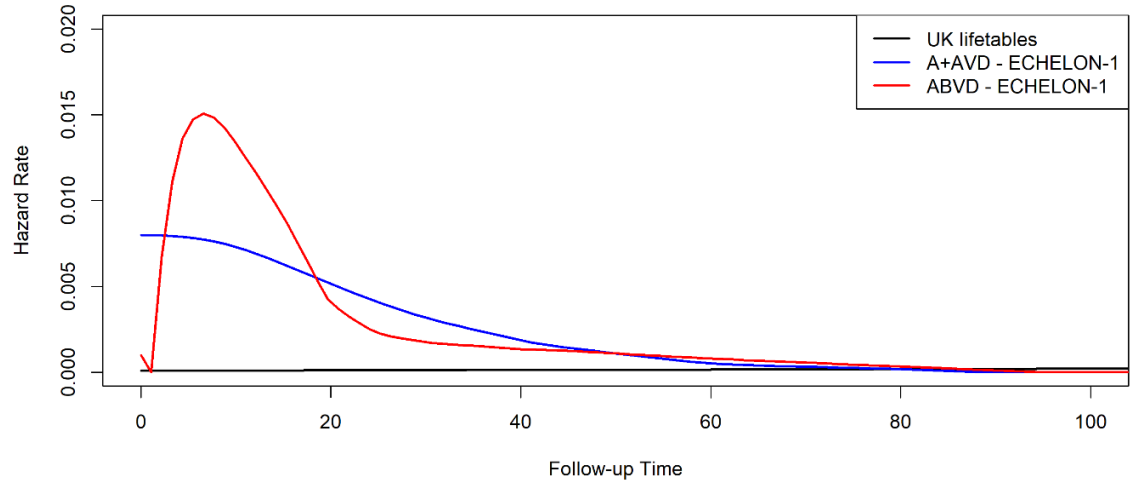
Where $\mathrm{k0}$ is a vector of knots and γ is the associated parameters.

Background mortality is applied based on the national UK lifetables 2020–2022.[200] The model incorporates SMRs to adjust background mortality and reflect the increased risk of death over the model time horizon, an SMR of 1.05 is applied in the A+AVD arm and 1.10 in the ABVD arm (Sections B.3.2.2.1 and B.3.3.2.1).

B.3.3.2.1 Excess mortality

As discussed in Section B.3.2.2.1, SMR-adjusted background mortality is applied within the analysis. The background mortality estimates are sourced from the UK lifetables from the Office of National Statistics 2020–2022 and applied based on the baseline characteristics presented in Table 21.[200] The ECHELON-1 data indicates that most events occur within the first 24 months (85.2% of PFS events). Thereafter, the number of events is low and suggests that survival could be predicted by the UK lifetables. Feedback from UK clinicians indicated that PFS is used to define cure in this setting (Section B.1.3.4), hence the observed hazards in the A+AVD and ABVD treatment arms for PFS in ECHELON-1 were compared with the general population hazards from the UK lifetables (Figure 17). These indicate that the hazards of progression or death in ECHELON-1 trend towards those seen in the UK lifetables, supporting the use of the UK lifetables to inform long-term extrapolations beyond the ECHELON-1 trial follow-up period.

Figure 17: Comparison of observed hazards for PFS in ECHELON-1 with UK lifetables

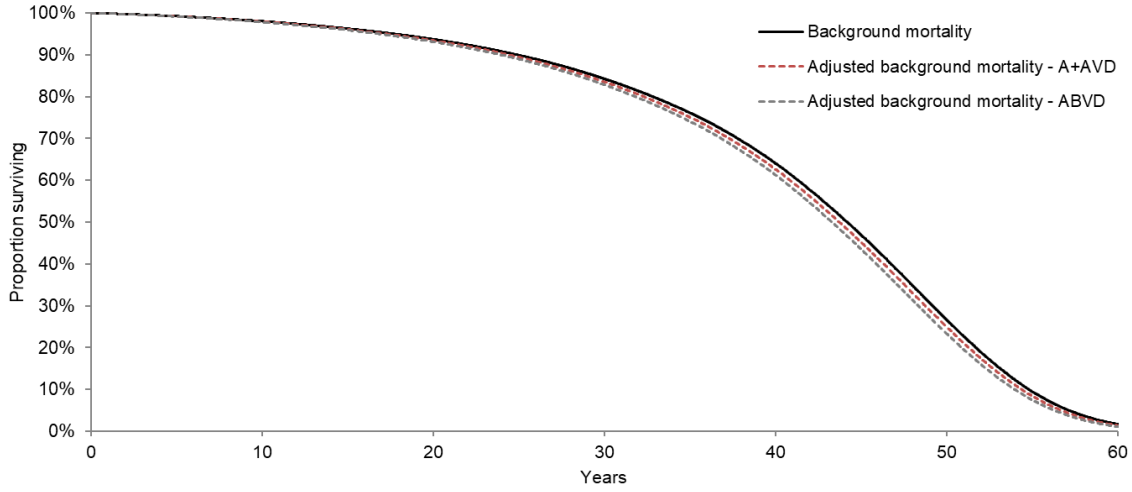


Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PFS, progression-free survival.

As discussed in Section B.3.2.2.1, SMRs of 1.05 and 1.10 are applied to background mortality for A+AVD and ABVD-based treatment, respectively. SMRs are applied to background mortality from baseline across the model time horizon. The PFS and OS extrapolations are informed by the maximum probability of an event as estimated from the

parametric curves (Sections B.3.3.2.2 and B.3.3.2.3 for PFS and OS, respectively) or the adjusted background mortality. Figure 18 compares the UK lifetables with the adjusted background mortality using SMRs of 1.05 and 1.10. In the base case, long-term outcomes are driven by the adjusted background mortality, which takes effect at [redacted] and [redacted] years for PFS and [redacted] and [redacted] years for OS, for A+AVD and ABVD-based treatment, respectively. Scenario analyses explore the impact of SMR 1.10 for A+AVD and 1.15 for ABVD-based treatment.

Figure 18: Background mortality with and without excess mortality from HL



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; HL, Hodgkin's Lymphoma.

B.3.3.2.2 Progression-free survival (PFS)

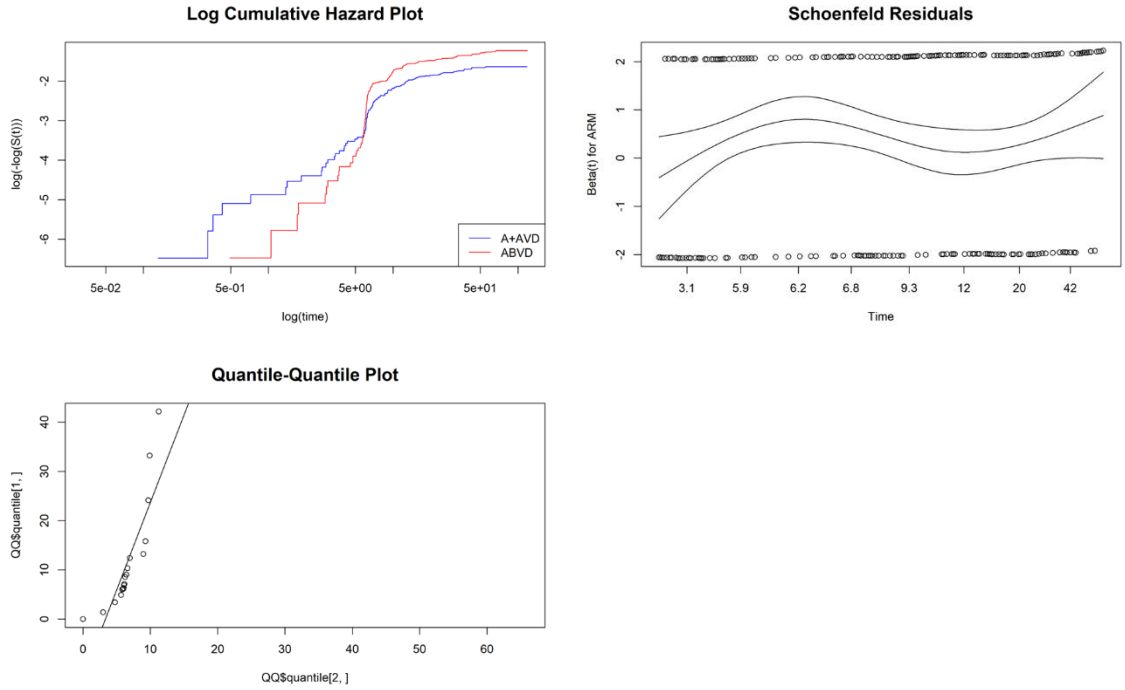
As described in Section B.2.6.1, INV and IRF assessments of disease progression were conducted in ECHELON-1. Investigator-assessed PFS (PFS per INV) data from the final data-cut were used in the analysis; independent review facility-assessed PFS (PFS per IRF) data were not collected beyond the first data-cut (April 2017; median follow-up of 24.6 months). Therefore, this approach uses the most mature data and hence supports a reduction in uncertainty in the cost-effectiveness estimates. The modified PFS endpoint was also collected in ECHELON-1; this is not considered in the analysis as it is considered less relevant by UK clinical experts (Section B.2.3.2.1).

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS per INV are presented in Figure 19. The Schoenfeld residuals and the Grambsch-Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.6800. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold. This is further supported by the different shapes shown in the observed hazard plots; the hazard of progression or death is shown to gradually decrease in the A+AVD arm (Figure 20), whereas the hazard of progression or death is shown to first increase before gradually decreasing in the ABVD arm (Figure 21). Additionally, the log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. This is further supported by the clear turning points observed in the hazard

plots. The quantile-quantile plot indicates that the accelerated failure time assumption may hold (Figure 19).

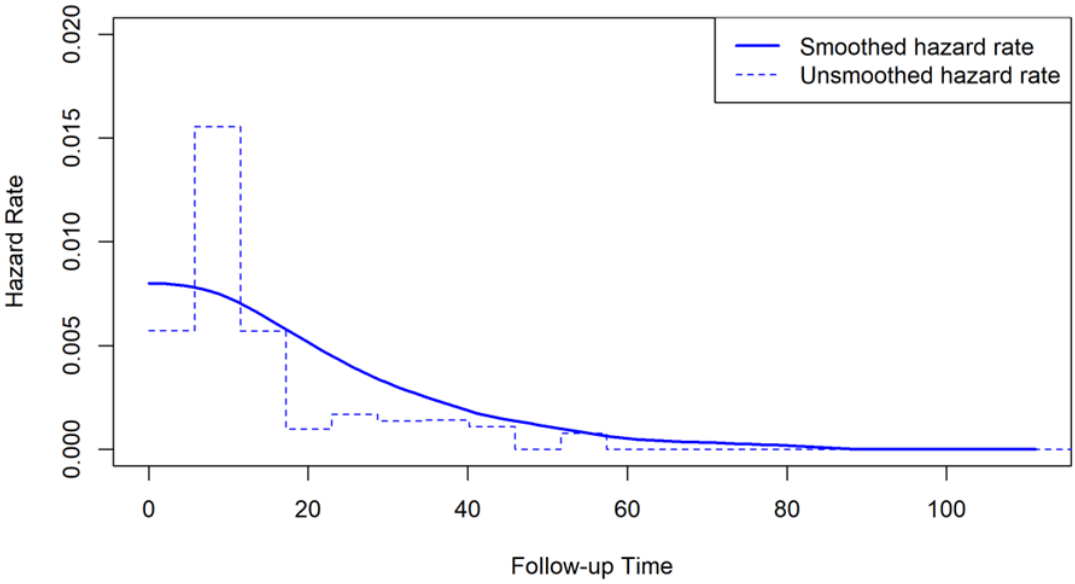
Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case. Dependent and standard parametric models are presented in Appendix O This aligns with Palmer *et al* (2023) and the NICE TSDs 14 and 21.[197–199]

Figure 19: PFS proportional hazards and accelerated failure time tests



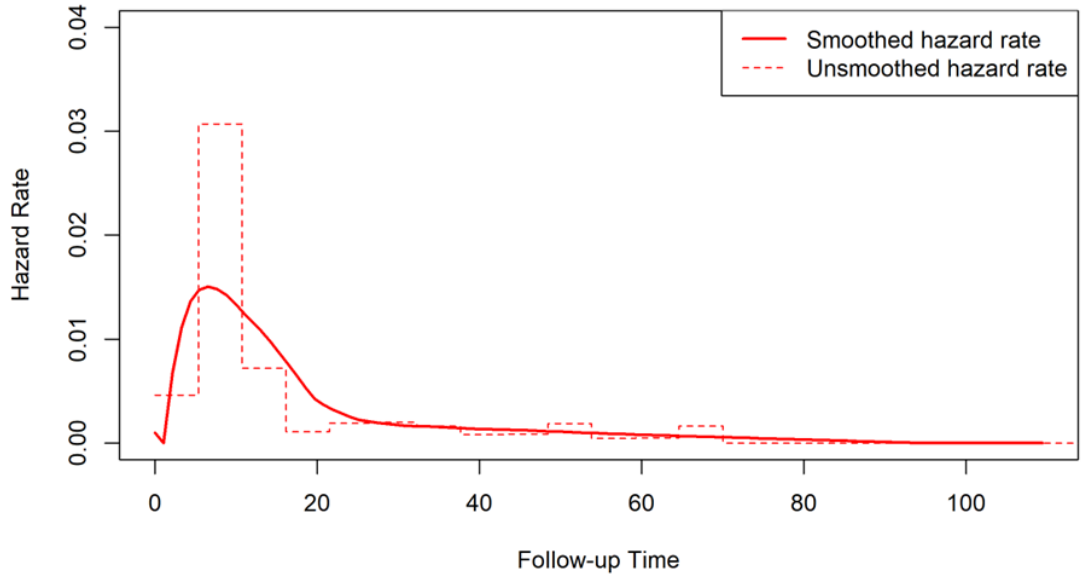
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 20: Observed hazards | A+AVD | PFS per INV



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

Figure 21: Observed hazards | ABVD | PFS per INV



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

As the assumption of a cure fraction for the intervention and comparator is plausible and supported with robust evidence, MCMs were fitted to the PFS per INV ECHELON-1 data. One-knot spline models were also explored (Appendix O); based on the maximum of one turning point observed in the hazard plots. These steps align with Palmer *et al* (2023) and the NICE TSDs 14 and 21.

Figure 22 presents the extrapolated independent MCMs for A+AVD, excluding adjusted background mortality. The corresponding AIC and BIC values are presented in Table 23 and the comparisons of predicted hazards vs. observed hazards are presented in Appendix O.1.1.1, Appendix Figure 29.

Figure 22: Independent MCMs | A+AVD | PFS

Notes: excluding adjusted background mortality
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival.

Table 23: Independent MCMs AIC and BIC values | A+AVD | PFS

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1380	5	1389	2
MCM: Weibull	1378	4	1392	4
MCM: Lognormal	1386	7	1400	7
MCM: Loglogistic	**1372**	**1**	**1385**	**1**
MCM: Gompertz	1382	6	1396	6
MCM: Generalised Gamma	1377	2	1395	5
MCM: Gamma	1377	2	1390	3

Notes: bold represents the base case
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; ITT, intention-to-treat; MCM, mixture cure model; PFS, progression-free survival

Figure 23 presents the extrapolated independent MCMs for ABVD, excluding adjusted background mortality. The corresponding AIC and BIC values are presented in Table 24 and the comparisons of predicted hazards vs. observed hazards are presented in Appendix O.1.1.1, Appendix Figure 30.

Figure 23: Independent MCMs | ABVD | PFS

Notes: excluding adjusted background mortality
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 24: Independent MCMs AIC and BIC values | ABVD | PFS

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1860	6	1869	5
MCM: Weibull	1856	5	1869	5
MCM: Lognormal	1811	3	1825	2
MCM: Loglogistic	**1802**	**1**	**1816**	**1**
MCM: Gompertz	1861	7	1874	7
MCM: Generalised Gamma	1810	2	1828	3

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Gamma	1846	4	1860	4

Notes: bold represents the base case
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; ITT, intention-to-treat; MCM, mixture cure model; PFS, progression-free survival.

For A+AVD, the log-logistic, generalised gamma, and gamma MCMs have the lowest AIC scores – with less than, or equal to, five scores across the three models. The log-logistic and gamma MCMs are also supported by low BIC scores. This is supported by close visual alignment from the predicted log-logistic, generalised gamma, and gamma MCM hazards with the observed hazards from ECHELON-1. For ABVD, the log-logistic MCM provides the best statistical fit to the observed data based on AIC and BIC scores. All distributions for both treatment arms had similar visual fit to the ECHELON-1 Kaplan–Meier data and the observed hazards.

Table 25 presents the predicted cure fractions for each of the MCMs. The predicted cure fractions are similar across all distributions for A+AVD [redacted] and ABVD [redacted], highlighting the consistency in predicted outcomes regardless of model choice. The higher cure rates predicted in the A+AVD arm align with the improved PFS observed for A+AVD vs. ABVD in ECHELON-1. The predicted cure rates for ABVD align with those seen in the literature (70–80%, Section B.1.3) and UK clinical opinion.

Table 25: PFS cure fractions

	A+AVD	ABVD
MCM: Exponential	[redacted]	[redacted]
MCM: Weibull	[redacted]	[redacted]
MCM: Lognormal	[redacted]	[redacted]
MCM: Loglogistic	[redacted]	[redacted]
MCM: Gompertz	[redacted]	[redacted]
MCM: Generalised Gamma	[redacted]	[redacted]
MCM: Gamma	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PFS, progression-free survival.

The independent log-logistic MCMs were associated with the lowest AIC and BIC scores for both treatment arms, supported by the accelerated failure time assumption, and the predicted hazards which aligned with the observed hazards based on visual inspection. In addition, clinical opinion elicited at the January 2024 UK market access advisory board (Section B.1.3.4), which advised that the PFS hazard profile would not differ based on treatment with frontline A+AVD vs. ABVD, and therefore the same parametric distribution across treatment arms was considered to be appropriate.[36] Based on this, independent log-logistic MCMs, were selected in the base case for both A+AVD and ABVD.

The choice of parametric modelling approach and base case curve selection was also validated at the January 2024 market access advisory board. Extrapolations from the observed Kaplan–Meier data followed by adjusted background mortality, independent standard parametric curves, independent MCMs, and independent one-knot splines were presented to the advisors, alongside the AIC/BIC scores from all models, predicted

proportion cured from the MCMs, and the predicted proportion progression-free and alive at 6 months, 1 year, 2 years, 5 years, and 10 years (including adjusted background mortality).

The clinical and health economic advisors unanimously agreed that the MCMs provided the best approach given the goal of treatment (i.e. cure), outcomes observed in ECHELON-1, and expectations in UK clinical practice. The clinical advisors acknowledged that the extrapolations across the different independent MCMs predicted very similar long-term outcomes, including predictions for the proportion cured. Therefore, it was considered that all independent MCMs explored could be plausible. However, the advisors agreed that the log-logistic MCM was the most appropriate base case selection. Of note, the clinical advisors stated that all standard parametric models, except for the Gompertz, resulted in implausible predictions. Additionally, the advisors highlighted that the predictions from the one-knot splines were supportive of the MCMs given the close alignment in predicted outcomes across curves. Nevertheless, the MCMs were considered most relevant to the decision problem, and the one-knot splines were viewed as supportive only. The use of the Kaplan–Meier data followed by adjusted background mortality was highlighted as a useful scenario to demonstrate the impact of using the observed data; as with the one-knot splines, this was considered supportive of the MCMs.

Figure 24 presents the base case MCMs log-logistic curves fit to the A+AVD and ABVD data, including adjusted background mortality with an SMR of 1.05 for A+AVD and 1.10 for ABVD (Section B.3.3.2.1).

Table 26 compares the predicted outcomes from the base case log-logistic MCMs with the observed data from ECHELON-1, demonstrating the extrapolated curves provide a good fit to the data, particularly across the plateau, from ECHELON-1. Table 26 also presents the observed data from the Stage III/IIV subgroup from the RATHL study; the predicted outcomes in the ABVD arm of ECHELON-1 align with the ABVD arm of the RATHL study (e.g. [redacted]% vs. 70.5% at 10 years).

Based on the feedback from clinical advisors, scenario analyses were conducted to explore all alternative MCMs, standard Gompertz independent parametric models for both A+AVD and ABVD, one-knot spline models and use of the Kaplan–Meier data directly until 89.2 months (ECHELON-1 median follow-up for PFS) followed by adjusted background mortality. Clinical advisors indicated that these scenarios represent plausible alternatives and are supportive of the base case assumptions. Exploration of plausible alternatives also aligns with the recommendations in NICE TSD 21 and Palmer *et al* (2023). Section B.3.11.3 presents the results of the scenario analyses; these do not have a material impact on the cost-effectiveness results given the similar fit and long-term outcomes predicted.

Figure 24: Base case PFS curve selections | Log-logistic MCMs including adjusted background mortality for A+AVD and ABVD

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 26: Observed vs. predicted PFS outcomes | Log-logistic MCMs including adjusted background mortality for A+AVD and ABVD

	ECHELON-1		Predicted		RATHL
	A+AVD	ABVD	A+AVD	ABVD	ABVD
Median	NR	NR	[redacted]	[redacted]	NR
Mean	NA	NA	[redacted]	[redacted]	NA
% progression-free at					
6 months	[redacted]	[redacted]	[redacted]	[redacted]	97.7%
1 year	[redacted]	[redacted]	[redacted]	[redacted]	89.0%
2 years	[redacted]	[redacted]	[redacted]	[redacted]	81.9%
3 years	[redacted]	[redacted]	[redacted]	[redacted]	79.6%
4 years	[redacted]	[redacted]	[redacted]	[redacted]	77.6%
5 years	[redacted]	[redacted]	[redacted]	[redacted]	75.4%
6 years	[redacted]	[redacted]	[redacted]	[redacted]	74.0%
7 years	[redacted]	[redacted]	[redacted]	[redacted]	73.1%
8 years	[redacted]	[redacted]	[redacted]	[redacted]	71.8%
10 years	[redacted]	[redacted]	[redacted]	[redacted]	70.5%
20 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
30 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
40 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
50 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
60 years	[redacted]	[redacted]	[redacted]	[redacted]	NR

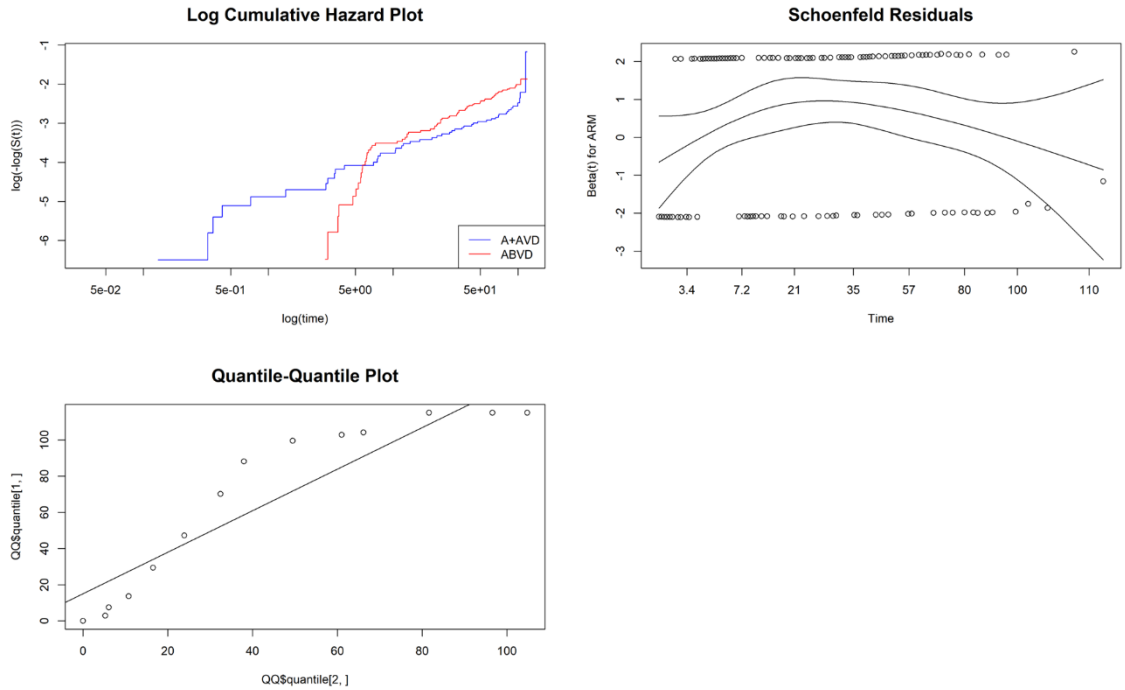
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival; vs., versus.

B.3.3.2.3 Overall survival (OS)

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions are presented in Figure 25. The Schoenfeld residuals and the Grambsch-Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.7216. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold. Additionally, the log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. This is further supported by the clear turning points observed in the hazard plots. The shape of the observed hazards shown in the hazard plots are similar for A+AVD and ABVD; the hazard of death is shown to gradually decrease before gradually increasing (Figure 26 and Figure 27 for A+AVD and ABVD, respectively). The quantile-quantile plot indicates that the accelerated failure time assumption may be violated (Figure 25).

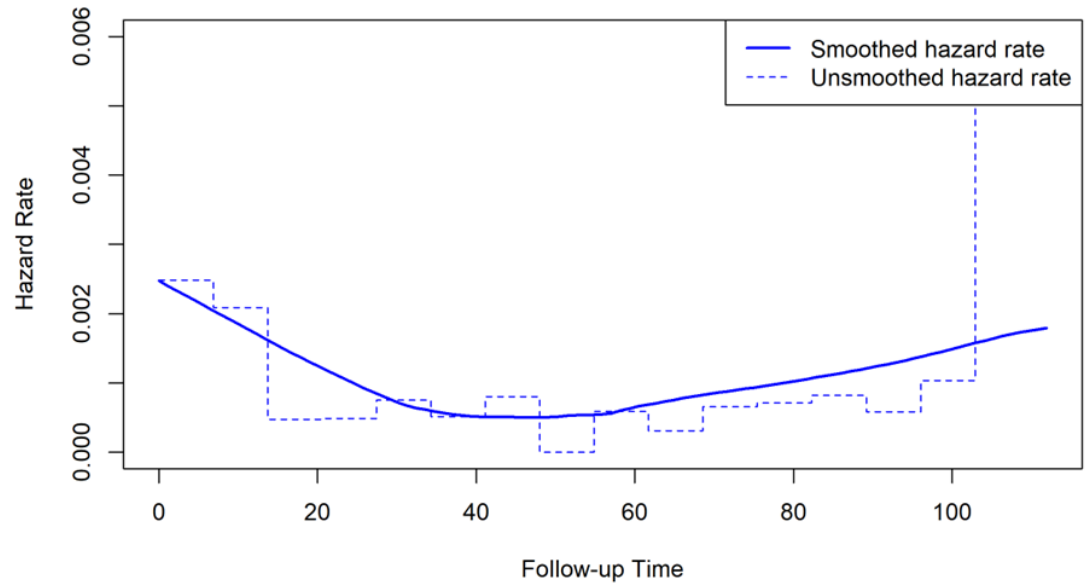
As per PFS and based on the above, independent models were pursued in the base case. Dependent models are presented in Appendix O. Standard parametric models are presented in Appendix O. These steps align with Palmer *et al* (2023) and the NICE TSDs 14 and 21.[197–199]

Figure 25: OS proportional hazards and accelerated failure time testing



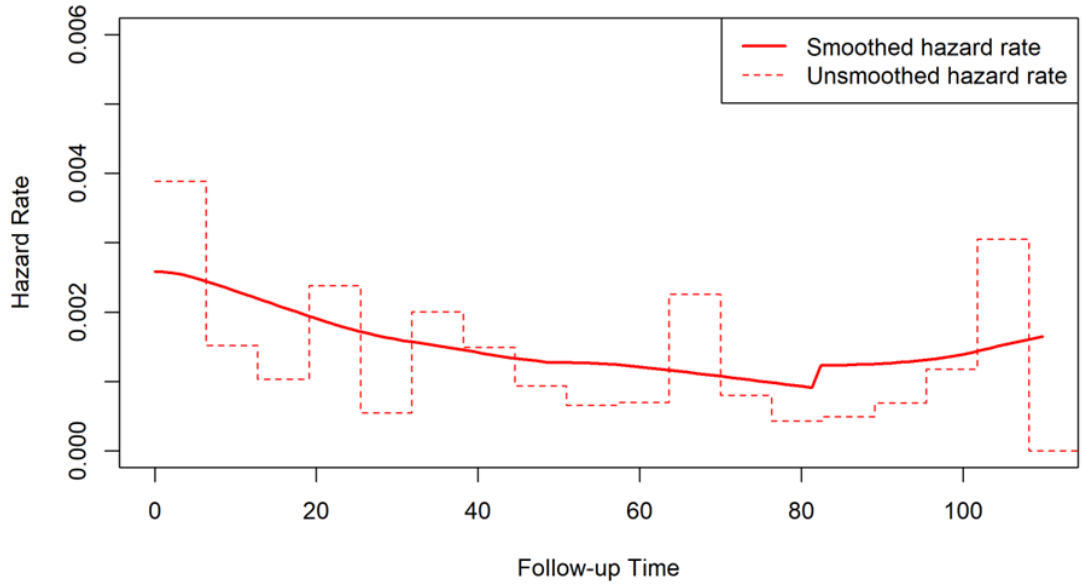
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival.

Figure 26: OS observed hazards | A+AVD



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; OS, overall survival.

Figure 27: OS observed hazards | ABVD



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival.

As discussed in Section B.3.2.2.1, in the base case, OS was extrapolated using one-knot splines, which reflect the complex hazard and survival function observed in ECHELON-1. Other approaches to extrapolate PFS and OS were explored in scenario analyses, including MCMs (Appendix O). These steps align with Palmer *et al* (2023) and the NICE TSDs 14 and 21.

Figure 28 presents the independent one-knot splines for A+AVD, excluding adjusted background mortality. The corresponding AIC and BIC values are presented in Table 27 and the comparisons of predicted hazards vs. observed hazards are presented in Appendix O.1.1.1, Appendix Figure 31.

Figure 28: OS independent one-knot splines | A+AVD

Notes: excluding adjusted background mortality
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival.

Table 27: OS independent one-knot splines AIC and BIC values | A+AVD

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	726	2	739	2
One-knot hazards	**726**	**1**	**739**	**1**
One-knot normal	726	3	739	3

Notes: bold represents the base case
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 29 presents the extrapolated independent one-knot splines for ABVD, excluding adjusted background mortality. The corresponding AIC and BIC values are presented in Table 28 and the comparisons of predicted hazards vs. observed hazards are presented in Appendix O.1.1.1, Appendix Figure 32.

Figure 29: OS independent one-knot splines | ABVD

Notes: excluding adjusted background mortality
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival.

Table 28: OS independent one-knot splines AIC and BIC values | ABVD

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	1034	2	1048	2
One-knot hazards	**1034**	**3**	**1048**	**3**
One-knot normal	1033	1	1046	1

Notes: bold represents the base case
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival.

For A+AVD and ABVD, there is little difference in statistical fit across the one-knot spline functions; a maximum difference of one in AIC scores and a maximum difference of two in BIC scores. This is supported by similar visual fit to the observed data and visual alignment of the one-knot spline hazards with the observed hazards from ECHELON-1.

Clinical expert opinion elicited at the January 2024 UK market access advisory board (Section B.1.3.4) indicated that the OS hazard profile would not differ based on treatment with frontline A+AVD vs. ABVD, and therefore the same parametric distribution across treatment arms was appropriate.[36] Therefore, the independent one-knot spline hazards were selected in the base case for both A+AVD and ABVD; these curves predict the most conservative (i.e. the lowest) proportion surviving in both treatment arms, have relatively low AIC and BIC scores for both treatment arms and the predicted hazards align with the observed hazards.

The choice of parametric modelling approach and base case curve selection was also validated at the market access advisory board. Extrapolations from the observed Kaplan–Meier data followed by adjusted background mortality, independent standard parametric curves, independent MCMs, and independent one-knot splines were presented to the advisors, alongside the AIC/BIC scores from all models, predicted proportion cured from the MCMs, and the predicted proportion alive at 6 months, 1 year, 2 years, 5 years, and 10 years (including adjusted background mortality).

The clinical and health economic advisors believed that the MCMs provided the best approach given the goal of treatment (i.e. cure), outcomes observed in ECHELON-1, and expectations in UK clinical practice. However, the clinical advisors acknowledged that the extrapolations across the different independent MCMs and independent one-knot splines provided similar long-term predictions when explored deterministically. Moreover, it was emphasised that predicted cure rates below 70% did not align with the literature nor UK clinical expectations. As predicted cure rates could fall outside this range in the probabilistic analyses conducted with the MCMs, due to wide confidence intervals reflecting the low number of events for cured and non-cured patients in ECHELON-1, predicted outcomes of MCMs, when explored probabilistically, were considered implausible. The one-knot splines do not explicitly make assumptions about the predicted proportion cured and fit a flexible parametric model to the data without considering subgroups i.e. cured vs. non-cured. Therefore, the one-knot splines were considered the most appropriate approach in the base case, and the MCMs were considered as supportive only. The use of the Kaplan–Meier data followed by adjusted background mortality was highlighted as a useful scenario to demonstrate the impact of using the observed data; as with the MCMs, this was considered supportive of the one-knot splines only.

Figure 30 presents the base case one-knot spline (hazards) curves fit to the A+AVD and ABVD data, including adjusted background mortality with an excess mortality rate of 1.05 for A+AVD and 1.10 for ABVD (Section B.3.3.2.1), and Table 29 presents the predicted outcomes with the observed data from ECHELON-1 and the Stage III or IV subgroup of the RATHL trial: the predicted outcomes closely align with the observed data. For example, at 10 years, the predicted outcomes in the ABVD arm align with outcomes from the RATHL study (e.g. [redacted]% vs. 85.7%, respectively).

Based on the feedback from clinical advisors, scenario analyses were conducted to explore the alternative one-knot spline models, exponential MCMs, Gompertz MCMs, independent standard Gompertz models, and use of the Kaplan–Meier data directly until 89.3 months (median follow-up for OS from ECHELON-1) followed by adjusted background mortality. Clinical advisors indicated that these scenarios represent plausible alternatives and are supportive of the base case assumptions. Exploration of plausible alternatives also aligns with the recommendations in NICE TSD 21 and Palmer *et al* (2023). Section B.3.11.3 presents the results of the scenario analyses; these do not have a material impact on cost-effectiveness results given the similar visual fit and long-term outcomes predicted.

Figure 30: Base case OS curve selections | one-knot spline (hazard) including adjusted background mortality for A+AVD and ABVD

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 29: Observed vs. predicted OS outcomes | one-knot splines (hazards) including adjusted background mortality for A+AVD and ABVD

	ECHELON-1		Predicted		RATHL
	A+AVD	ABVD (6-cycles)	A+AVD	ABVD	ABVD (PET-adapted)
Medians	NR	NR	[redacted]	[redacted]	NR
Means	NA	NA	[redacted]	[redacted]	NA
% surviving at					
1 year	[redacted]	[redacted]	[redacted]	[redacted]	99.2%
2 years	[redacted]	[redacted]	[redacted]	[redacted]	98.2%
3 years	[redacted]	[redacted]	[redacted]	[redacted]	96.5%
4 years	[redacted]	[redacted]	[redacted]	[redacted]	94.4%
5 years	[redacted]	[redacted]	[redacted]	[redacted]	92.2%
6 years	[redacted]	[redacted]	[redacted]	[redacted]	91.3%
7 years	[redacted]	[redacted]	[redacted]	[redacted]	90.3%
8 years	[redacted]	[redacted]	[redacted]	[redacted]	88.7%
9 years	[redacted]	[redacted]	[redacted]	[redacted]	87.0%
10 years	NR	NR	[redacted]	[redacted]	85.7%
20 years	NR	NR	[redacted]	[redacted]	NR
30 years	NR	NR	[redacted]	[redacted]	NR
40 years	NR	NR	[redacted]	[redacted]	NR
50 years	NR	NR	[redacted]	[redacted]	NR
60 years	NR	NR	[redacted]	[redacted]	NR

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; NR, not reported; OS, overall survival; vs., versus.

B.3.3.2.4 Summary of survival extrapolations

Figure 31 presents the base case curve selections for PFS and OS including adjusted background mortality. Independent log-logistic MCMs and independent one-knot splines (hazards) were selected for PFS and OS for both treatments, respectively.

Figure 31: Base case PFS and OS extrapolations

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

B.3.3.3 Safety

B.3.3.3.1 Drug-related treatment-emergent adverse events (TEAEs)

For A+AVD, the base case analysis includes Grade ≥3 drug-related treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients from ECHELON-1. For ABVD-based treatment, although efficacy was assumed equivalent, there are differences in tolerability between the six-cycles and PET-adapted approaches. Therefore, the base case analysis includes Grade ≥3 drug-related TEAEs occurring in ≥5% of patients from ECHELON-1 for six cycles of ABVD, and Grade ≥3 AEs occurring in ≥5% of patients from the RATHL trial to reflect PET-adapted ABVD. These input data were weighted to reflect use of ABVD-based treatment in UK clinical practice (10% and 90%, respectively; Section B.3.2.3.2).

In ECHELON-1, a TEAE was defined as any AE that occurred after administration of the first dose of any study drug and up through 30 days after the last dose of frontline therapy.[34] The assessment of relatedness was attributed to any of the study drugs in the combination regimen. In the RATHL study, Grade ≥3 AEs were only reported for patients in the ITT population (i.e. including Stage IIB) with PET3-negative findings based on a third later scan e.g. these data include patients who were PET2-positive after two cycles and received escBEACOPP but then later became PET3-negative. Therefore, these data were considered an appropriate proxy for Grade ≥3 AEs experienced with PET-adapted ABVD in the Stage III or IV population.

To determine the proportion of patients experiencing each Grade ≥3 drug-related TEAE for A+AVD and ABVD-based treatment, the number of drug-related TEAE events observed in ECHELON-1 or RATHL were divided by the total number of patients from the respective trial (Table 30).

For ABVD via the PET-adapted approach, the RATHL study reported Grade ≥3 AEs for patients treated with ABVD (cycles 1–2), AVD (cycles 3–6), and escBEACOPP (cycles 3–6).[77] Therefore, the proportion of patients experiencing specific Grade ≥3 AEs for PET-adapted ABVD was estimated by taking a weighted average of the proportion of patients who were PET2-negative and PET2-positive in the RATHL study; 100% of patients receive ABVD (cycles 1-2), 83.7% of patients were PET2-negative and receive AVD, and 16.3% were PET2-positive and receive escBEACOPP. Of note, in the RATHL study, patients received BEACOPP-14 or escBEACOPP rather than escBEACOPDac, which is used in UK clinical practice due to its improved safety profile. However, data specifically for patients who escalate from ABVD to escBEACOPDac are unavailable. The AEs reported for BEACOPP-14 in the RATHL study were not considered an appropriate proxy based on clinical feedback highlighting that patients treated with BEACOPP-14 would have a worse toxicity profile than escBEACOPDac. It was advised that the safety profile reported for escBEACOPP may be an appropriate proxy for escBEACOPDac. As escBEACOPDac is only relevant for the small proportion of patients who are PET2-positive (16.3%), this is not anticipated to be a driver of cost-effectiveness results.

Table 31 presents the distribution of Grade ≥3 drug-related TEAEs applied in the base case. These proportions were used to estimate the costs (Section B.3.5.3) and utility decrement (Section B.3.4.6) associated with drug-related Grade ≥3 TEAEs, which were applied as a one-off cost and QALY decrement in the first cycle of the model. The one-off impact was considered appropriate given the short and fixed duration of therapy.

Table 30: Grade ≥3 drug-related TEAEs | ≥5% of patients | ECHELON-1 and RATHL

	ECHELON-1		PET-adapted ABVD (RATHL)			
	A+AVD	ABVD (6 cycles)	ABVD (cycles 1–2)	AVD (cycles 3–6)	escBEACOPP (cycles 3–6)	Weighted PET-adapted ABVD*
N	662	659	1203	457	78	1598
Anaemia, n (%)	46 (6.95%)	18 (2.73%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Febrile neutropenia, n (%)	120 (18.13%)	46 (6.98%)	24 (2%)	10 (2.19%)	52 (66.67%)	41 (2.56%)
Neutropenia, n (%)	344 (51.96%)	242 (36.72%)	694 (57.69%)	269 (58.86%)	20 (25.64%)	922 (57.71%)
Neutrophil count decreased, n (%)	81 (12.24%)	64 (9.71%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3–6), and 16.3% escBEACOPP (cycles 3–6).
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; N, number; TEAE, treatment-emergent adverse events.

Table 31: Grade ≥3 drug-related TEAEs used in the base case | ≥5% of patients | ECHELON-1 and ABVD-based treatment

Event	A+AVD	ABVD-based treatment*
Anaemia, n (%)	46 (6.95%)	2 (0.12%)
Febrile neutropenia, n (%)	120 (18.13%)	41 (2.75%)
Neutropenia, n (%)	344 (51.96%)	854 (56.8%)
Neutrophil count decreased, n (%)	81 (12.24%)	6 (0.43%)

*weighted based on 10% ABVD (six cycles) and 90% ABVD (PET-adapted).
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; N, number; TEAE, treatment-emergent adverse events.

B.3.3.3.2 Second malignancies

As discussed in Section B.2.10.4.4, second malignancies after first-line chemotherapy are the largest cause of mortality in long-term survivors of HL, and patients who relapse following frontline treatment for HL and undergo SCT are at an increased risk of developing second malignancies.[5, 24, 26] In ECHELON-1, second malignancies were reported in numerically fewer patients treated with A+AVD vs. ABVD (33 vs. 39).

The long-term increased risk of death associated with second malignancies is captured in the base case via the application of differential SMRs for A+AVD and ABVD (Section B.3.3.2.1). However, as well as a mortality impact, second malignancies are associated with a significant HRQoL and cost burden. The HRQoL and cost impact of second malignancies is not well documented in the literature. Therefore, the HRQoL and cost impact was excluded in the base case analysis and explored in a scenario analysis only. As such, the base case may represent a conservative estimation of the cost-effectiveness of A+AVD.

In the scenario analysis, the proportions of patients with second malignancies were sourced from ECHELON-1 (for A+AVD and ABVD [six cycles]) and the RATHL study (for PET-adapted ABVD). These data were weighted in alignment with use of ABVD-based treatment in UK clinical practice (10% and 90%, respectively; Section B.3.2.3.2).

Second malignancies were only reported in the RATHL study for patients in the ITT population (i.e. including Stage IIB). However, as safety is a key factor in distinguishing ABVD (six cycles) and PET-adapted ABVD in UK clinical practice, these data were used in the base case as an approximation for second malignancies with PET-adapted ABVD in the Stage III or IV population. The proportion of patients with a second malignancy was determined by dividing the number of second malignancies observed in ECHELON-1 or RATHL by the total number of patients (Table 32).

The RATHL study reports second malignancies among patients receiving AVD and escBEACOPP as part of the PET-adapted ABVD regimen. As for AEs, the proportion of patients with a second malignancy for PET-adapted ABVD, as a whole, was estimated by weighting these data by the proportion of patients who are expected to be PET2-negative and PET2-positive (83.7% and 16.3%, respectively).

Table 32 presents the distribution of second malignancies applied in the scenario analysis. These proportions were used to estimate the cost (Section B.3.5.4.2) and utility decrement (Section B.3.4.5) associated with second malignancies, which were applied as a one-off cost

and QALY decrement in the first cycle of the model. The one-off impact was considered appropriate given the exploratory nature of the scenario analysis.

Table 32: Second malignancies | ≥5% of patients | ECHELON-1 and RATHL

	A+AVD	ABVD (6 cycles)	PET-adapted ABVD*	ABVD-based treatment**
N	662	659	416	441
Second malignancies	33 (4.98%)	39 (5.92%)	19 (4.58%)	21 (4.78%)

*weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3-6), and 16.3% escBEACOPP (cycles 3-6).
**weighted based on 10% ABVD (six cycles) and 90% PET-adapted ABVD.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; N, number; TEAE, treatment-emergent adverse events.

B.3.4 Measurement and valuation of health effects

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

In ECHELON-1, PROs were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30), the Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnea 10 questionnaire, the EQ-5D-3L questionnaire and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) neurotoxicity subscale. The EQ-5D-3L tariff from Dolan *et al* was applied to individual responses to generate EQ-5D-3L index scores.[201] This tariff uses a time-trade-off (TTO) methodology to elicit utility values from the general population.

In line with the NICE reference case, the EQ-5D-3L data were analysed for use in the CEM.[175, 202] HRQoL analyses are based on the 11 March 2023 data cut. In ECHELON-1, EQ-5D-3L data were collected at screening, day 1 of every treatment cycle, at the end of treatment (30 [±7] days after last dose of frontline therapy) and during post-treatment follow-up every 3 months until 3 years after the last dose of frontline therapy or development of confirmed progressive disease, whichever occurs first.

Of the 1,334 patients in ECHELON-1, 1,328 patients reported EQ-5D-3L TTO scores and of these patients, 1,307 patients recorded a baseline utility score. To be eligible for inclusion in the analysis, patients were required to have a baseline record and at least one post-baseline assessment, so a further 28 patients were excluded due to only reporting baseline EQ-5D-3L utility scores with no subsequent follow-up measurements. A further eight patients were excluded as all their HRQoL assessments occurred after censoring for disease progression, and three patients with either disease Stage II (one patient was excluded because of protocol violation) or missing information on disease stage were also excluded, leaving a total of 1,268 patients (16,557 post-baseline records) in the analysis. Specifically, 16,040 (for 1,267 patients) and 517 (for 158 patients) post-baseline records were available to inform the progression-free (PF) and progressive disease (PD) health states, respectively. The median number of post-baseline HRQoL assessments per patient was 15 (range: 1–21) and 2 (range: 1–12) for PF and PD health states, respectively.

The observed mean baseline utility score was 0.764 (SD: 0.245) for all patients; 0.765 (SD: 0.247) and 0.763 (SD: 0.242) for A+AVD and ABVD arms, respectively. Health state utilities were estimated using mixed-effects repeated-measures linear regression models fitted to the EQ-5D-3L data from ECHELON-1 for the 1,268 patients previously described. All factors included in the regression model were added as fixed-effects, and a random-effect term for patient ID was included to account for the correlation of utility scores due to multiple observations recorded for any given patient.

Two regression models were fitted: (1) a “saturated model” and (2) a “reduced model”. The saturated model included covariables for all factors considered to be prognostic of HRQoL outcomes. The reduced model was determined based on stepwise selection methods using backward elimination to identify an alternative model; this is a systematic approach which starts with the saturated model (i.e. inclusion of a complete set of factors considered to be potential predictors of HRQoL) and at each step gradually eliminated variables, based on the

least significant variable as assessed by the p-values from the regression model, to identify a refined model that best explains the data and which contains the variables considered to be statistically significant predictors of HRQoL. In the reduced model, all remaining predictors are associated with a p-value of less than 0.05 (p-values for fixed-effect terms are calculated from an F-test based on Satterthwaite's approximation). There are limitations associated with stepwise selection procedures, and specifically, backward elimination may be challenging when there is a large number of candidate variables. However, this approach has been considered as an exploratory analysis and may be useful to help identify an alternative model based on retaining important predictors.

Twelve factors were identified as potentially prognostic and predictive of HRQoL outcomes, and considered for inclusion in the saturated model:

- Treatment with A+AVD vs. ABVD
- On-treatment vs. off-treatment
- Baseline age
- Gender (male vs. female)
- Baseline utility score
- Receipt of primary G-CSF (yes vs. no)
- IPS risk factor (0 vs. 1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6 vs. 7)
- ECOG performance score (0 vs. 1 vs. 2)
- Disease stage (III vs. IV)
- B symptoms (present vs. absent)
- Grade 3+ AE (yes vs. no)
- Progression status (progressed disease vs. progression-free)

These factors were identified based on a review of relevant NICE appraisals (TA874, TA641, TA641, TA478, TA524 and TA577), hand-searching the literature, and clinical feedback.[39–42, 170, 173] Factors were further refined based on a correlation assessment (Appendix N.1.6), conducted to explore the multicollinearity between factors measured at baseline. Following this research, treatment arm was excluded based on feedback from UK clinical experts and anticipated correlation with Grade ≥3 AEs, and ECOG performance score, disease stage, and B symptoms were excluded based on mild statistical correlation with IPS risk factor. However, there was a preference from UK clinical experts to include IPS in the model. Therefore, the final saturated model included eight factors.

Table 33 presents a summary of the output from the saturated model. Five factors were associated with a statistically significant impact on HRQoL ($p<0.05$), including baseline utility, treatment status, age, Grade 3/4 AEs and progression status.

Table 34 presents a summary of the output from the reduced model. Model coefficients after applying stepwise selection methods aligned with those estimated in the saturated model.

Table 33: Output from the saturated regression model

Factor	Estimate	SE	t-value	p-value
(Intercept)	0.7399	0.0251	29.4938	<0.0001
Treatment status (ref=Off treatment) On treatment	−0.0805	0.0028	−29.1613	<0.0001
Age (years)	−0.0028	0.0003	−10.3958	<0.0001
Sex (ref=Female) Male	0.0087	0.0089	0.9817	0.3264
Baseline utility score	0.2846	0.0172	16.5523	<0.0001
Receipt of G-CSF (ref=No) Yes	−0.0107	0.0138	−0.7781	0.4367
IPS risk factors (ref=0)				(overall: 0.2834)
1	0.0051	0.0222	0.2298	0.8183
2	0.0065	0.0219	0.2987	0.7652
3	0.0089	0.0222	0.4025	0.6874
4	0.0164	0.0235	0.6980	0.4853
5	0.0407	0.0264	1.5417	0.1234
6	0.0826	0.0405	2.0397	0.0416
7	0.0165	0.0687	0.2398	0.8105
Grade3/4 AE (ref=No) Yes	−0.0268	0.0044	−6.1037	<0.0001
Progression status (ref=PF) PD	−0.0698	0.0089	−7.8853	<0.0001

Bold denotes statistically significant p-value using 5% significance level.
Abbreviations: AE, adverse event; G-CSF, granulocyte colony stimulating factor; IPS, International Prognostic Score; PD, progressive disease; PF, progression-free; ref, reference; SE, standard error.

Table 34: Output from the stepwise selected reduced regression model

	Estimate	SE	t-value	p-value
(Intercept)	0.7527	0.0170	44.2875	<0.0001
Treatment status (ref=Off treatment) On treatment	−0.0803	0.0028	−29.1176	<0.0001
Age (years)	−0.0026	0.0003	−10.1001	<0.0001
Baseline utility score	0.2775	0.0167	16.5743	<0.0001
Grade3/4 AE (ref=No) Yes	−0.0269	0.0044	−6.1158	<0.0001
Progression status (ref=PF) PD	−0.0691	0.0088	−7.8043	<0.0001

Bold denotes statistically significant p-value using 5% significance level.
Abbreviations: AE, adverse event; PD, progressive disease; PF, progression-free; ref, reference; SE, standard error.

Table 35 presents the mean health state utility values based on the mean covariate values (for continuous covariates) from ECHELON-1 for both the saturated and reduced models. Table 36 presents the baseline characteristics informing the utility regression models informed by ECHELON-1. The saturated model was applied in the base case to ensure that all identified prognostic factors were accounted for in the estimation. A scenario analysis was conducted to explore the impact of applying the reduced model; this had a minimal impact on cost-effectiveness results.

Table 35: Predicted health state utility values from the HRQoL regression models

Health state[a]	Mean	SE	95% CIL	95% CIU
Saturated model				
On treatment, PF	0.783	0.020	0.744	0.822
Off treatment, PF	0.864	0.020	0.825	0.903
PD[b]	0.794	0.022	0.752	0.836
Grade ≥3 AEs	−0.027	0.004	−0.029	−0.025
Age	−0.003	0.0003	−0.0032	−0.0025
Reduced model				
On treatment, PF	0.782	0.005	0.773	0.790
Off treatment, PF	0.862	0.004	0.854	0.870
PD[b]	0.793	0.009	0.775	0.811
Grade ≥3 AEs	−0.027	0.004	−0.030	−0.024
Age	−0.003	0.0003	−0.0027	−0.0026

[a]mean covariate values (for continuous factors), median number of IPS risk factors, and the category which included the greatest proportion of patients (for dichotomous factors) were used to predict health state utility values (Sex=Male; Receipt of G-CSF=No; Grade ≥3 AE=No)
[b]set as off treatment
Abbreviations: AE, adverse event; CIL, confidence interval lower; CIU, confidence interval upper; PD, progressive disease; PF, progression-free; SE, standard error

Table 36: Baseline characteristics informing HRQoL regression models

Variable	Value (95% CI)	Source
Age	39.53 (38.68–40.39)	ECHELON-1 baseline characteristics
Gender	58.17% (55.51–60.81%)	
Baseline utility score	0.76 (0.60–0.90)	
Receipt of G-CSF (ref: no)	9.45% (7.68–11.37%)	
IPS risk factor 0	4.2% (3.65–4.71%)	
IPS risk factor 1	17.02% (17.11–16.94%)	
IPS risk factor 2	27.59% (28.49–26.69%)	
IPS risk factor 3	25.79% (26.53–25.03%)	
IPS risk factor 4	15.52% (15.5–15.54%)	
IPS risk factor 5	7.87% (7.4–8.29%)	
IPS risk factor 6	1.65% (1.19–2.11%)	
IPS risk factor 7	0.37% (0.14–0.67%)	

Abbreviations: CI, confidence interval; G-CSF, granulocyte colony stimulating factor; HRQoL, health-related quality of life; IPS, International Prognostic Score.

B.3.4.2 Mapping

The 3-level UK tariff from Dolan *et al* (1997) was applied to individual responses to generate EQ-5D-3L index scores.[201] Therefore, there was no need to apply mapping algorithms.

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

An SLR was conducted, with searches run 29th July 2016 and updated 23rd May 2018, 22nd June 2022, and 27th December 2023, to identify HRQoL data in patients with newly-diagnosed advanced HL (defined as Stage IIb–IV in the SLR) from the published literature. The broader definition of advanced CD30+ HL (i.e. Stage IIb–IV) was considered given the expected paucity in data. A complete description of the search methodology, search strategies, a PRISMA flow diagram, and detailed results are presented in Appendix H.

No studies were identified reporting utility values in patients with untreated Stage IIb-IV CD30+ HL from a UK perspective. Therefore, the literature identified in this SLR does not inform the CEM inputs.

From the 28 studies identified by the SLR, only two reported EQ-5D: Brandt *et al* (2010) and Ramchandren *et al* (2019) from a German and US perspective, respectively.[79, 203] Table 37 summarises these study characteristics.

Table 37: Studies assessing EQ-5D in patients with advanced HL

Study, year	Study design	Patient population	Patient population, N	Age	Measures	Utilities
Patients from Germany						
Brandt *et al* (2010)[79]	Cohort, cross-sectional	Previously untreated patients treated with high dose chemotherapy followed by transplant (HDCT+PBSCT) vs. previously untreated patients treated with conventional chemotherapy. Patients had to be in complete remission. Stage II–IV.	N=98 HCT+PBSCT=37 Conventional chemotherapy=61	Median age: • HDCT+PBSCT=46 • Conventional chemotherapy=41	• EORTC QLQ-C30 • EQ-5D-3L VAS • EQ-5D-3L index (German time trade off value set)	Mean utility: • HDCT+PBSCT=0.88 • Conventional chemotherapy=0.92
Patients from the US						
Ramchandren *et al* (2019)[203]	NR	Adults with untreated, advanced-stage classical HL, with ECOG performance status of 0–1. Nivolumab followed by nivolumab + doxorubicin, vinblastine and dacarbazine	N=51	Median age: 37	• EQ-5D VAS • EQ-5D index (unknown which version)	NR

Abbreviations: EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, European quality of life 5 dimensions 3 level; EQ-VAS, EQ-visual analogous scale; HDCT, high-dose chemotherapy; HL, Hodgkin Lymphoma; HRQoL, health-related quality of life; N, number; NR, not reported; PBSCT, peripheral blood stem cell transplant; United States.

Brandt *et al* (2010) investigated the HRQoL of long-term survivors with Hodgkin lymphoma who received high-dose chemotherapy (HDCT) followed by peripheral blood stem cell transplantation (PBSCT). HRQoL of this group was compared with HRQoL of patients who were treated with conventional chemotherapy and with HRQoL of the healthy German population. The EORTC QLQ-C30 and the EQ-5D, including the visual analogue scale (VAS) were applied. The EQ-5D was reported to be 0.88 for the HDCT group and 0.92 for the conventional chemotherapy group.

Ramchandren *et al* (2019) is an abstract only and reports HRQoL results for patients with newly-diagnosed disease included in the CheckMate 205 trial (Cohort D, N=51), as assessed using the EQ-5D-3L and EQ-VAS. In this trial, patients received one cycle of nivolumab monotherapy followed by six cycles of nivolumab plus doxorubicin, vinblastine and dacarbazine (N-AVD). Mean EQ-VAS scores increased from baseline both during therapy (69–77 vs. 66 at baseline) and during follow-up (78–87). Consistent with this, the proportion of patients reporting some/extreme problems on the five EQ-5D-3L domains generally increased during combination therapy and returned to baseline or lower levels during follow-up after the end of therapy. Whilst the EQ-5D-3L results were commented on, these were not presented within the abstract.

Overall, the SLR indicated a paucity of HRQoL data in patients with advanced HL and, in particular, studies assessing the longitudinal trajectory of HRQoL from initial diagnosis to long-term survivorship according to different treatments.

B.3.4.4 Adverse reactions

In the base case, the impact of Grade ≥3 drug-related TEAEs on HRQoL was captured through the utility regression model fit to the ECHELON-1 data (Section B.3.4.6).

The regression equation estimates a utility decrement of −0.0269 per Grade ≥3 drug-related TEAE event. This utility decrement was multiplied by the proportion of each Grade ≥3 drug-related TEAE (Table 30) and the mean duration of each drug-related TEAE (Table 38), equating to a QALY loss of −0.0007 and −0.0005 for A+AVD and ABVD, respectively, applied in the first treatment cycle. The one-off impact was considered appropriate given the short and fixed duration of therapy. The mean durations of each drug-related TEAE were based on the average of values reported in TA641 and TA874.

Scenario analyses were conducted to explore the impact of AE utility decrements from the literature and excluding the impact of AE utility decrements. In the literature-based scenario, utility decrements were based on the average of values reported in TA641 and TA874 (Table 38). The resulting one-off QALY losses were −0.0025 and −0.0016 for A+AVD and ABVD, respectively, applied in the first treatment cycle. The QALY losses predicted from the literature are greater than those predicted by the utility regression analysis fit to the ECHELON-1 data. The ECHELON-1 data reflect the experience of patients with previously untreated HL, and therefore these data are used in the base case to align with the NICE reference case.[175]

Table 38: Drug-related TEAE utility decrements and durations from the literature

Event	Utility decrement	Duration (days)	Sources[40, 170]
Anemia	−0.17 *(average calculated from -0.09 and -0.25 reported in TA641 and TA874, respectively)*	11.60 *(average calculated from 7.2 and 16 days reported in TA641 and TA874, respectively)*	NICE TA641 and NICE TA874
Febrile neutropenia	−0.12 *(average calculated from -0.09 and -0.15 reported in TA641 and TA874, respectively)*	6.40 *(average calculated from 6.8 and 6 days reported in TA641 and TA874, respectively)*	
Neutropenia	−0.09 *(based on -0.09 reported in TA641)*	13.05 *(average calculated from 11.1 and 15 days reported in TA641 and TA874, respectively)*	
Neutrophil count decreased	−0.05 *(average calculated from 0 and -0.09 reported in TA641 and TA874, respectively)*	7.50 *(average calculated from 0 and 15 days reported in TA641 and TA874, respectively)*	

Abbreviations: TA, technology appraisal; TEAE, treatment-emergent adverse events

B.3.4.5 Second malignancies

Patients who develop a second malignancy are likely to suffer a significant HRQoL impact which likely varies across the different malignancy types. As described in Section B.3.3.3.2, the impact of second malignancies on HRQoL and costs is explored in a scenario analysis only, which is described below.

As identified in the economic SLR, Vijenthira *et al* (2020; Section B.3.1) explored the impact of second malignancies on HRQoL. In this study, Canadian clinical experts advise that patients with a second malignancy are likely to have a utility value of approximately 0.5 (0.4–0.6). This utility value is applied from the development of the second malignancy for the remaining time horizon. In the scenario analysis presented in this submission, the utility decrement associated with second malignancies is calculated as the difference between the average utility across all model cycles for the 'pre-progression, off-treatment' health state (0.76) estimated from the ECHELON-1 data (Section B.3.4.1) and 0.5 i.e. −0.26. This approach accounts for the average utility patients are experiencing in the health state prior to developing a second malignancy. This utility decrement is multiplied by the proportion of patients diagnosed with second malignancies (Section B.3.3.3.2) and the mean duration of each second malignancy (due to lack of data this was conservatively assumed to be 2 years), equating to a QALY loss of −0.0260 and −0.0308 for A+AVD and ABVD, respectively, applied in the first treatment cycle. The one-off impact was considered appropriate given the exploratory nature of the scenario analysis.

In Vijenthira *et al* (2020), the utility impact of a second malignancy was applied for the entire time horizon. In this submission, a more conservative assumption of 2 years was applied to reflect the improvement of patients' HRQoL with treatment for the second malignancy.

However, this is a highly uncertain parameter and supports the inclusion of this as a scenario.

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 39 summarises the utility data applied in the base case. The EQ-5D-3L collected in ECHELON-1 informs the progression-free and progressed disease health state utilities, and the Grade ≥3 AE and age decrements. In line with the NICE reference case, a multiplier is applied from Alava-Hernandez *et al* (2022) to all utilities to adjust for increasing age across the model time horizon.[171] Although an age decrement has been estimated, and is applied, as part of the HRQoL regression equations, this reflects aging throughout the ECHELON-1 trial period only. Therefore, to accurately model declining HRQoL due to age across a lifetime horizon, the multipliers from the literature are applied.

It is assumed that patients remaining in the progression-free health state after the cure time point (24 months following treatment discontinuation) experience a utility aligned with the general population, this was considered reasonable based on:

- Figure 32 presents the mean EQ-5D-3L scores over time for the ITT population from ECHELON-1 for patients in the progression-free health state (based on 1,268 patients, pooled across treatment arms). These data demonstrate that patients who are progression-free are associated with a lower utility whilst receiving treatment with either A+AVD or ABVD compared to the general population, which improves following treatment discontinuation.

- These data have been plotted alongside the age- and gender-adjusted UK general population utility values reported in Alava-Hernandez *et al* (2022) in Figure 33.[171] Following feedback from the Evidence Assessment Group at the Decision Problem meeting, Figure 34 compares the data with the age- and gender-adjusted UK general population utility values specifically for 24−36 months (y-axis between 0.8 and 0.9). Following discontinuation of treatment with A+AVD or ABVD, utility values align with the UK general population. This is maintained from treatment discontinuation throughout the HRQoL follow-up period. The alignment across utilities is further demonstrated in Figure 34. Therefore, assuming that patients who are progression-free experience the same utility value as the general population from 24 months post treatment discontinuation is a conservative assumption, as the ECHELON-1 data indicates that this improvement may be earlier.

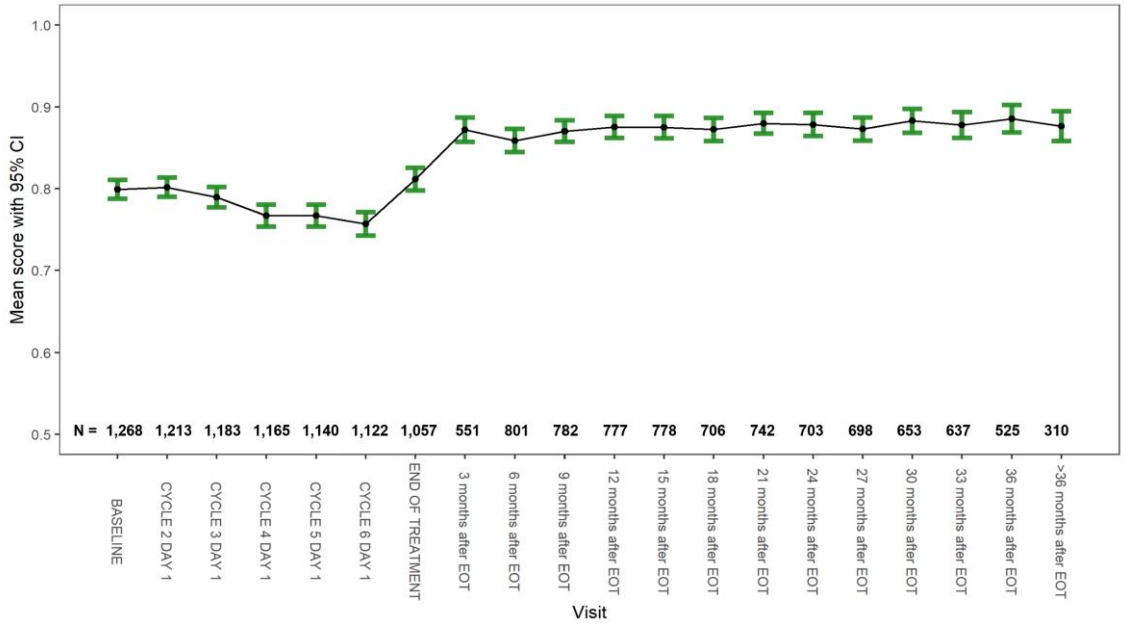
- Only one study was identified in the HRQoL SLR which reports utilities measured by the EQ-5D (Brandt *et al* [2010]; Section B.3.4.3).[79] This study reported a utility of 0.92 for patients in complete remission treated with conventional chemotherapy in the frontline setting using the German value set. This aligns with the general population utility values and supports the assumption of general population utility values for patients who are cured.

- The approach of assuming general population utility for patients who are cured is consistent with NICE TA874 and later line lymphoma appraisals.[170, 172, 173] Scenario analyses explore alternative cure timepoints where the utility value for patients who

are cured does not return to the general population utility values until 36 and 60 months after treatment discontinuation, respectively. This has a minimal impact on the cost-effectiveness results.

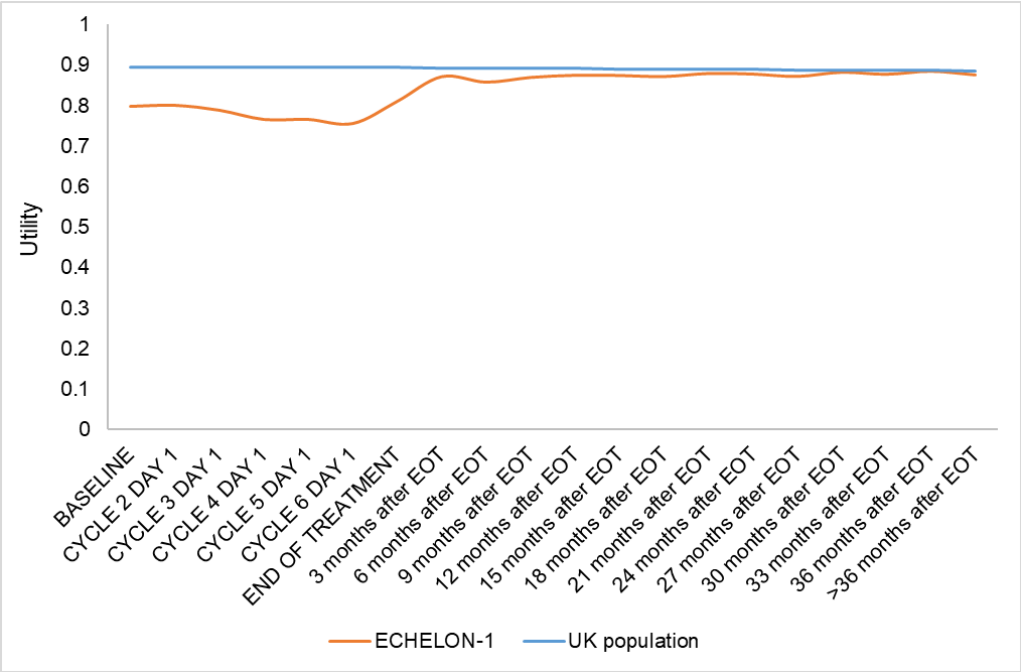
The analysis models general population utility values from the cure point (24 months after treatment discontinuation) for patients who remain progression-free; this is not a sudden change in utility as these patients are already experiencing a utility close to the general population (as estimated through the HRQoL regression model); in the base case, the utility increases from 0.85 to 0.89. This further validates that the observed ECHELON-1 data for patients who are pre-progression and off-treatment are aligned with the general population values. Section B.3.2.2 provides further rationale supporting the 24-month timepoint as the point of cure.

Figure 32: Mean EQ-5D-3L UK TTO scores over time in the progression-free health state | ECHELON-1



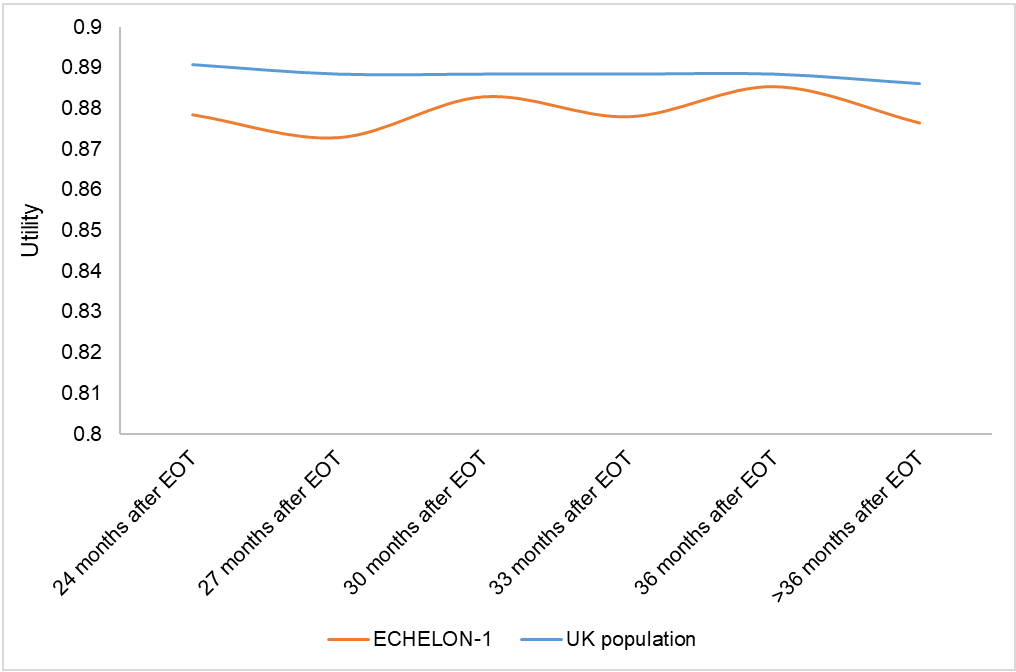
Abbreviations: CI, confidence interval; EOT, end of treatment; EQ-5D-3L, European Quality of Life 5-Dimension Three Level version; N, number of patients; TTO, time trade-off; UK, United Kingdom.

Figure 33: A comparison of the progression-free utilities observed with UK population utilities from baseline to >36 months after EOT | ECHELON-1



Abbreviations: EOT, end of treatment; EQ-5D-3L, European Quality of Life 5-Dimension Three Level version; UK, United Kingdom

Figure 34: A comparison of the progression-free utilities observed with UK population utilities between 24–36 months | ECHELON-1



Abbreviations: EOT, end of treatment; EQ-5D-3L, European Quality of Life 5-Dimension Three Level version; UK, United Kingdom.

Table 39: Summary of utility values for the base case cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Progression-free, on treatment	0.781	0.756, 0.805	Section B.3.4.1	Based on the saturated regression model fit to the EQ-5D-3L data collected in ECHELON-1.
Progression-free, off treatment	0.861	0.841, 0.881		
Progressed disease	0.791	0.755, 0.828		
Grade 3+ AEs	−0.0268	−0.0288, −0.0249	Section B.3.4.1 and B.3.4.4	Grade 3+ AEs were included in the regression model fit to the EQ-5D-3L data collected in ECHELON-1. Therefore, the decrement applied in the base case reflects the ECHELON-1 utility analysis.
Age	−0.0028	−0.0032, −0.0025	Section B.3.4.1	Age was included in the regression model fit to the EQ-5D-3L data collected in ECHELON-1. Therefore, the decrement applied in the base case reflects the ECHELON-1 utility analysis.
Cured (remaining in the progression-free health state for 24 months after treatment discontinuation)	Age 30 0.923 (males) 0.904 (females) Age 50 0.879 (males) 0.859 (females) Age 70 0.817 (males) 0.781 (females) Age 90 0.738 (males) 0.672 (females)	Uncertainty not reported. +/−10% assumed.	Section B.3.4.6	A linear relationship has been assumed between the time points presented in Alava-Hernandez *et al* (2022). The utilities are then weighted based on the proportion of males and females in the CEM. The cure timepoint is supported by the ECHELON-1 clinical data, UK clinical expert feedback, and previous NICE appraisals in lymphoma. Alava-Hernandez *et al* (2022) report on the latest EQ-5D-3L collected in the UK setting, aligning with the NICE reference case.

Abbreviations: EQ-5D-3L, European Quality of Life 5-Dimension Three Level version.

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

An SLR was conducted, with searches run on the 29th July 2016 and updated on the 23rd May 2018, 22nd June 2022 and 27th December 2023, to identify relevant published evidence of the economic burden of current first-line treatments in the management of newly-diagnosed patients with advanced HL (defined as Stage IIb–IV in the SLR). The broader definition of advanced CD30+ HL (i.e. Stage IIb–IV) was considered given the expected paucity in data. A complete description of the search methodology, search strategies, a PRISMA flow diagram, and detailed results are presented in Appendix I.

No studies were identified reporting cost and resource use values in patients with untreated CD30+ Stage IIB-IV HL from a UK perspective. Therefore, the literature identified by this SLR has not been used to inform the model inputs.

B.3.5.1 Intervention and comparators' costs and resource use

Costs reflect the latest available source i.e. eMIT accessed February 2024, British National Formulary (BNF) accessed February 2024, NHS Reference Costs 2021/22, and the PSSRU 2022.[178–180, 182] Costs collected from other sources are inflated to 2021/22 using inflation indices in the PSSRU, where appropriate.

B.3.5.1.1 Acquisition costs

Drug acquisition costs are calculated based on dosing regimens, duration of therapy, RDI and unit costs.

The A+AVD regimen comprises 1.2 mg/kg of brentuximab vedotin, 25 mg/m^2 of doxorubicin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine. Brentuximab vedotin is administered as an IV infusion with AVD, which is also administered as an IV infusion on days 1 and 15 of each 28-day treatment cycle for up to six cycles. This dosing regimen aligns with the SmPC for A+AVD.[43] In ECHELON-1, patients were treated with up to six treatment cycles of A+AVD. The mean number of treatment cycles observed in ECHELON-1 is applied for each of the individual components of the combination therapy (Table 40).

As described in Section B.3.2.3.2, ABVD-based treatment was costed as a weighted average of ABVD (six cycles; 10%) and PET-adapted ABVD (90%). The ABVD (six cycles) regimen comprises 25 mg/m^2 of doxorubicin, 10 U/m^2 of bleomycin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine – ABVD is administered as an IV infusion on days 1 and 15 of each 28-day treatment cycle for up to six cycles. The PET-adapted ABVD approach consists of:

- ABVD (25 mg/m^2 of doxorubicin, 10 U/m^2 of bleomycin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine) all administered as an IV infusion on days 1 and 15 of each 28-day treatment cycle for up to two cycles.[190–196]
- A PET scan after two cycles
- AVD for patients who are PET2-negative (25 mg/m^2 of doxorubicin, 10 U/m^2 of bleomycin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine) all administered as an IV infusion on days 1 and 15 of each 28-day treatment cycle from the third cycle up to six cycles i.e. a maximum of four cycles.[77, 88, 151] As detailed in

Section B.3.2.3.2, it is assumed that 83.7% of patients receiving PET-adapted ABVD will have PET2-negative findings and receive AVD.

- escBEACOPDac for patients who are PET2-positive (40 mg/m^2 of prednisolone days 1-14, 35mg/m2 doxorubicin day 1, 1,250 mg/m^2 cyclophosphamide day 1, 200 mg/m^2 etoposide days 1–3, 250 mg/m^2 dacarbazine days 2–3, 1.4 mg/m^2 vincristine day 8 and 10U/m^2 of bleomycin day 8) all administered as an IV infusion, except for prednisolone, in each 21-day cycle from the third cycle up to six cycles i.e. a maximum of four cycles.[184–189] As detailed in Section B.3.2.3.2, it is assumed that 16.3% of patients receiving PET-adapted ABVD will have PET2-positive findings as per the RATHL trial and receive escBEACOPDac.

The dosing regimen for ABVD (six cycles) aligns with ECHELON-1 and NHS protocols.[184–196] The dosing for PET-adapted ABVD aligns with NHS protocols (Section B.1.3.4).The mean number of treatment cycles observed in ECHELON-1 is applied for each of the individual components for ABVD (six cycles) (Table 40). In the PET-adapted approach, it is assumed that all patients receive the initial two cycles of ABVD followed by either 3.7 cycles of AVD or 3.7 cycles of escBEACOPDac, dependent of the outcome of the PET2 scan. This sums to 5.7 cycles and aligns with the non-bleomycin regimens in the ABVD arm of ECHELON-1.

Drug doses were calculated using the recommended dose multiplied by the mean RDI and assuming no vial sharing. Including RDI in the base case captures the ratio of actual vs. planned drug delivery. RDI is included in the base case to reflect the actual dose received by patients experiencing the observed outcomes in ECHELON-1. The mean RDI observed in ECHELON-1 is assumed for A+AVD, and for ABVD and AVD components of the PET-adapted ABVD approach. The median RDI reported in Borchmann *et al* (2017) is assumed for escBEACOPDac.[204] No vial sharing is assumed as patient numbers in each centre would likely be too low to allow for any vial sharing; this assumption is in line with all previous brentuximab vedotin NICE submissions.[39–42]

In the base case, the method of moments approach assumes a log-normal distribution for body weight and BSA – with mean values and standard deviation obtained from ECHELON-1 (Table 21) – and calculates the proportion of patients requiring each possible number of vials based upon the log-normal distributions. This approach is the most accurate method of accounting for wastage when assuming that no vial sharing occurs. Where multiple costs are available across different formulations and pack sizes, the CEM uses the minimum cost per vial size. A scenario analysis was conducted which explores the impact of 100% RDI for both treatments.

Table 40 presents the number of administrations required per cycle, the mean number of treatment cycles and the RDI inputs.

Table 40: Duration of therapy and dose intensity

	Number of administrations per cycle	Mean number of treatment cycles	RDI
A+AVD			
Brentuximab vedotin	2	5.50 (5.41–5.59)	94.01% (93.06–94.89%)
Doxorubicin	2	5.60 (5.50–5.70)	99.11% (98.66–99.47%)
Vinblastine	2	5.60 (5.51–5.69)	96.56% (95.73–97.30%)
Dacarbazine	2	5.60 (5.52–5.69)	99.12% (98.77–99.41%)
ABVD (six cycles)			
Doxorubicin	2	5.70 (5.63–5.77)	99.54% (99.17–99.80%)
Bleomycin	2	5.40 (5.31–5.50)	93.51% (92.20–94.71%)
Vinblastine	2	5.70 (5.63–5.77)	96.91% (96.13–97.61%)
Dacarbazine	2	5.70 (5.63–5.77)	98.93% (98.42–99.34%)
PET-adapted ABVD			
All patients			
Doxorubicin	2	2.00 (1.91–2.00)	99.54% (99.17–99.80%)
Bleomycin	2	2.00 (1.93–2.00)	93.51% (92.20–94.71%)
Vinblastine	2	2.00 (1.92–2.00)	96.91% (96.13–97.61%)
Dacarbazine	2	2.00 (1.93–2.00)	98.93% (98.42–99.34%)
PET2-negative			
Doxorubicin	2	3.70 (3.61–3.80)	99.54% (99.17–99.80%)
Vinblastine	2	3.70 (3.62–3.78)	96.91% (96.13–97.61%)
Dacarbazine	2	3.70 (3.63–3.77)	98.93% (98.42–99.34%)
PET2-positive			
Bleomycin	1	3.70 (3.61–3.80)	97.00% (96.45–97.50%)
Etoposide	3	3.70 (3.61–3.80)	97.00% (96.45– 97.50%)
Doxorubicin	1	3.70 (3.61–3.80)	97.00% (96.45–97.50%)
Cyclophosphamide	1	3.70 (3.61–3.80)	97.00% (96.45–97.50%)
Vincristine	1	3.70 (3.61–3.80)	97.00% (96.45–97.50%)
Dacarbazine	2	3.70 (3.61–3.80)	97.00% (96.45–97.50%)
Prednisone	14	3.70 (3.61–3.80)	97.00% (96.45–97.50%)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; RDI, relative dose intensity.

Table 41 presents the unit costs for the individual components of the A+AVD and ABVD-based treatment. These were sourced from eMIT where available, otherwise the BNF. A confidential PAS approved by the Department of Health for brentuximab vedotin is already in place for the current indications. Under the PAS, a simple discount of [redacted] off the list price is applied.

The total acquisition cost per patient is then calculated by multiplying the distribution of vial sizes (as estimated from the methods of moments approach) by the relevant costs per vial and the number of administrations per treatment cycle. The analysis applies the cost per dose based on the administration schedule across the relevant treatment cycles.

Table 41: Drug acquisition costs

Drug	Size per unit (mg)/units	Units per pack	Total size (mg)	Price per pack	Total acquisition cost per patient based on mean treatment duration	Source[178, 179]
A+AVD						
Brentuximab vedotin	50	1	50	£2,500 (list price) [redacted] (with PAS)	£61,793 (list price) [redacted] (with PAS)	BNF; 50mg powder for solution for infusion
Doxorubicin	200	1	200	£17.18		eMIT. 200mg/100ml solution for infusion vials/Pack size 1
Vinblastine	10	1	10	£17.00		BNF; 1mg/ml solution for injection – 10mg/10ml
Dacarbazine	500 1000	1 1	500 1000	£37.50 £70.00		BNF. 500mg powder for solution for infusion BNF; 1g powder for solution for infusion
ABVD-based treatment						
Doxorubicin	200	1	200	£17.18	£1,478*	eMIT. 200mg/100ml solution for infusion vials/Pack size 1
Bleomycin	15000	1	15000	£19.06		BNF; 15,000-unit powder for solution for injection vials
Vinblastine	10	1	10	£17.00		BNF; 1mg/ml solution for injection – 10mg/10ml
Dacarbazine	500 1000	1 1	500 1000	£37.50 £70.00		BNF. 500mg powder for solution for infusion BNF; 1g powder for solution for infusion
Etoposide	100	1	100	£11.50		BNF. 100mg/5ml concentrate for solution for infusion vials
Cyclophosphamide	500 1000	1 1	500 1000	£8.61 £12.96		eMIT. 500mg powder for solution for injection vials/Pack size 1. eMIT. 1g powder for solution for injection vials/Pack size 1
Vincristine	1 2	5 5	1 2	£25.38 £33.89		eMIT. Vincristine 1mg/1ml solution for injection vials/Pack size 5

Drug	Size per unit (mg)/units	Units per pack	Total size (mg)	Price per pack	Total acquisition cost per patient based on mean treatment duration	Source[178, 179]
						eMIT. Vincristine 2mg/2mL solution for injection vials/Pack size 5
Prednisone	5 10 20 25 30	28 28 28 56 28	5 10 20 25 30	£0.83 £9.70 £19.46 £42.41 £29.12		BNF. 5mg, 10mg, 20mg, 25mg, and 30mg tablets

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BNF, British National Formulary; eMIT, electronic marketing information tool; mg, milligram; PAS, patient access scheme
*weighted based on 10% ABVD (six cycles) and 90% PET-adapted ABVD.

B.3.5.1.2 Administration costs

A+AVD and ABVD-based treatment are administered in an outpatient setting. This reflects available NHS protocols for ABVD (both via six cycles and the PET-adapted approach) and escBEACOPDac administration, and was validated by UK clinical experts.[190–196]

The relevant NHS Reference Costs HRG codes are based on the 2020/21 National Tariff Payment System (Annex B) which defined each of the relevant NHS Reference Costs based on nurse and chair time, as well as first vs. subsequent attendance in a chemotherapy cycle (Table 42).[180, 205] Feedback from UK clinical experts highlighted that SB13Z most closely reflected the nurse and chair time required in the administration of A+AVD and ABVD. Therefore, SB13Z is assumed for the first IV administration in each treatment cycle (£381.05). SB15Z is assumed for subsequent IV administrations in each treatment cycle (£383.54), per the published definition. For escBEACOPDac, an additional cost of dispensing an oral therapy (prednisolone) is assumed (£13.75, 15-minutes of a pharmacist's time, PSSRU 2022) per cycle.[182]

Whilst the inputs are assumed for A+AVD and ABVD when costing administration, feedback from UK clinical experts highlighted that use of A+AVD, instead of ABVD-based treatment, could reduce administration time. It was highlighted that the AVD component takes approximately 90 minutes for both treatments. However, the bleomycin in ABVD adds an additional 60 minutes, whereas brentuximab vedotin in A+AVD only adds an additional 30 minutes, and there may therefore be a 30-minute time saving which has not been captured in the analysis. Therefore, there may be additional cost savings associated with A+AVD not reflected in the cost-effectiveness results.

The resulting administration costs per treatment cycle are £583.42 for A+AVD, £583.42 for ABVD, £583.42 for AVD and £1,138.58 for escBEACOPDac. For ABVD-based treatment, these costs were weighted based on 10% of patients receiving ABVD via six cycles and 90% of patients receiving PET-adapted ABVD. For PET-adapted ABVD, administration costs reflect 100% of patients receiving ABVD for cycles 1−2, and a weighted cost based on 83.7% of patients de-escalating to AVD and 16.3% escalating to escBEACOPDac from cycle 3−6 (Section B.3.5.1.1).

Table 42: 2020/21 National Tariff Payment System | Chemotherapy delivery HRGs[205]

HRG code	Definition	Cost (95% CI)	Explanation
SB12Z	Deliver simple parenteral chemotherapy	£207.59 (£126.22–£288.97)	Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.
SB13Z	Deliver more complex parenteral chemotherapy	£256.95 (£156.23–£357.68)	Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.
SB14Z	Deliver complex chemotherapy, including prolonged infusional treatment	£440.71 (£267.95–£613.46)	Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.
SB15Z	Deliver subsequent elements of a chemotherapy cycle	£326.46 (£198.49 – £454.43)	Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance, for example day 8 of a day 1 and

HRG code	Definition	Cost (95% CI)	Explanation
			8 regimen or days 8 and 15 of a day 1, 8 and 15 regimen.

Abbreviations: CI, confidence interval; HRG, healthcare resource group

B.3.5.1.3 Concomitant medication costs

Concomitant medications were recorded in ECHELON-1 from the point of signing the informed consent through to 30 days after the last dose of frontline therapy; 100% of patients in the A+AVD arm and 99% of patients in the ABVD arm received concomitant medication. Concomitant medications included treatments for primary prophylaxis with growth-factor support (G-CSF), anti-emesis, anti-infectives, and pain management. Specific medications are based on those received by the highest proportion of patients in ECHELON-1 and clinical feedback to ensure relevance in the UK setting.

ECHELON-1 informs the proportion of patients receiving concomitant medications in the model except for primary prophylaxis with G-CSF. No data were available from RATHL with regards to concomitant medication use. Therefore, concomitant medication use was assumed equal between ABVD (six cycles) and PET-adapted ABVD.

UK clinical feedback, obtained at the Takeda advisory boards, highlighted that the primary prophylaxis use with G-CSF observed in ECHELON-1 does not align with UK clinical practice. Feedback indicated that, as per the SmPC, all patients receiving A+AVD in the UK would receive primary prophylaxis with G-CSF (filgrastim), whereas in the ECHELON-1 clinical trial, only 12.5% of patients received primary prophylaxis in the A+AVD arm.[43] Feedback further indicated that, as per the NHS protocols, patients would not receive primary prophylaxis with G-CSF whilst receiving bleomycin as part of ABVD; in the ECHELON-1 clinical trial 6.4% of patients received primary prophylaxis in the ABVD arm.[179, 184–196] UK clinical advisors indicated that in the PET-adapted ABVD approach, patients would not receive primary prophylaxis with G-CSF following de-escalation to AVD. However, patients would receive primary prophylaxis with G-CSF following escalation to escBEACOPDac. Therefore, the base case assumes the following rates of primary prophylaxis: 100% of patients receive 10 days of G-CSF support with filgrastim in every A+AVD treatment cycle, 0% in an ABVD treatment cycle, 0% in an AVD treatment cycle, and 100% of patients receive 5 days of G-CSF support with filgrastim in every escBEACOPDac treatment cycle. The dosing frequencies reflect relevant NHS protocols.[179, 184–196] Scenario analyses explore primary prophylaxis G-CSF use with filgrastim as per ECHELON-1 i.e. 12.5% and 6.4% of patients receive 10 days of G-CSF support with filgrastim in every A+AVD treatment cycle and in every ABVD treatment cycle, respectively.

In relation, Straus *et al* (2020) demonstrate that the use of primary prophylaxis may result in improved outcomes for A+AVD compared to ABVD, supported by an analysis of the subgroup of patients in the A+AVD arm who received primary prophylaxis in ECHELON-1.[129] Therefore, the model may underestimate outcomes for A+AVD and hence incremental QALYs informing the ICER may be conservative.

Concomitant medication dosing regimens were informed by NHS protocols for ABVD-based treatment (six cycles and the PET-adapted approaches), and BNF guidelines. Unit costs were informed by eMIT (accessed February 2024) where available and BNF (accessed February 2024), otherwise.[178, 180] Concomitant medication costs were accrued whilst patients

were on treatment with A+AVD or ABVD-based treatment. As per acquisition and administration costs, concomitant medication costs for ABVD-based treatment were estimated based on 10% of patients receiving six cycles of ABVD and 90% of patients receiving PET-adapted ABVD. Within the PET-adapted ABVD approach, concomitant medication costs reflected 100% of patients receiving ABVD for cycles 1–2, and then a weighted cost based on 83.7% of patients de-escalating to AVD (PET2-negative) and 16.3% escalating to escBEACOPDac (PET2-positive) (Section B.3.5.1.1).

Table 43 presents the total concomitant medication costs per treatment cycle. Table 44 presents the dosing inputs and unit costs for each concomitant medication.

Table 43: Total concomitant medication cost per treatment cycle

	Anti-emesis	Growth-factor support	Anti-infectives	Pain management
A+AVD	£18.28	£659.29	£0.58	£0.28
ABVD-based regimens				
Cycles 1–2	£18.28	£0.00	£0.45	£0.19
Cycles 3–6	£18.28	£48.36*	£0.45	£0.19

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

*weighted based on 83.7% receiving AVD and no G-CSF and 16.3% receiving escBEACOPDac and 100% G-CSF

Table 44: Dosing, unit costs, and assumptions for concomitant medications

Treatment	Daily dose (mg)	Admins per cycle	Product size (mg)	Units per pack	Price per pack	Cost per cycle	% receiving A+AVD	% receiving ABVD	Source
Primary prophylaxis with growth-factor support									
Filgrastim	0.38	10	0.6 mg	0.5	£52.70	£659.29	100.0%	0.0%	Dosing: NHS protocols. Costs: BNF (accessed February 2024) 30million units/0.5ml solution for injection pre-filled syringes Proportion: UK clinical feedback and NHS protocols
	0.38	5	0.6 mg	0.5	£52.70	£329.65	0.0%	16.3% in cycles 3-6 i.e. patients receiving escBEACOPDac	
Anti-emesis									
Dexamethasone (day 1)	8	2	8	50	£68.06	£2.72	100.0%	100.0%	Dosing: NHS protocols. Costs: eMIT (accessed February 2024) Proportion: ECHELON-1
Dexamethasone (days 2 and 3)	4	4	4	50	£35.95	£2.88	100.0%	100.0%	
Ondansetron	8	2	8	10	£0.54	£0.11	100.0%	100.0%	
Aprepitant (day 1)	125	2	125	5	£10.81	£4.32	100.0%	100.0%	
Aprepitant (days 2 and 3)	80	4	80	2	£4.12	£8.25	100.0%	100.0%	
Anti-infectives									
Acyclovir	1000	5	200	25	£0.78	£0.78	21.2%	15.7%	Dosing: NHS protocols and BNF guidelines. Costs: eMIT (accessed February 2024) Proportion: ECHELON-1
Levofloxacin	500	7	500	5	£1.46	£2.05	20.5%	17.2%	

Treatment	Daily dose (mg)	Admins per cycle	Product size (mg)	Units per pack	Price per pack	Cost per cycle	% receiving A+AVD	% receiving ABVD	Source
Pain management									
Oxycodone	20	7	20	56	£13.53	£1.69	13.2%	8.5%	Dosing: NHS protocols and BNF guidelines. Costs: eMIT (accessed February 2024) Proportion: ECHELON-1
Tramadol	100	7	50	30	£0.59	£0.28	13.0%	9.4%	

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BNF, British National Formulary; eMIT, electronic marketing information tool; mg, milligram; NCCN, National Comprehensive Cancer Network

B.3.5.2 Health-state unit costs and resource use

Monitoring and follow-up care resource use were based on the BSH guidelines and clinical feedback from UK clinicians.[15, 36] Resource use inputs were also informed by the ESMO guidelines. Resource use estimates for A+AVD and ABVD-based treatment were assumed to be equivalent based on UK clinical expert feedback.

The BSH guidelines state that patients who remain progression-free are usually followed-up for 2 years following first-line therapy. This was corroborated by clinicians at the January 2024 UK market access advisory board; clinicians indicated that after 24 months following treatment discontinuation, patients who remain progression-free are discharged from routine follow-up and considered cured. Therefore, the model assumes no monitoring and follow-up care costs for patients remaining in the progression-free health state after the cure time point of 24 months post-discontinuation. This assumption is consistent with the two previously published frontline lymphoma NICE appraisals; TA874 assumed no further costs beyond 24 months post-discontinuation in the progression-free health state and TA641 assumed no further costs after 36 months post discontinuation.[40, 170] Similar assumptions were also considered in later line lymphoma NICE appraisals.[172–174]

For patients who remain progression-free, the ESMO guidelines indicate that patients should have a consultation, a full blood count, ESR testing, and a blood chemistry every 3 months for the first 6 months, and every 6 months thereafter. UK clinical experts highlighted that ESR tests are only conducted upfront for the purpose of staging and are not used in the UK throughout follow-up. Additionally, UK clinical experts advised that up to two PET scans and up to one CT scan may be given in the first 6 months. Therefore, these inputs informed the progression-free resource use up to the cure timepoint.

For patients in the progressed disease health state, resource use was based on previous NICE submissions of BV (TA446) and nivolumab (TA462), with the exception of the use of ESR testing as per UK clinical feedback.[39, 116]

Monitoring and follow-up care costs were based on the NHS Reference Costs 2021/22.[180] Table 45 presents the unit costs and annual resource use. Resulting weekly health state resource use costs are £46.14 for pre-progression from 0–6 months, £8.20 for pre-progression from 6 months to the cure timepoint, £0.00 for pre-progression from the cure timepoint, and £67.05 for progressed disease.

Table 45: Health state resource use and unit costs

Resource	Unit cost	Frequency per year			
		0–6 months pre-progression	6–24 months pre-progression	Cured	Progressed disease
Full blood count	£2.96	4.0	2.0	0.0	10.4
Blood chemistry	£1.55	4.0	2.0	0.0	10.4
Consultation	£209.41	4.0	2.0	0.0	10.4
CT scan	£146.34	1.0	0.0	0.0	1.5
PET scan	£702.78	2.0	0.0	0.0	1.5
Sources	NHS Reference Cost 2021/22[180]	ESMO guidelines for full blood count, blood chemistry and consultation.[28] UK clinical expert feedback for CT scan and PET scan.[36]		BSH guidelines and UK clinical expert feedback[15, 36]	NICE appraisals (TA446 and TA462)[116, 206]

Abbreviations: BSH, British Society for Haematology; CT, computerised tomography; ESMO, European Society of Medical Oncology; PET, positron emission tomography

B.3.5.3 Adverse reaction unit costs and resource use

Febrile neutropenia, neutropenia, and decrease in neutrophil count were costed based on the NHS Reference Costs 2021/22. Anaemia was assumed to require an outpatient IV transfusion at a cost of £333.13, sourced from the NHS Reference Costs 2021/22, and two standard red cell components at a cost of £158.18 per unit, sourced from the NHS Blood and Transplant Price List 2023/24.[180, 207] The costs per drug-related Grade ≥3 TEAEs are presented in Table 46. Unit costs for Grade ≥3 drug-related TEAEs align with previous NICE submissions for brentuximab vedotin.[39–42]

The cost per drug-related TEAE was multiplied by the proportion of patients experiencing each TEAE (Section B.3.3.3.1) and totalled to calculate the total cost of managing drug-related TEAEs by treatment arm. TEAE costs were accrued as a one-off cost in the first cycle of the model. This was considered a reasonable approach due to the fixed and short duration of treatment.

Table 46: Unit costs | Grade ≥3 drug-related TEAEs

TEAE	Mean cost per event	Source
Anaemia	£649.49	NHS Blood and Transplant. Price List 2023/24. Blood and Components – Contract Equivalent Cost per Item. BC001. Standard Red Cells.[207] NHS reference costs 2021/22; Outpatient procedure; SA44A 303; Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over[180]
Febrile neutropenia	£646.71	NHS reference costs 2021/22; Non-elective short stay; SA35B; Agranulocytosis with CC Score 9-12
Neutropenia	£655.34	NHS reference costs 2021/22; Non-elective short stay; SA35C; Agranulocytosis with CC Score 5-8
Neutrophil count decreased	£655.34	Assumed equal to neutropenia

Abbreviations: NHS, National Health Service; TEAE, treatment-emergent adverse events

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatments

Subsequent therapy costs were included in the model to align with the clinical pathway of care (Section B.1.3).

In the UK, subsequent treatments may include multiagent chemotherapies, stem cell transplants (autologous or allogeneic), PD-1 monotherapy (nivolumab [TA462] or pembrolizumab [TA772]), and brentuximab vedotin monotherapy (TA524).[115–117, 119] UK clinical experts at the medical advisory board in December 2023 developed a predicted UK treatment pathway for patients progressing following frontline treatment with A+AVD or ABVD-based treatment, including the proportion of patients expected to receive each therapy in the pathway.

Table 47 compares the subsequent treatments observed in ECHELON-1 with those from the predicted UK treatment pathway; estimates are shown as a proportion of patients receiving at least one subsequent therapy. In ECHELON-1, 136 and 159 patients received at least one subsequent therapy in the A+AVD and ABVD treatment arms, respectively, i.e. 20.5% and 23.7% of the total population receive at least one subsequent therapy, respectively. The data from ECHELON-1 are considered the most appropriate to inform the base case to align with the OS data in the analysis. Of those who progress to subsequent treatments, the distribution and type of therapies are similar across treatment arms in ECHELON-1. Therefore, subsequent treatments are not considered to impact the relative treatment effect from the trial.

No subsequent therapy data are available from the RATHL study. Therefore, subsequent therapies are assumed to be the same for ABVD (six cycles) and PET-adapted ABVD and are informed by the ECHELON-1 data.

In the base case, the distribution of subsequent therapies observed in ECHELON-1 is applied. A scenario analysis explores the use of the distribution informed by UK clinical experts.

Table 47: Comparison of subsequent treatments in patients who receive at least one subsequent treatment from UK clinical opinion and ECHELON-1

	Clinical opinion; A+AVD	Clinical opinion; ABVD-based treatment	ECHELON-1; A+AVD	ECHELON-1; ABVD-based treatment
Patients with at least one subsequent therapy, % (n)	NA	NA	20.48% (136)	23.73% (159)
ASCT, % (n)	57.9% (NA)	60.08% (NA)	31.25% (43)	33.96% (54)
Pembrolizumab, % (n)	65.85% (NA)	52.04% (NA)	1.55% (2)	3.65% (6)
Nivolumab, % (n)	8.05% (NA)	8.24% (NA)	13.16% (18)	14.59% (23)
Brentuximab vedotin monotherapy, % (n)	23.53% (NA)	47.88% (NA)	8.09% (11)	44.03% (70)
alloSCT or donor lymphocyte infusion, % (n)	3.13% (NA)	3.82% (NA)	7.72% (11)	14.47% (23)
Multiagent chemotherapy, % (n)	106.59% (NA)	108.26% (NA)	78.68% (107)	87.42% (139)
Radiation, % (n)	0% (NA)	0% (NA)	41.18% (56)	37.11% (59)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; NA, not available; UK, United Kingdom

Note: the sum of proportions across subsequent therapies may be greater than one due to multiple lines of subsequent therapy.

The costs associated with subsequent treatments are applied as a one-off cost upon disease progression. Subsequent therapy costs comprise drug acquisition, drug administration, stem cell transplant and radiation costs. Drug acquisition costs are sourced from eMIT (accessed February 2024), where available, or from the BNF (accessed February 2024; Table 48).[178, 180] List prices were used for all therapies, except for brentuximab vedotin, which uses the simple PAS applied in the frontline setting. Based on UK clinical feedback, multiagent chemotherapy is costed based on GDP (gemcitabine, dexamethasone and cisplatin). The duration of each subsequent therapy is sourced from NICE TA462 and TA478 (Table 48).[41, 116]

Drug administration costs were based on the NHS Reference Costs 2021/22 SB12Z for the first dose in a nivolumab, pembrolizumab, and brentuximab vedotin monotherapy treatment cycle i.e. costs of delivering a simple parenteral chemotherapy at first attendance based on infusion time (Table 42).[180] Nivolumab and pembrolizumab are only given once per treatment cycle. Subsequent doses of brentuximab vedotin monotherapy are based on the NHS Reference Costs 2021/22 SB15Z. For GDP, administration costs for first attendance are based on the NHS Reference Costs 2021/22 SB14Z i.e. costs of delivering complex chemotherapy, including prolonged infusion treatment at first attendance. Subsequent doses of GDP are based on the NHS Reference Costs 2021/22 SB15Z. Stem cell transplant costs were sourced from the NHS Reference Costs 2021/22 and TA874 for long-term follow-up costs (values uplifted from 2019/20 values). It was assumed that the NHS Reference Costs do not reflect the costs associated with long-term follow-up following a transplant. Therefore, long-term follow-up costs are applied in addition to the NHS Reference costs; this assumption aligns with the approach used in TA874.[170, 180] Subsequent radiation costs assume a dose of 30 Gy at 1.5 Gy per fraction based on BSH guidelines and are costed based on the NHS Reference Costs 2021/22.

Table 48: Subsequent therapy costs

Drug	Size per unit (mg)/units	Units per pack	Total size (mg)	Price per pack/procedure	Duration	Total acquisition and administration cost per patient based on treatment duration	Source[170, 178–180, 182]
ASCT							
ASCT	NA	NA	NA	£19,136	NA	£32,786	NHS Reference Costs (2021/22)
Bone marrow harvest	NA	NA	NA	£5,808			NHS Reference Costs (2021/22)
Long-term follow-up	NA	NA	NA	£7,842			TA874 and PSSRU (2021)
PD-1 monotherapy							
Nivolumab	40	1	40	£439	13-cycles (TA462)	£36,941	BNF. 40mg/4ml concentrate for solution for infusion vials. Accessed February 2024
Pembrolizumab	100	1	100	£2,630	13-cycles (assumed the same as nivolumab)	£71,079	BNF. 100mg/4ml concentrate for solution for infusion vials. Accessed February 2024
Brentuximab vedotin							
Brentuximab vedotin	50	1	50	£2,500 (list price) [redacted] (with PAS)	9.24-cycles (TA446)	[redacted]	BNF. 50mg powder for solution for infusion. Accessed February 2024
alloSCT							
alloSCT	NA	NA	NA	£51,390	NA	£98,412	NHS Reference Costs (2021/22)

Drug	Size per unit (mg)/units	Units per pack	Total size (mg)	Price per pack/procedure	Duration	Total acquisition and administration cost per patient based on treatment duration	Source[170, 178–180, 182]
Peripheral blood stem cell harvest	NA	NA	NA	£5,375			NHS Reference Costs (2021/22)
Long-term follow-up	NA	NA	NA	£41,648			TA874 and PSSRU (2021)
Multiagent chemotherapy – GDP							
Gemcitabine	1000	1	1000	£10.90	2-cycles (TA462)	£1,658	eMIT. 1g powder for solution for infusion vials/Packsize 1. Accessed February 2024
Cisplatin	50	1	50	£5.58			eMIT. 50mg/50ml solution for infusion vials/Packsize 1. Accessed February 2025
	10	1	10	£2.42			eMIT. 10mg/10ml solution for infusion vials/Packsize 1. Accessed February 2025
Dexamethasone	2	50	100	£2.62			eMIT. 2mg tablets/Packsize 50. Accessed February 2024
Radiation							
Preparation for simple radiotherapy with imaging and dosimetry	NA	NA	NA	£575.00	30Gy	£4,079	NHS reference costs 2021/22; Outpatient; SC45Z

Drug	Size per unit (mg)/units	Units per pack	Total size (mg)	Price per pack/procedure	Duration	Total acquisition and administration cost per patient based on treatment duration	Source[170, 178–180, 182]
Deliver a fraction of treatment on a megavoltage machine	1.5Gy	1	1.5Gy	£175.19			NHS reference costs 2021/22; Outpatient; SC22Z

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BMT, bone marrow transplant; BV, brentuximab vedotin; DHAP, dexamethasone, high-dose cytarabine (Ara-C) and cisplatin; NA, not applicable; PAS, patient access scheme; SCT, stem cell transplant; WoSCC, West of Scotland Cancer Centre

B.3.5.4.2 Second malignancies

As described in Section B.3.3.3.2, the impact of second malignancies on HRQoL and costs is explored in a scenario analysis only, which is described below.

The cost impact likely varies across the different second malignancy types. However, to avoid introducing uncertainty through heterogenous patient populations and study approaches, a singular cost per patient is assumed and applied for all second malignancies based on the most common second malignancy observed in the ECHELON-1 data. Therefore, as prostate cancer (n=6) was the most common second malignancy in ECHELON-1, the cost of treating prostate cancer was applied for all second malignancies in this scenario.

A targeted search was conducted to identify costs associated with new prostate cancer cases in the UK, one study (Laudicella *et al* [2016]) was identified conducting a retrospective cohort study matching cost of care data to population-based, patient-level data on patients with cancer, including prostate cancer, in England.[208] The average incidence costs per patient, defined as the total cost of care delivered to all patients who are alive at the beginning of the considered period, were £18,056 for the 18–64 years subgroup based on 2010 prices. This value was inflated to 2020/2021 values using the PSSRU (2022) and results in a cost of £21,655.[182] This calculated cost was multiplied by the proportion of second malignancies and is applied in the first treatment cycle.

Vijenthira *et al* (2020; Section B.3.1) consider the impact of second malignancies on costs from a Canadian perspective. In this study, the cost per second malignancy per patient was estimated between $50,000 and $180,000 Canadian Dollars (2018).[167, 168] Therefore, the cost of second malignancies in this scenario is considered conservative.

B.3.6 Severity

A+AVD does not meet the criteria for the severity modifier in adult patients with previously untreated CD30+ Stage III or IV HL (Table 49).

Absolute and proportional QALY shortfalls were calculated as per the NICE methods guide. The QALYs for the general population without previously untreated CD30+ Stage III or IV HL over their remaining lifetime were estimated using UK lifetables from the Office of National Statistics 2020-2022, aligning with the background mortality in the CEM, and utilities from Hernandez-Alava *et al* (2022). A mean starting age of 39.5 years and a 58.2% male population was assumed as per ECHELON-1. Life years and QALYs were discounted based on 3.5%. The discount rate is only used to derive age- and sex-specific QALY norm values. The remaining QALYs of the untreated patient population is not discounted.

Patients without the disease have expected discounted life years of 22.0 and 18.7 remaining discounted QALYs; undiscounted values are 42.2 and 34.9, respectively. Expected life years and QALYs for patients with the disease were informed by the CEM using the base case settings. Patients who receive ABVD-based treatment are expected to accrue [redacted] and [redacted] discounted life years and QALYs respectively, leading to absolute and proportional shortfall estimates of [redacted] and [redacted], respectively.

Table 49: Summary of QALY shortfall analysis

Expected total discounted QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute and proportional QALY shortfall
18.65	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year

B.3.7 Uncertainty

As described in Section B.1.3.4, the goal of first-line HL treatment is cure, with 70–80% of patients with advanced-stage disease cured by first-line treatment. The uncertainties when modelling the cost-effectiveness of treatments with a goal of cure are well documented in the literature, and typically include the clinical plausibility of cure, the assumed cure timepoint and the approach to extrapolation and associated SMR.[198, 209, 210]

As previously described, cure is a well-recognised goal of treatment in this patient population; cure is recognised throughout the literature, well supported within the HL clinical community, and is clearly observed in the ECHELON-1 PFS Kaplan–Meier data, which are informed by a large, randomised dataset (1,334 patients) with over 7 years of follow-up.[6, 15, 36, 123] As well as the clinical data, a cure timepoint of 24 months after treatment discontinuation is supported by UK clinical experts and the BSH guidelines, which state that patients are typically followed up for two years after first-line treatment. Scenario analyses were conducted to explore the cure timepoint, demonstrating an immaterial impact on cost-effectiveness, and therefore, neither the clinical plausibility of cure, nor the cure timepoint, are considered to be decision-related uncertainties.

PFS was extrapolated using MCMs and included SMR-adjusted background mortality, applied as a competing risk. NICE TSD 21 states that sufficient numbers at risk in the Kaplan–Meiers are required to reliably estimate the cure fraction when fitting MCMs.[198] In ECHELON-1, plateaus observed in the PFS data are maintained from approximately 24 months and, critically, the numbers of patients at risk informing the analyses of PFS remain high throughout trial follow-up (1,185 and 949 patients at two and five years, respectively). MCMs were explored for OS (Appendix O). Whilst the deterministic MCMs provided a good fit to the Kaplan–Meier data and predicted cure proportions aligning with UK clinical feedback and the literature, the probabilistic MCMs were derived from large confidence intervals and frequently predicted clinically implausible results. This is thought to be due to the MCMs fitting functions based on two subgroups in the data i.e. cured and non-cured and an insufficient number of events in the OS data from ECHELON-1 to support this separation of the data. In line with NICE TSD 21 and Palmer *et al* (2023) one-knot splines were also explored and were shown to provide similar fits to the deterministic MCMs. However, as these functions avoid the assumption of explicitly defining subgroups within the data, the uncertainty associated with the extrapolations was considered more realistic and reflective of the ECHELON-1 data and expectations from clinical experts. Therefore, in the base case, OS was extrapolated using one-knot splines (hazards) and included SMR-adjusted background mortality, applied as a competing risk. Importantly, a number of scenario analyses were conducted to explore alternative approaches to extrapolating OS; all

plausible scenarios (see Section B.3.11.3) were associated with ICERs within 14.1% of the base case.

In relation, SMRs specific for A+AVD and ABVD in Stage III and IV HL were uncertain in the absence of published data identified by the SLR and were hence informed by UK clinical expert opinion. Clinical expert opinion highlighted that a small increase in the risk of death for patients beyond the cure timepoint was expected vs. the general population, and indicated that the additional risk of death lay somewhere between 5 and 10%, with a greater risk expected for ABVD due to increased use of subsequent therapies, numerically higher second malignancies, and more long-term pulmonary toxicities vs. A+AVD. A scenario analysis was also conducted to explore the SMR assumption, demonstrating an immaterial impact on cost-effectiveness (+1.0%). Therefore, the approach to extrapolation and associated SMR is not considered to be a decision-related uncertainty.

Although ECHELON-1 provides over 7 years of follow-up (median follow-up of 89.2 months for PFS and 89.3 months for OS) for A+AVD and ABVD-based treatment, it could be perceived that some residual uncertainty remains in long-term OS beyond the trial due to the low numbers of events observed, and hence the high proportion of patients who are still alive at the end of trial follow-up. However, this is unavoidable for this patient population where cure is the outcome for the majority of patients. This is supported by the ten-year follow-up from RATHL, where long-term outcomes predicted for the ABVD arm of ECHELON-1 align closely with the Stage III and IV population in RATHL (extrapolated 10-year OS for ABVD from ECHELON-1 was estimated to be [redacted]% vs. 85.7% in RATHL). Moreover, clinical expert opinion elicited at the market access advisory board confirmed that the entire disease pathway for these patients, including those with progressed disease, is expected to be captured within 7 years, and would hence be reflected in the extensive ECHELON-1 follow-up period. Therefore, it is reasonable to expect that patients who are event-free at the end of follow-up in ECHELON-1 reflect only those patients who are ‘cured’ of their HL, and long-term outcomes are expected to follow a similar shape to background mortality, adjusted by an SMR.

Another uncertainty relates to the relative efficacy of ABVD (six cycles) vs. PET-adapted ABVD. In the analysis, six cycles of ABVD (per ECHELON-1) was assumed to be equivalent with respect to PFS and OS to PET-adapted ABVD. This was considered reasonable based on the rationale previously described, but briefly, the non-inferiority results concluded by the RATHL study, the low proportion of PET2-positive patients in clinical practice, results of the unadjusted and adjusted indirect treatment comparisons (Section B.3.2.3.2 and Appendix D) and UK clinical expert opinion, who agreed that they expected outcomes for patients receiving six cycles of ABVD (as per ECHELON-1) to be equivalent to the PET-adapted ABVD strategy followed in the RATHL trial. In addition, and importantly, the use of PFS and OS from the ABVD arm of ECHELON-1 facilitates use of the large (N=1,334), multicentre, randomised, open-label, Phase III clinical trial and preserves the benefits of a within-trial comparison, and was hence deemed to be the most robust approach based on the available data. Moreover, the safety profile and costs of PET-adapted ABVD were accurately captured in the base case and explored in scenario analyses, all of which had an immaterial impact on cost-effectiveness. Notably, this approach was also supported by clinical and health economic experts at the market access advisory board.

Finally, as discussed in Section B.3.12, there are likely additional benefits of A+AVD which have not been captured in the analysis. Notably, previously untreated HL is a cancer commonly diagnosed in younger working adults, and the increased proportion of patients who are cured with A+AVD may be able to continue working, leading to an increase in lifetime earnings and contribution to the UK economy. The impact of early death in cancer is well-documented in the literature; however, the specific impact in CD30+ Stage III or IV HL in the UK is uncertain.[107, 109] Therefore, whilst this is discussed qualitatively in this submission, it has not been quantitatively incorporated into the analysis. Similarly, the impact of A+AVD on second malignancies as well as the potential fertility impact have also not been quantitatively incorporated into the analysis. Therefore, the cost-effectiveness results for A+AVD may be conservative.

B.3.8 Managed access proposal

The company's preferred funding of A+AVD is through routine NHS funding via baseline commissioning. However, should the NICE committee feel unable to make a positive recommendation for routine NHS funding, Takeda would be open to discussions with NICE and NHS England to explore potential inclusion in the Cancer Drugs Fund. However, of note, the appraisal is informed by the final analysis of ECHELON-1 with over 7 years of follow-up.

In addition, as previously described, brentuximab vedotin has an existing simple PAS in place, based on the multiple indications that already have positive NICE recommendations. Even with this PAS, Takeda is aware that the submitted base case ICER is greater than NICE's usual £20,000–£30,000 per QALY threshold. [redacted]

B.3.9 Summary of base case analysis inputs and assumptions

B.3.9.1 Summary of base case analysis inputs

Table 50 presents the base case inputs, as well as the measurement of uncertainty and distribution, and the reference to the relevant Section in this submission.

Table 50: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General settings			
Discount rate (costs)	3.5%	1.5–6% (NA)	B.3.2.2
Discount rate (benefits)	3.5%	1.5–6% (NA)	
HRQoL			
Baseline utility score	0.76	0.16–1 (Beta)	B.3.4.6
Receipt of G-CSF (ref: no)	0.09	0.09–0.09 (Beta)	
IPS risk factor 0	0.04	0.04–0.05 (Dirichlet)	
IPS risk factor 1	0.17	0.17–0.17 (Dirichlet)	
IPS risk factor 2	0.28	0.28–0.27 (Dirichlet)	
IPS risk factor 3	0.26	0.27–0.25 (Dirichlet)	
IPS risk factor 4	0.16	0.15–0.16 (Dirichlet)	
IPS risk factor 5	0.08	0.07–0.08 (Dirichlet)	
IPS risk factor 6	0.02	0.01–0.02 (Dirichlet)	
IPS risk factor 7	0.00	0–0.01 (Dirichlet)	
Saturated HRQoL model: Intercept	0.74	0.69 –0.79 (Multivariate normal)	
Saturated HRQoL model: Treatment status (ref: off treatment)	−0.08	−0.09 to −0.08 (Multivariate normal)	
Saturated HRQoL model: Age (years)	0.00	−0.0032 to −0.0025 (Multivariate normal)	
Saturated HRQoL model: Sex (ref: female)	0.01	−0.01 to 0.03 (Multivariate normal)	
Saturated HRQoL model: Baseline utility score	0.28	0.29 to 0.28 (Multivariate normal)	
Saturated HRQoL model: Receipt of G-CSF (ref: no)	−0.01	−0.04 to 0.02 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 1	0.01	0.06 to -0.05 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 2	0.01	0.07 to -0.06 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 3	0.01	0.07 to −0.06 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 4	0.02	0.08 to −0.04 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 5	0.04	0.1 to −0.02 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 6	0.08	0.1 to 0.06 (Multivariate normal)	
Saturated HRQoL model: IPS risk factor 7	0.02	−0.02 to 0.05 (Multivariate normal)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Saturated HRQoL model: Grade 3+ AE (ref: no)	−0.03	−0.03 to −0.02 (Multivariate normal)	
Saturated HRQoL model: Progression status (ref: PF)	−0.07	−0.09 to −0.05 (Multivariate normal)	
Patient characteristics – ECHELON-1			
Age (years)	39.53	38.68–40.39 (Normal)	B.3.2.1
Proportion male	0.58	0.56–0.61 (Beta)	
Body weight (kg)	75.06	74.03–76.09 (Normal)	
BSA (m2)	1.88	1.87–1.89 (Normal)	
Probability of adverse events			
A+AVD: Anaemia	6.95%	5.14–9.00% (Beta)	B.3.3.3
A+AVD: Febrile neutropenia	18.13%	15.29–21.15% (Beta)	
A+AVD: Neutropenia	51.96%	48.16–55.76% (Beta)	
A+AVD: Neutrophil count decreased	12.24%	9.85–14.84% (Beta)	
ABVD: Anaemia	0.12%	0.01–0.35% (Beta)	
ABVD: Febrile neutropenia	2.75%	1.98–3.63% (Beta)	
ABVD: Neutropenia	56.80%	54.28–59.29% (Beta)	
ABVD: Neutrophil count decreased	0.43%	0.16–0.81% (Beta)	
A+AVD: Total second malignancies	4.98%	[redacted]% (Beta)	B.3.3.3.2
ABVD: Total second malignancies	[redacted]%	[redacted]% (Beta)	
Relative dose intensity			
A+AVD: Brentuximab (IV)	94.01%	93.06–94.89% (Beta)	B.3.5.1.1
A+AVD: Doxorubicin (IV)	99.11%	98.66–99.47% (Beta)	
A+AVD: Vinblastine (IV)	96.56%	95.73–97.3% (Beta)	
A+AVD: Dacarbazine (IV)	99.12%	98.77–99.41% (Beta)	
PET-adapted ABVD: Doxorubicin (IV)	99.54%	99.17–99.8% (Beta)	
PET-adapted ABVD: Bleomycin (IV)	93.51%	92.2–94.71% (Beta)	
PET-adapted ABVD: Vinblastine (IV)	96.91%	96.13–97.61% (Beta)	
PET-adapted ABVD: Dacarbazine (IV)	98.93%	98.42–99.34% (Beta)	
PET-adapted ABVD: Doxorubicin (IV)	99.54%	99.17–99.8% (Beta)	
PET-adapted ABVD: Vinblastine (IV)	93.51%	96.13–97.61% (Beta)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
PET-adapted ABVD: Dacarbazine (IV)	96.91%	98.42–99.34% (Beta)	
PET-adapted ABVD: Bleomycin (IV)	98.93%	96.45– 97.5% (Beta)	
PET-adapted ABVD: Etoposide (IV)	99.54%	96.45–97.5% (Beta)	
PET-adapted ABVD: Doxorubicin (IV)	96.91%	96.45–97.5% (Beta)	
PET-adapted ABVD: Cyclophosphamide (IV)	98.93%	96.45–97.5% (Beta)	
PET-adapted ABVD: Vincristine (IV)	97.00%	96.45–97.5% (Beta)	
PET-adapted ABVD: Dacarbazine (IV)	97.00%	96.45–97.5% (Beta)	
PET-adapted ABVD: Prednisone (PO)	97.00%	96.45–97.5% (Beta)	
Time-on-treatment			
A+AVD: Brentuximab (IV)	5.50	5.41–5.59 (Gamma)	B.3.5.1.1
A+AVD: Doxorubicin (IV)	5.60	5.5–5.7 (Gamma)	
A+AVD: Vinblastine (IV)	5.60	5.51–5.69 (Gamma)	
A+AVD: Dacarbazine (IV)	5.60	5.51–5.69 (Gamma)	
PET-adapted ABVD: Doxorubicin (IV)	2.00	1.91–2 (Gamma)	
PET-adapted ABVD: Bleomycin (IV)	2.00	1.93–2 (Gamma)	
PET-adapted ABVD: Vinblastine (IV)	2.00	1.92–2 (Gamma)	
PET-adapted ABVD: Dacarbazine (IV)	2.00	1.93–2 (Gamma)	
PET-adapted ABVD: Doxorubicin (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Vinblastine (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Dacarbazine (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Bleomycin (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Etoposide (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Doxorubicin (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Cyclophosphamide (IV)	3.70	3.61–3.8 (Gamma)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
PET-adapted ABVD: Vincristine (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Dacarbazine (IV)	3.70	3.61–3.8 (Gamma)	
PET-adapted ABVD: Prednisone (PO)	3.70	3.61–3.8 (Gamma)	
% receiving different components of PET-adapted ABVD			
% of patients receive AVD	83.7%	84.73–82.7% (Dirichlet)	B.3.5.1
% of patients receive escBEACOPP	0.0%	0–0% (Dirichlet)	
% of patients receive escBEACOPDac	16.3%	15.28–17.3% (Dirichlet)	
% receiving primary prophylaxis			
A+AVD: primary prophylaxis	100.00%	100–100% (Beta)	B.3.5.1.3
ABVD: primary prophylaxis	0.00%	0–0% (Beta)	
PET-adapted ABVD (ABVD): primary prophylaxis	0.00%	0–0% (Beta)	
PET-adapted ABVD (AVD): primary prophylaxis	0.00%	0–0% (Beta)	
PET-adapted ABVD (escBEACOPP): primary prophylaxis	100.00%	100–100% (Beta)	
PET-adapted ABVD (escBEACOPDac): primary prophylaxis	100.00%	100–100% (Beta)	
% receiving concomitant medications			
A+AVD: Dexamethasone (day 1)	100.00%	100–100% (Beta)	B.3.5.1.3
A+AVD: Dexamethasone (day 2 and 3)	100.00%	100–100% (Beta)	
A+AVD: Ondansetron (day 1)	100.00%	100–100% (Beta)	
A+AVD: Aprepitant (day 1)	100.00%	100–100% (Beta)	
A+AVD: Aprepitant (days 2 and 3)	100.00%	100–100% (Beta)	
A+AVD: Acyclovir	22.36%	19.27–25.61% (Beta)	
A+AVD: Levofloxacin	19.79%	16.84–22.91% (Beta)	
A+AVD: Opioids; oxycodone	14.35%	11.79–17.12% (Beta)	
A+AVD: Tramadol	14.35%	11.79–17.12% (Beta)	
ABVD: Dexamethasone	100.00%	100–100% (Beta)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
ABVD: Dexamethasone (day 2 and 3)	100.00%	100–100% (Beta)	
ABVD: Ondansetron (day 1)	100.00%	100–100% (Beta)	
ABVD: Aprepitant (day 1)	100.00%	100–100% (Beta)	
ABVD: Aprepitant (days 2 and 3)	100.00%	100–100% (Beta)	
ABVD: Acyclovir	15.33%	12.68–18.17% (Beta)	
ABVD: Levofloxacin	16.08%	13.38–18.98% (Beta)	
ABVD: Opioids; oxycodone	9.71%	7.57–12.08% (Beta)	
ABVD: Tramadol	9.26%	7.17–11.58% (Beta)	
% receiving monitoring resource (0-0.5 year)			
Full blood count	100%	100–100% (Beta)	B.3.5.2
ESR	0%	0–0% (Beta)	
Blood chemistry	100%	100–100% (Beta)	
Consultation	100%	100–100% (Beta)	
CT scan	100%	100–100% (Beta)	
PET scan	100%	100–100% (Beta)	
% receiving monitoring resource (0.5-cure timepoint years)			
Full blood count	100%	100–100% (Beta)	B.3.5.2
ESR	0%	0–0% (Beta)	
Blood chemistry	100%	100–100% (Beta)	
Consultation	100%	100–100% (Beta)	
CT scan	100%	100–100% (Beta)	
PET scan	0%	0–0% (Beta)	
% receiving monitoring resource (>cure timepoint years)			
Full blood count	100%	100–100% (Beta)	B.3.5.2
ESR	0%	0–0% (Beta)	
Blood chemistry	100%	100–100% (Beta)	
Consultation	100%	100–100% (Beta)	
CT scan	100%	100–100% (Beta)	
PET scan	0%	0–0% (Beta)	
% receiving monitoring resource (post-progression)			
Full blood count	100%	100–100% (Beta)	B.3.5.2
ESR	0%	0–0% (Beta)	
Blood chemistry	100%	100–100% (Beta)	
Consultation	100%	100–100% (Beta)	
CT scan	100%	100–100% (Beta)	
PET scan	100%	100–100% (Beta)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Frequency per cycle (0–0.5 year)			
Full blood count	4.00	3.25–4.82 (Gamma)	B.3.5.2
ESR	0.00	0–0 (Gamma)	
Blood chemistry	4.00	3.25–4.82 (Gamma)	
Consultation	4.00	3.25–4.82 (Gamma)	
CT scan	3.50	0.81–1.21 (Gamma)	
PET scan	2.00	1.63–2.41 (Gamma)	
Frequency per cycle (0.5–cue timepoint years)			
Full blood count	2.00	1.63–2.41 (Gamma)	B.3.5.2
ESR	0.00	0–0 (Gamma)	
Blood chemistry	2.00	1.63–2.41 (Gamma)	
Consultation	2.00	1.63–2.41 (Gamma)	
CT scan	0.00	0–0 (Gamma)	
PET scan	0.00	0–0 (Gamma)	
Frequency per cycle (>cure timepoint years)			
Full blood count	0.00	0–0 (Gamma)	B.3.5.2
ESR	0.00	0–0 (Gamma)	
Blood chemistry	0.00	0–0 (Gamma)	
Consultation	0.00	0–0 (Gamma)	
CT scan	0.00	0–0 (Gamma)	
PET scan	0.00	0–0 (Gamma)	
Frequency per cycle (post-progression)			
Full blood count	10.40	8.46–12.54 (Gamma)	B.3.5.2
ESR	0.00	0–0 (Gamma)	
Blood chemistry	10.40	8.46–12.54 (Gamma)	
Consultation	10.40	8.46–12.54 (Gamma)	
CT scan	1.50	1.22–1.81 (Gamma)	
PET scan	1.50	1.22–1.81 (Gamma)	
Subsequent therapy | ECHELON-1			
A+AVD: ASCT	31.25%	23.77–39.26% (Beta)	B.3.5.4
A+AVD: PD-1 monotherapy	14.71%	9.29–21.1% (Beta)	
A+AVD: BV monotherapy	8.09%	4.14–13.2% (Beta)	
A+AVD: alloSCT or donor lymphocyte infusion	7.72%	3.87–12.74% (Beta)	
A+AVD: Multiagent chemotherapy	78.68%	71.44–85.12% (Beta)	
A+AVD: Radiation	41.18%	33.07–49.53% (Beta)	
ABVD: ASCT	33.96%	26.83–41.48% (Beta)	
ABVD: PD-1 monotherapy	18.24%	12.65–24.58% (Beta)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
ABVD: BV monotherapy	44.03%	36.42–51.78% (Beta)	
ABVD: alloSCT or donor lymphocyte infusion	14.47%	9.46–20.32% (Beta)	
ABVD: Multiagent chemotherapy	87.42%	81.86–92.09% (Beta)	
ABVD: Radiation	37.11%	29.79–44.73% (Beta)	
Administration costs			
Oral dispensing fee	£13.75	£8.36–£19.14 (Normal)	B.3.5.1.2
SB12Z	£207.59	£126.22 - £288.97 (Normal)	
SB13Z	£256.95	£156.23 - £357.68 (Normal)	
SB14Z	£440.71	£267.95 - £613.46 (Normal)	
SB15Z	£326.46	£198.49 - £454.43 (Normal)	
Monitoring and follow-up care costs			
Full blood count	£2.96	£1.80–£4.12 (Normal)	B.3.5.2
ESR	£7.61	£4.63–£10.59 (Normal)	
Blood chemistry	£1.55	£0.94–£2.15 (Normal)	
Consultation	£209.41	£127.32–£291.50 (Normal)	
CT scan	£146.34	£88.98–£203.70 (Normal)	
PET scan	£702.78	£427.30–£978.27 (Normal)	
Adverse events management costs			
Grade 3: Anaemia	£649.49	£394.90–£904.09 (Normal)	B.3.5.3
Grade 3: Febrile neutropenia	£646.71	£393.20–£900.21 (Normal)	
Grade 3: Neutropenia	£655.34	£398.45–£912.23 (Normal)	
Grade 3: Neutrophil count decreased	£655.34	£398.45–£912.23 (Normal)	
Second malignancies (scenario only)			
Total second malignancies	£21,654.77	£13,166.26 - £30,143.28 (Normal)	B.3.5.2
Radiotherapy costs			
Preparation for simple radiotherapy with imaging and dosimetry	£575.00	£349.60–£800.39 (Normal)	B.3.5.4

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Deliver a fraction of treatment on a megavoltage machine	£175.19	£106.52–£243.86 (Normal)	
Number of deliveries of treatment on a megavoltage machine	20.00	16.08–23.92 (Normal)	
Concomitant medication costs			
Dexamethasone (PO): 8mg	£68.06	£67.72–£68.40 (Normal)	B.3.5.1.3
Dexamethasone (PO): 4mg	£35.95	£35.93–£35.97 (Normal)	
Ondansetron (PO): 8mg	£0.54	£0.53–£0.55 (Normal)	
Aprepitant (PO): 125mg	£10.81	£10.75–£10.87 (Normal)	
Aprepitant (PO): 80mg	£4.12	£4.08–£4.17 (Normal)	
Filgrastim	£52.70	£32.04–£73.36 (Normal)	
Aciclovir	£0.78	£0.78–£0.78 (Normal)	
Levofloxacin	£1.46	£1.45–£1.47 (Normal)	
Opioids; oxycodone	£13.53	£13.22–£13.84 (Normal)	
Tramadol	£0.59	£0.59–£0.60 (Normal)	
Subsequent therapy costs			
ASCT	£32,786.31	£19,934.31–45,638.31 (Normal)	B.3.5.4
PD-1 monotherapy (pembrolizumab)	£71,078.69	£43,216.36–98,941.03 (Normal)	
PD-1 monotherapy (nivolumab)	£36,940.69	£22,460.21–51,421.18 (Normal)	
BV monotherapy	£74,272.16	£45,158.01–103,386.31 (Normal)	
alloSCT or donor lymphocyte infusion	£98,412.03	£59,835.22–136,988.84 (Normal)	
Multiagent chemotherapy	£1,657.71	£1,007.90–2,307.53 (Normal)	
Radiation	£4,078.75	£2,479.91–5,677.59 (Normal)	

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BSA, body surface area; IV, intravenous; kg, kilogram; SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; HRQoL, health-related quality of life; NA, not applicable; SCT, stem cell transplant

B.3.9.2 Assumptions

Table 51 details the key assumptions underpinning the economic model and the justification supporting these.

Table 51: Summary of assumptions applied in the economic model

Parameter	Base case	Justification
Composition of ABVD-based treatment	ABVD (six cycles): 10% PET-adapted ABVD: 90%	Reflecting current UK clinical practice, based on feedback from UK clinical experts. Scenario analyses explore variations in UK clinical practice i.e. 0% vs. 100% and 5% vs. 95% for ABVD (six cycles) and PET-adapted ABVD, respectively.
Composition of PET-adapted ABVD	De-escalation AVD: 83.7% Escalation escBEACOPDac: 16.3%	The proportion of patients de-escalating to AVD and escalating to escBEACOPDac is based on the proportion of patients with PET2-negative and PET2-positive results in the RATHL study. UK clinical experts confirmed that the RATHL study is reflective of PET-adapted ABVD in clinical practice, therefore justifying this approach in the base case. These proportions are used to weight acquisition costs, administration costs, concomitant medication costs, and adverse event costs.
Therapy used for escalation in PET-adapted ABVD approach	escBEACOPDac: 100% escBEACOPP: 0%	UK clinical experts advised that, in clinical practice, escalation of treatment within the PET-adapted ABVD approach would be to escBEACOPDac, rather than escBEACOPP or BEACOPP-14, which are used in the RATHL study. Clinical experts further advised that efficacy was thought to be similar across the regimens. However, the safety profile of escBEACOPDac is considered more favourable.
SMRs	SMR=1.05 for A+AVD SMR=1.10 for ABVD	As discussed in Section B.3.2.2.1, current treatment strategies in previously untreated HL are associated with burdensome side effects, including long-term treatment-related toxicities (particularly pulmonary toxicity associated with bleomycin containing regimens) and second malignancies, that are associated with a long-term increased risk of death, even in patients who are considered cured from their HL.[5, 21, 66] Moreover, for patients who relapse on first-line therapy, subsequent treatment options (including stem-cell transplantation) are associated with substantial toxicity, and patients experience ongoing disease burden and poorer survival outcomes at each subsequent line of treatment.[12, 27] Therefore, SMRs were applied to reflect the increased risk of death in the A+AVD and ABVD treatment arms vs. the general population. The use of SMRs is supported by approaches used in frontline and later line lymphoma NICE appraisals.[172, 173] To reflect the increased risk of mortality vs. the general population after being cured with A+AVD and ABVD-based treatment, and to accurately reflect expert clinical opinion, the base case assumed differential SMRs of 1.05 and 1.10, respectively.
PFS and OS extrapolations	MCMs for PFS and one-knot splines for OS	The goal of first-line HL treatment is cure. Aligning with this goal, the data from ECHELON-1 indicate complex hazard and survival functions. The

Parameter	Base case	Justification
		recommendations outlined in NICE TSD 14 and 21, and Palmer *et al* (2023) support the use of independent MCMs for PFS and independent one-knot splines in the base case for both endpoints.[197–199]
Efficacy for PET-adapted ABVD	Efficacy for PET-adapted ABVD was assumed equal to ABVD (six cycles) and informed by the ECHELON-1 clinical trial data.	This assumption is supported by the outcomes from the RATHL study, unadjusted and adjusted, unanchored comparisons of the ABVD arm of ECHELON-1 with the RATHL study data, and UK clinical expert opinion (Section B.3.2.3.2).
Cure timepoint	After 24 months post treatment discontinuation patients who are progression-free are assumed to be cured. From this point, these patients accrue no additional costs and experience a utility aligned with the general population.	The cure timepoint is supported by: • The plateau observed in the PFS Kaplan–Meier data. • Clinical advisors at the January 2024 advisory board indicated that they would discharge patients who had not relapsed within 24 months after treatment discontinuation and would consider them cured. • BSH guidelines state that patients who remain progression-free are usually followed-up for 2 years following first-line treatment. • The HRQoL data collected in ECHELON-1 aligns with the general population utility values reported in Hernandez-Alava *et al* (2022) after 24 months post treatment discontinuation.[171] Case precedence in previous frontline and later line lymphoma NICE appraisals.[40, 170, 172, 173]
Wastage	Included	No vial sharing is assumed as patient numbers in each centre would likely be too low to allow for any vial sharing. This is aligned with previous NICE appraisals of brentuximab vedotin.[40–42, 117]
RDI	Include	RDI is included to accurately cost the doses received in ECHELON-1 for A+AVD, ABVD and AVD. RDI inputs were sourced from the Borchmann *et al* (2017) paper for escBEACOPDac.[204] This approach aligns with real-world clinical practice where patients may not receive the full dose of therapy e.g. due to adverse events.
Subsequent therapy source	ECHELON-1	Aligning with the OS data used in the CEM. The subsequent therapies are assumed to be the same for ABVD (six cycles) and PET-adapted ABVD.
Subsequent therapy cost application	Applied as a one-off cost upon progression	This is a simplification. However, UK clinical experts indicated that the whole disease pathway would be complete within 7 years. Therefore, modelling subsequent therapy costs over time would cause a limited impact from discounting.
Primary prophylaxis G-CSF use source	A+AVD: 100% ABVD (six cycles): 0% PET-adapted ABVD: ABVD: 0%	Aligning with UK clinical practice and NHS protocols for ABVD-based treatment and UK clinical expert feedback:[179, 184–196] • All patients receiving A+AVD would receive G-CSF as primary prophylaxis

Parameter	Base case	Justification
	AVD: 0% escBEACOPDac: 100%	• Patients receiving ABVD would not receive G-CSF as primary prophylaxis. • All patients receiving escBEACOPDac would receive G-CSF as primary prophylaxis
Regression model fit to the EQ-5D-3L data	Saturated model	The saturated model ensures that all identified prognostic factors are accounted for in the estimation.
Include AE decrements from the literature	Exclude	The impact of Grade ≥3 drug-related TEAEs on HRQoL is captured within the utility regression fit to the EQ-5D-3L data collected in ECHELON-1.
AE utility decrements application	Applied as a one-off impact in the first cycle	The treatment duration with A+AVD and ABVD is short and fixed at a maximum of six cycles.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

B.3.10 Base case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

There is an existing PAS for brentuximab vedotin in the NHS in the form of a simple discount of [redacted]. All costs and results presented in this dossier include the PAS. In the base case analysis and using the PSA price for brentuximab vedotin, A+AVD accrues [redacted] additional QALYs at an additional cost of [redacted], resulting in an ICER of [redacted] (Table 52). Whilst A+AVD is associated with greater total costs vs. ABVD, A+AVD is associated with cost savings in subsequent therapies ([redacted]), post progression monitoring costs and follow-up care ([redacted]), and administration ([redacted]). These savings are driven by the increased proportion of patients cured in the A+AVD arm vs. the ABVD arm, and the increased administration burden associated with the escBEACOPDac for patients who escalate treatment, respectively. The net health benefit (NHB) is [redacted] and [redacted] and the net monetary benefit (NMB) is [redacted] and [redacted], based on WTP thresholds of £20,000 and £30,000, respectively (Table 52).

Appendix J presents the predicted clinical outcomes and disaggregated results.

Table 52: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALY, quality adjusted life year.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

The PSA explored the joint uncertainty of all relevant model parameters and their associated impact on cost-effectiveness results, by randomly varying all parameters within assigned distributions and then re-estimating and recording the ICERs at each random sample (referred to as an iteration). This was repeated for 1,000 iterations; the PSA can be run for a maximum of 5,000 iterations; however, the average ICER was reasonably stable after 1,000 iterations. Therefore, the results presented below are based on 1,000 iterations. The results of each PSA iteration are visually shown on a scatterplot of the incremental costs against the incremental QALYs. A cost-effectiveness acceptability curve (CEAC), corresponding to the PSA results, illustrates the probability that a treatment provides a cost-effective treatment option at varying WTP thresholds.

Parameters and their distributions and ranges used are presented in Table 50. The average incremental costs over the simulated results are [redacted] and the average incremental QALYs are [redacted], giving a probabilistic ICER of [redacted]. This is congruent with the deterministic ICER of [redacted], as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 35). The proportion of simulations considered cost-effective at a threshold of £20,000 and £30,000 per QALY is [redacted]% and [redacted]%, respectively. The cost-effectiveness plane and CEAC are depicted in Figure 35 and Figure 36, respectively.

Figure 35: Cost-effectiveness plane | 1,000 iterations

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Figure 36: Cost-effectiveness acceptability curve

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CEAC, cost-effectiveness acceptability curve

B.3.11.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by the 95% CI, or ±20% of the mean value for costs and ±10% of the mean value for utilities and other inputs where no estimates of precision were available. Each parameter is varied individually, except for the parameters informing the PFS extrapolations, the OS extrapolations, and the utility analyses. The parameters informing these analyses are linked and the 95% confidence intervals are based on a multivariate normal distribution. Therefore, it does not make sense to vary each parameter individually, as varying one impacts the other parameters. For this reason, these parameters are varied between their lower and upper bounds simultaneously.

Results for the ten most influential parameters are shown in Table 53 and depicted in a tornado diagram in Figure 37, Figure 38, and Figure 39, based on the ICER, NMB at a WTP of £20,000 and NMB at a WTP of £30,00, respectively.

The SMR has the biggest impact on results, with ICERs varying from [redacted] (upper bound of SMR for ABVD) to [redacted] (upper bound of SMR for A+AVD). However, the results of this scenario should be interpreted carefully as varying these parameters independently, as per the objective of the OWSA, leads to results which are misaligned with clinical opinion. Specifically, the lower bounds for the SMRs for A+AVD and ABVD are 1.0 and 1.0, respectively, whereas the upper bounds for the SMRs for A+AVD and ABVD are 1.27 and 1.33, respectively, based on 10% uncertainty and a gamma distribution. When varying the upper bound for the SMR for A+AVD, the analysis assumes that the excess mortality is 27% greater than the general population in the A+AVD arm, compared to only 10% greater than the general population in the ABVD arm i.e. the base case. This is not considered clinically plausible (Section B.3.2.2.1). Additionally, as explained in Section B.3.2.2.1, UK clinical experts highlighted that excess mortality in frontline HL is expected to be lower than

in the frontline lymphomas considered in TA641 and TA874 (sALCL and DLBCL, respectively), and the maximum SMR explored in these appraisals was 1.1 i.e. 10% greater than the general population. To explore the uncertainty associated with the SMRs, clinically plausible SMR alternatives are explored in scenario analyses (Section B.3.11.3).

The costs associated with subsequent brentuximab vedotin monotherapy also influence the cost-effectiveness results. As there is a higher proportion of patients receiving subsequent brentuximab vedotin monotherapy in the ABVD treatment arm (44.0%) compared to the A+AVD treatment arm (8.1%) based on ECHELON-1, varying this parameter has a larger impact on the costs accrued in the ABVD arm compared to the A+AVD arm. A probabilistic scenario analysis explores the subsequent therapy distribution as informed by UK clinical experts with a smaller difference i.e. 23.5% brentuximab vedotin monotherapy use in the A+AVD arm and 47.9% in the ABVD arm (Section B.3.11.3).

Remaining parameters are shown to have a limited impact on results.

Table 53: One-way sensitivity analysis

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
SMR: A+AVD	[redacted]	[redacted]
SMR: ABVD	[redacted]	[redacted]
Subsequent therapy costs (including number of cycles and administration costs) - brentuximab vedotin monotherapy	[redacted]	[redacted]
Parametric curves for PFS	[redacted]	[redacted]
Concomitant medication costs (including dose and frequency) - filgrastim	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 - ABVD: brentuximab vedotin monotherapy	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 - ABVD: alloSCT or donor lymphocyte infusion	[redacted]	[redacted]
Subsequent therapy costs - alloSCT or donor lymphocyte infusion	[redacted]	[redacted]
Time-on-treatment | A+AVD: brentuximab	[redacted]	[redacted]
HRQoL - Saturated HRQoL model	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogenic stem cell transplant; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate.

Figure 37: Tornado diagram | ICER

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio

Figure 38: Tornado diagram | NMB at a WTP of £20,000

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; NMB, net monetary benefit; WTP, willingness to pay

Figure 39: Tornado diagram | NMB at a WTP of £30,000

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; NMB, net monetary benefit; WTP, willingness to pay

B.3.11.3 Scenario analysis

Scenario analyses were performed to explore the structural uncertainty within the economic model. A full list of scenarios tested is presented in Table 54. Table 55 presents the results from the deterministic scenario analyses.

Due to the number of scenario analyses explored, the ten scenarios that demonstrated the biggest impact on the cost-effectiveness results in the deterministic analyses were conducted probabilistically. Probabilistic scenario analyses involved running the PSA across 1,000 iterations, under the assumptions of each scenario, methods aligning with the base case PSA in Section B.3.11.1.

Probabilistic scenario analyses included discount rates of 0% for costs and health outcomes, discount rates of 1.5% for costs and health outcomes, OS independent exponential MCMs for A+AVD and ABVD, primary prophylaxis with G-CSF as per ECHELON-1, OS independent standard Gompertz curves for A+AVD and ABVD, OS KM with adjusted background mortality for A+AVD and ABVD, baseline characteristics from the RATHL study, OS independent Gompertz MCMs for A+AVD and ABVD, excluding RDI, and a subsequent therapy distribution informed by UK clinical experts. Table 56 presents the results of the probabilistic scenario analyses compared to the base case probabilistic ICER.

As discussed in Section B.3.2.2.1, when explored probabilistically, the independent Gompertz MCM for OS yielded implausible predicted outcomes. Specifically, the predicted cure rates range from 46.1% to 96.8% and 13.6% to 98.5% based on the 95% confidence intervals for the MCM Gompertz curves fitted to A+AVD for ABVD, respectively. These ranges are considered clinically implausible and do not fit the ECHELON-1 data, nor the literature, and hence lead to implausibly wide variations in the probabilistic ICER. Therefore, the probabilistic ICER for the parametric MCMs for OS should be interpreted with caution.

The remaining results are congruent to the deterministic scenarios and vary the ICER from −56.0% to +14.1% compared to the base case probabilistic ICER.

Table 54: Scenario analyses

	Base case	Scenario	Rationale
Time horizon	Lifetime (60 years)	50 years 70 years	After 60 years, 99.96% of patients are predicted to have died in the A+AVD arm. Scenario analyses explore the uncertainty associated with the definition of lifetime.
Half cycle correction	Included	Excluded	To explore the impact of the cycle length.
Discount rates	3.5% costs, LYs and QALYs	0.0% 1.5%	The base case reflects the NICE recommendations. However, a non-reference-case discount rate of 1.5% may be particularly relevant in this disease setting as A+AVD satisfies the three criteria described in the NICE methods and process guide: A+AVD is for people who would otherwise die – as demonstrated by the OS benefit in ECHELON-1, a higher proportion of

	Base case	Scenario	Rationale
			patients survive following treatment with A+AVD compared to ABVD, A+AVD is likely to restore a large proportion of patients to full or near-full health, and the benefits from A+AVD are likely to be sustained over a lifetime i.e. a very long period. Additionally, the treatment costs are fixed, predictable, and are accrued in the first six treatment cycles.
Baseline characteristics for age and gender	ECHELON-1	RATHL	In the base case, the baseline characteristics align with the ECHELON-1 clinical trial, which is the primary evidence source informing the analysis. However, a scenario analysis uses the baseline characteristics from RATHL
PFS – parametric curves	Independent MCM log-logistic	Kaplan–Meier data followed by adjusted background mortality, independent MCMs, independent standard Gompertz, and one-knot spline models.	All independent MCMs, the standard Gompertz, and one-knot splines predicted plausible outcomes for PFS. The log-logistic MCM was considered the most appropriate base case selection. However, the alternative parametric forms may also be plausible.
OS – parametric curves	One-knot spline (hazards) for both treatment arms	Kaplan–Meier data followed by adjusted background mortality, independent one-knot splines (odds and normal), MCMs exponential and Gompertz, and independent standard Gompertz.	All independent one-knot splines predicted plausible outcomes for OS. The one-knot splines (hazards) were considered the most appropriate base case selection by UK clinical experts. However, the one-knot odds and normal also predicted plausible extrapolations. The deterministic MCMs were viewed as supportive of the base case.
Weighted ABVD-based treatment comparator	10% ABVD (six cycles) and 90% PET-adapted ABVD	0% ABVD (six cycles) and 100% PET-adapted ABVD; 5% ABVD (six cycles) and 95% PET-adapted ABVD	The base case reflects feedback from UK clinical experts. However, scenarios explore the heterogenous treatment approaches in UK clinical practice.
Excess mortality	1.05 for A+AVD and 1.10 for ABVD	1.10 for A+AVD and 1.15 for ABVD	The base case SMRs align with published NICE appraisals for frontline and later line lymphoma appraisals and UK clinical expert feedback. The treatment-specific

	Base case	Scenario	Rationale
			SMRs are supported by the plateau in PFS data observed in the over 7-year follow-up from ECHELON-1 and UK clinical expert feedback. However, as these are uncertain, scenario analyses explore alternative plausible inputs.
Cure timepoint	24 months after treatment discontinuation	36 months and 60 months after treatment discontinuation	The cure timepoint is supported by the ECHELON-1 clinical trial data, BSH guidelines, UK clinical expert opinion, and the literature. However, as this is uncertain, scenario analyses explore alternative plausible inputs.
AE disutilities	Utility regression fit to ECHELON-1 data	Literature and excluded.	In line with the estimation of health-state utilities, AE disutilities are predicted by the utility regression in the base case. However, alternative assumptions are explored in scenario analyses.
Cost and HRQoL impact from second malignancies	Excluded	Included	Due to uncertainty associated with cost and utilities related to second malignancies, these are not considered in the base case. However, a scenario analysis explores the impact using the information that is available.
Subsequent therapy source	ECHELON-1	UK clinical opinion	In the base case, the subsequent therapy distribution aligns with the ECHELON-1 clinical trial, which is the source of OS data. However, a scenario explores the impact of a distribution informed by UK clinical experts, which may be more reflective of UK clinical practice.
RDI	Include	Exclude	To explore the impact of patients receiving the full dose.
Primary prophylaxis with G-CSF	UK clinical practice	ECHELON-1	G-CSF use observed in ECHELON-1 does not align with the anticipated use of G-CSF in clinical practice, the NHS protocols available for ABVD-based regimens, nor UK clinical expert feedback. Therefore, the base case is informed by UK clinical practice and a scenario explores use observed in ECHELON-1 to ensure alignment with efficacy.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

Table 55: Deterministic scenario analyses results

Scenario	Deterministic base case	Change from deterministic base case	% change from deterministic base case
Time horizon: 50-years	[redacted]	[redacted]	1.7%

Scenario	Deterministic base case	Change from deterministic base case	% change from deterministic base case
Time horizon: 70-years	[redacted]	[redacted]	−0.1%
Exclude half-cycle correction	[redacted]	[redacted]	0.0%
Discount rates: 0%	[redacted]	[redacted]	−56.3%
Discount rates: 1.5%	[redacted]	[redacted]	−35.6%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	−7.7%
PFS: KM and adjusted background mortality	[redacted]	[redacted]	2.9%
PFS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	3.2%
PFS: independent MCMs Weibull for A+AVD and ABVD	[redacted]	[redacted]	3.0%
PFS: independent MCMs log-normal for A+AVD and ABVD	[redacted]	[redacted]	0.5%
PFS: independent MCMs log-logistic for A+AVD and ABVD	[redacted]	[redacted]	0.0%
PFS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	4.0%
PFS: independent MCMs generalised gamma for A+AVD and ABVD	[redacted]	[redacted]	2.5%
PFS: independent MCMs gamma for A+AVD and ABVD	[redacted]	[redacted]	2.2%
PFS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	3.3%
PFS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	−2.0%

Scenario	Deterministic base case	Change from deterministic base case	% change from deterministic base case
PFS: independent one-knot splines (hazard) for A+AVD and ABVD	[redacted]	[redacted]	−0.2%
PFS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	−0.3%
OS: KM and adjusted background mortality	[redacted]	[redacted]	9.0%
OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	9.7%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	6.2%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	9.1%
OS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	0.5%
OS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	0.5%
PET-adapted ABVD: 100% of ABVD-based comparator	[redacted]	[redacted]	−0.1%
PET-adapted ABVD: 95% of ABVD-based comparator	[redacted]	[redacted]	−0.1%
SMR 1.10 for A+AVD and 1.15 for ABVD	[redacted]	[redacted]	1.0%
Cure timepoint: 36-months	[redacted]	[redacted]	−0.5%
Cure timepoint: 60-months	[redacted]	[redacted]	−0.1%
AE disutilities: literature	[redacted]	[redacted]	0.1%
AE disutilities: excluded	[redacted]	[redacted]	0.0%
Second malignancies: included	[redacted]	[redacted]	0.2%

Scenario	Deterministic base case	Change from deterministic base case	% change from deterministic base case
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	4.7%
RDI: excluded	[redacted]	[redacted]	5.6%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	−9.2%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

Table 56: Probabilistic scenario analyses results

	Deterministic ICER	Probabilistic ICER	Change from probabilistic base case	% change from probabilistic base case
Base case	[redacted]	[redacted]	NA	NA
Discount rates: 0%	[redacted]	[redacted]	[redacted]	−56.0%
Discount rates: 1.5%	[redacted]	[redacted]	[redacted]	−34.7%
OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	10.4%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	[redacted]	−8.6%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	14.1%
OS: KM and adjusted background mortality	[redacted]	[redacted]	[redacted]	10.6%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	[redacted]	−6.3%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	87.2%
RDI: excluded	[redacted]	[redacted]	[redacted]	7.3%
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	[redacted]	5.1%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

B.3.12 Benefits not captured in the QALY calculation

B.3.12.1 Impaired fertility

Impaired fertility associated with HL treatments has the potential to create a major psychosocial burden for patients and their relatives, making starting a family an uncertainty or impossibility for survivors.[50, 81, 82] Cumulative doses of alkylating agents and ovarian radiation exposure can lead to reduced fertility and early menopause.[48–50] Treatment with either ABVD- or BEACOPP-based regimens can result in marked deterioration in sperm count or elevated levels of follicle-stimulating hormone (FSH), indicative of abnormal spermatogenesis or testicular failure; such results are often temporary with ABVD, whereas treatment with 6–8 cycles of BEACOPP regimens can have a more permanent effect.[49, 213] In a sub-study of the RATHL trial, ovarian function was measured by the use of serum antimüllerian hormone, used as a biomarker for ovarian ageing (i.e. low hormone levels indicate low egg reserve).[50] Reduced ovarian function was observed in women ≥35 years treated with ABVD, AVD or BEACOPP-based treatment. In women treated with ABVD or AVD, ovarian function recovered to similar levels as before starting treatment one year after the end of chemotherapy. However, in women treated with BEACOPP-based regimens, very little recovery was seen, with 71% of participants having undetected biomarker levels after 3 years from the end of treatment.[50] Therefore, potential impairment of fertility is a key concern for both clinicians and patients when deciding treatment options (Section B.1.3.4.1).[13, 70]

The potential for impaired fertility affects patients differently based on their age and desire, or lack thereof, to start a family. Fertility considerations are an important factor for UK clinicians in selecting appropriate therapy, and have the potential to levy a heavy psychosocial burden on patients and their families.[50, 81, 214] UK clinical experts were reassured by the reported pregnancies and live births in the A+AVD arm in ECHELON-1 (Appendix N.1.4).[70, 123] Though pregnancy outcomes were not statistically compared between treatment arms, both patients and clinicians are expected to place high value on the additional survival benefit provided by A+AVD, which showed a trend towards a reduced risk of fertility impairment vs. ABVD, which cannot be captured in the QALY calculation. Therefore, A+AVD can offer improved efficacy compared with ABVD-based treatment, whilst avoiding the fertility concerns associated with escBEACOPP/escBEACOPDac treatment.

B.3.12.2 Societal costs

A US study has assessed the estimated impact of frontline treatment choice in previously untreated HL on mortality and productivity using an oncology simulation model informed by ECHELON-1.[109] Individual productivity was estimated using the human capital approach and reported via PVLE estimates. Deaths avoided and life-years saved with and without A+AVD were calculated using a model informed by real-world treatment-specific OS, and expert clinicians' opinions. A+AVD use in the base case was 27% (range: 0–80%). In 2031, 3,645 patients were estimated to be newly diagnosed with CD30+ Stage III or IV HL. In the base case, it was predicted that there would be 14% fewer deaths (2,290 vs. 2,650 patients) and 14% less total PVLE losses ($1.438 vs. $1.664 billion) with A+AVD compared with no A+AVD over 10 years. In a scenario where A+AVD use would be between 40% and 80%, the analyses showed a 20–32% decrease in PVLE losses ($1.331–1.137 billion vs.

$1.664 billion), saving up to $527 million over 10 years with A+AVD compared with no A+AVD.

These data are supported by Hanly *et al* (2014), identified in the cost and resource use SLR (Section B.3.5), who estimated costs of lost productivity due to premature cancer-related mortality across Europe, for all cancers, including Hodgkin's lymphoma.[107] The average lost productivity cost per Hodgkin's lymphoma death was €306,628.

Therefore, it is predicted that increasing use of A+AVD for patients with previously untreated CD30+ Stage III or IV HL would reduce productivity cost losses as deaths are avoided, based on ECHELON-1 OS results (Section B.2.6.2).[109]

B.3.13 Validation

B.3.13.1 Internal validation of the cost-effectiveness analysis

A quality check of the electronic model was conducted by one internal Takeda health economic expert not involved in the development of the model. The internal quality check was based on a standardised checklist informed by Drummond *et al* (1996), Phillips *et al* (2004), the NICE manual suggested checklist.[175, 215, 216]

Additionally, the model was reviewed independently by three further health economists, with reviews being conducted using both a checklist and a targeted sheet-by-sheet approach. The review assessed the accuracy and transparency of the model calculations and functionality. The reviewers also advised on the validity of the modelling approach, and whether any specific base-case model settings and assumptions required further justification. The checklist used to review the model covered tests included in the Philips and TECH-VER checklists.[217, 218] Focus was paid to the technical implementation of the survival analysis methodology used to produce extrapolations of PFS and OS over the modelled lifetime horizon, with the spline models and MCMs reviewed in detail. Topics identified as part of the quality check have been addressed in the version of the model included alongside this submission.

In the early stages of model conceptualisation, a state transition model was explored in addition to the PartSA approach. At the time of conceptualisation, the OS data were immature, and the state transition allowed more flexibility to explore different assumptions on long-term survival. However, as the data matured with later data cuts, the PartSA enabled the use of the key endpoints from ECHELON-1 (PFS and OS), aligned with all previous NICE submissions in frontline lymphoma, and aligned with all previous NICE submissions for brentuximab vedotin. The use of PFS and OS directly allowed for use of published data and enabled comparison with external data sources e.g. RATHL.

The data from ECHELON-1 informing this submission reflect a median follow-up of 89.2 months for PFS and 89.3 months for OS. Feedback from clinicians indicated that any events related to this disease would occur within the initial 2 years in the frontline setting, and within 7 years including the relapsed setting. Therefore, with more mature data from ECHELON-1, the PartSA approach was considered to appropriately reflect long-term predictions, with outcomes validated by clinical experts (Section B.3.13.2).

B.3.13.2 External validation of the cost-effectiveness analysis

The outcomes predicted by the extrapolated survival curves were compared to the ECHELON-1 trial data from baseline up to eight years (Table 26; Section B.3.3.2.2 for PFS and Table 29; Section B.3.3.2.3 for OS). A comparison of the landmark analyses highlights that the extrapolated curves provide a good fit to the data, with limited differences observed.

The observed outcomes for ABVD from ECHELON-1 were compared with RATHL via unadjusted and adjusted comparisons (Section B.3.2.3.2). The observed data are shown to be very similar for ABVD from ECHELON-1 and the Stage III–IV subgroup from the RATHL study:

- The 7-year PFS rate for ABVD in ECHELON-1 vs. RATHL was 74.5% (95% CI: 70.8–77.7%) vs. 73.4% (95% CI: 69.7–76.8%), respectively. The 5-year PFS rates for ABVD in ECHELON-1 were 75.3% (95% CI: 71.8–78.5%) and [redacted]% (95% CI: [redacted]%) for ABVD in RATHL.
- The 7-year OS for ABVD in ECHELON-1 was 87.5% (95% CI: 84.2–90.2%) and ABVD in RATHL was 88.7% (95% CI: 85.7–91.0%), whereas the 5-year OS rates were 91.2% (95% CI: 88.6–93.2%) and [redacted]% (95% CI: [redacted]%), respectively.[88, 123]

Clinical feedback was sought at three advisory boards, each with a unique objective: one discussing clinical experience with first-line treatments for HL and providing expert insights into possible positioning of A+AVD in this patient population (2022); one providing insights regarding the evolving and potential future first-line treatment landscape of advanced-stage HL in the UK, based on recent data releases (2023); and one focusing on the current HTA submission, discussing the applicability of ECHELON-1 (Section B.2.3) in the context of the UK clinical practice for HL and the approach to modelling its cost-effectiveness for this submission (2024).[13, 36, 70] Further input and clarification was received by UK clinical experts following these advisory boards through unstructured one-to-one interviews. The detailed feedback from these interactions has been presented alongside the relevant assumptions in this submission. Clinical input has been critical to inform base case parameters and align these with current and expected UK clinical practice, and to determine appropriate scenario analyses.

The SLR reported in Section B.3.1 identified two studies (Connors *et al* [2018] and Delea *et al* [2019]) that estimated total QALYs accrued by A+AVD and ABVD based on the ITT population from ECHELON-1. The incremental QALYs across a lifetime horizon from the two studies ranged from 0.56 to 0.76 for A+AVD vs. ABVD. The incremental QALYs of 0.56 reported in the Connors *et a*l (2018) publication are based on digitised data, whereas the incremental QALYs of 0.76 reported in the Delea *et al* (2019) publication are based on the patient-level data from ECHELON-1. The greater incremental QALYs estimated in this submission ([redacted]) reflect the significant OS benefit observed in the final data cut from ECHELON-1; both Connors *et a*l (2018) and Delea *et al* (2019) use data from the first data cut (median follow-up of 24.6 months). This submission makes use of a much longer follow-up from the final data cut (median follow-up of [redacted] months for PFS and [redacted] months for OS) from ECHELON-1 and extensive validation of assumptions by UK clinical experts and is therefore considered more appropriate for decision-making.

Two studies were identified in the SLR which had access to the patient-level data from the first data cut from ECHELON-1 (Delea *et al* [2019] and pCODR Expert Review Committee [2020]); both studies extrapolated PFS and OS using MCM parametric models. This aligns with the approach in the base case presented in this submission for PFS and highlights the requirement for flexible approaches for modelling OS (Section B.3.3.2). Four studies were also identified that included excess mortality in addition to background mortality (Delea *et al* [2019], pCODR Expert Review Committee [2020], Vijenthira *et al* [2018], and Vijenthira *et al* [2020]); all four used differential rates for A+AVD and ABVD, acknowledging differing mortality due to treatment-related toxicities and second malignancies.[159, 167–169] The application of differential SMRs to adjusted background mortality aligns with the approach undertaken in this submission (Section B.3.3.2.1).

Throughout the submission dossier, the approach and assumptions were compared to the two published frontline lymphoma NICE appraisals (TA874 and TA641).[40, 170] Where an alternative approach was pursued, the rationale for this deviation has been detailed and supported by feedback from UK clinical experts. The approach was also compared to later line lymphoma NICE appraisals throughout.[40, 170, 172, 173]

B.3.14 Interpretation and conclusions of economic evidence

B.3.14.1 Main findings

The analysis indicates that A+AVD is associated with an incremental LY and QALY gain of [redacted] and [redacted] compared to ABVD-based treatment, respectively, at an additional cost of £[redacted]. The resulting ICER for A+AVD vs. ABVD-based treatment is £[redacted] per QALY gained. The increased LYs and QALYs predicted by the analysis are driven by the improved PFS and OS for A+AVD vs. ABVD observed in ECHELON 1 (OS; HR: [redacted]; 95% CI: [redacted]; PFS HR: [redacted]; 95% CI: [redacted]). Whilst A+AVD is associated with greater total costs vs. ABVD, A+AVD is associated with cost savings in subsequent therapies, post progression monitoring costs and follow-up care, and administration. These savings are driven by the increased proportion of patients cured in the A+AVD arm vs. the ABVD arm, and the increased administration burden associated with the escBEACOPDac for patients who escalate treatment, respectively.

Results were found to be robust in a series of sensitivity analyses, including a PSA, OWSA, and in scenario analyses where model assumptions were explored. The results were most sensitive to the method of extrapolating OS, SMR assumptions, discount rates, and primary prophylaxis assumptions. Except for the discount rates and one implausible OS probabilistic scenario (see Section B.3.11.3), all probabilistic scenarios demonstrated a minimal impact on the ICER (between −8.6% to +14.1%).

There are benefits related to A+AVD which are not reflected in the base case ICER. Firstly, the cost and HRQoL impact from the lower number of second malignancies observed in ECHELON-1 for A+AVD vs. ABVD is not included in the base case due to challenges with sourcing reliable inputs for these data. Secondly, as discussed in Section B.3.12, there may be fertility benefits associated with use of A+AVD rather than ABVD which are not reflected in the modelling. Finally, as patients with previously untreated CD30+ Stage III or IV HL are

often young and of working age, there may be considerable societal benefits from curing a higher proportion of patients with A+AVD compared to ABVD. Therefore, the base case ICER for A+AVD may be conservative. In relation, given the incidence of HL is bimodal and cases are highest in younger patients, this raises the potential importance of the scenario which explores a discount rate of 1.5% for costs and benefits.

B.3.14.2 Strengths and limitations

A key strength of the cost-effectiveness analysis is that it was informed by the randomised, controlled study ECHELON-1, which enrolled 1,334 patients in the population of interest with substantial follow-up of over 7 years. Of the reviewed lymphoma NICE appraisals, none had such large number of patients or such an extensive follow-up available.[40, 170, 172–174]

The typical limitations and challenges of modelling the cost-effectiveness of treatments with a goal of cure commonly include the clinical plausibility of cure, the cure timepoint and outcomes beyond the trial. As described throughout this appraisal, cure is a well-recognised goal of treatment for this patient population. As well as the clinical data, a cure timepoint of 24 months after treatment discontinuation is supported by UK clinical experts and the BSH guidelines, which state that patients are typically followed up for two years after first-line treatment. Scenario analyses were conducted to explore the cure timepoint, demonstrating an immaterial impact on cost-effectiveness, and therefore, neither the clinical plausibility of cure, nor the cure timepoint, are considered to be decision-related uncertainties.

All survival analyses were conducted in line with NICE TSD recommendations, resulting in survival extrapolations that fit well to the observed data, align with clinical opinion on long-term survival estimates, as well as long-term data from the RATHL trial (extrapolated 10-year OS for ABVD from ECHELON-1 was estimated to be [redacted]% vs. 85.7% in RATHL). Critically, PFS and OS were extrapolated using MCMs and one-knot splines, respectively, and included SMR-adjusted background mortality, applied as a competing risk.

In relation to PFS, NICE TSD 21 states that sufficient numbers at risk in the KMs are required to reliably estimate the cure fraction when fitting MCMs.[198] In ECHELON-1, plateaus observed in the PFS data are maintained from approximately 24 months, and critically, the numbers of patients at risk informing the analyses of PFS remain high throughout trial follow-up (1,185 and 949 patients at two and five years, respectively). Moreover, whilst cure is still relevant for OS, one-knot splines facilitate the modelling of the complex hazard and survival function without the need to assume distinct heterogeneous subgroups which reduces the uncertainty reflected in the estimates, leading to plausible predictions in the probabilistic results. However, MCMs are explored in scenario analyses and detailed in Appendix O.

Additionally, EQ-5D-3L data were collected in ECHELON-1 and were used to inform utility for both treatments of interest, leveraging data from the multicentre, Phase III, randomised trial in the population of interest to align with the NICE reference case. Importantly, in the analysis, 16,040 (for 1,267 patients) and 517 (for 158 patients) post-baseline records were available to inform the progression-free and progressive disease health states, respectively, meaning utility for all model health states were informed by the same source and same patients. The scenario analysis which explored the alternative mixed-effects repeated-measures model did not yield material changes in cost-effectiveness estimates, indicating this is not a source of decision uncertainty.

Moreover, the analysis has undergone extensive validation. In particular, the methods, parameter inputs and assumptions used to inform the analysis were validated by UK clinical experts and health economists at a market access advisory board, clinical expert feedback elicited at two further UK-specific advisory boards and post-advisory board follow-up discussions.[36] Notably, extrapolated PFS and OS aligned with clinical expert feedback, and any remaining uncertainties, such as resource use and the SMR were informed by UK-based clinical experts.

Importantly, ECHELON-1 provided direct comparative evidence for A+AVD vs. ABVD-based treatment. However, there are a lack of head-to-head data comparing A+AVD with PET-adapted ABVD, and therefore, in the analysis, six cycles of ABVD (per ECHELON-1) was assumed to be equivalent with respect to PFS and OS to PET-adapted ABVD. This was considered reasonable based on the extensive rationale previously described. Importantly, use of PFS and OS from the ABVD arm of ECHELON-1 facilitates use of the large (n=1,334), multicentre, randomised, open-label, Phase III clinical trial and preserves the benefits of a within-trial comparison, and was hence deemed to be the most robust approach based on the available data. Moreover, the analysis accurately captures the cost and tolerability impact of ABVD-based treatment, which comprised a weighted average of the cost and tolerability impact of ABVD (six cycles) and PET-adapted ABVD. Of note, the associated assumptions were explored in scenario analyses, all which had an immaterial impact on cost-effectiveness.

Finally, the PartSA model structure was selected based on the extended follow-up from ECHELON-1 for the OS outcome, enabling use of this outcome directly within the modelling. Additionally, for consistency with previous NICE appraisals of other brentuximab vedotin 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.

B.3.14.3 Conclusions

In line with the improved PFS and significant OS observed with A+AVD compared to ABVD in ECHELON-1, this analysis demonstrates that A+AVD accrues [redacted] additional LYs and [redacted] additional QALYs compared to ABVD, at an additional cost of [redacted]. The resulting ICER is [redacted] per QALY gained.

Overall, a positive NICE recommendation for A+AVD would provide patients and clinicians with a new treatment option, which improves PFS and OS vs. ABVD (PET-adapted or six cycles) with an acceptable tolerability profile, for patients with previously untreated Stage III or IV HL who would otherwise be suitable for treatment with ABVD.

References

1. Cancer Research UK. Hodgkin lymphoma statistics. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma.
2. Singh D, Vaccarella S, Gini A, De Paula Silva N, Steliarova-Foucher E, Bray F. Global patterns of Hodgkin lymphoma incidence and mortality in 2020 and a prediction of the future burden in 2040. *International Journal of Cancer*. 2022;150(12):1941–1947. https://doi.org/10.1002/ijc.33948.
3. Donato EM, Fernández-Zarzoso M, Hueso JA, de la Rubia J. Brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma: an evidence-based review. *Onco Targets Ther*. 2018;11:4583–4590. https://doi.org/10.2147/OTT.S141053.
4. Schönberger S, van Beekum C, Götz B, *et al.* Brentuximab vedotin exerts profound antiproliferative and pro-apoptotic efficacy in CD30-positive as well as cocultured CD30-negative germ cell tumour cell lines. *J Cell Mol Med*. 2018;22(1):568–575. https://doi.org/10.1111/jcmm.13344.
5. Shanbhag S, Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. *CA Cancer J Clin*. 2018;68(2):116–132. https://doi.org/10.3322/caac.21438.
6. Kaseb H, Babiker H M. Hodgkin Lymphoma. *Hodgkin Lymphoma*. StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499969/; 2023.
7. Lymphoma Action. Hodgkin Lymphoma. Last accessed: 04/10/2024. https://lymphoma-action.org.uk/types-lymphoma/hodgkin-lymphoma.
8. Connors JM, Jurczak W, Straus DJ, *et al.* Brentuximab Vedotin Plus Doxorubicin, Vinblastine, Dacarbazine (A+AVD) As Frontline Therapy Demonstrates Superior Modified Progression-Free Survival Versus ABVD in Patients with Previously Untreated Stage III or IV Hodgkin Lymphoma (HL): The Phase 3 Echelon-1 Study. *Blood*. 2017;130:6. https://doi.org/10.1182/blood.V130.Suppl_1.6.6.
9. Cancer Research UK. Hodgkin Lymphoma | Symptoms. 2020. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/symptoms.
10. Cancer Research UK. Hodgkin lymphoma | Survival. 2020. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/survival.
11. NHS England, National Disease Registration Service. Cancer Registration Statistics, England 2021 - first release, counts only. 10/19/2023. Last accessed: 04/10/2024. https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only.
12. Mina A, Vakkalagadda C, Pro B. Novel Therapies and Approaches to Relapsed/Refractory HL Beyond Chemotherapy. *Cancers*. 2019;11(3):421. https://doi.org/10.3390/cancers11030421.
13. Takeda. Data on file: medical advisory board. 2023.
14. Dryver ET, Jernström H, Tompkins K, Buckstein R, Imrie KR. Follow-up of patients with Hodgkin's disease following curative treatment: the routine CT scan is of little value. *Br J Cancer*. 2003;89(3):482–486. https://doi.org/10.1038/sj.bjc.6601052.
15. Follows GA, Barrington SF, Bhuller KS, *et al.* Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. *British Journal of Haematology*. 2022;197(5):558–572. https://doi.org/10.1111/bjh.18083.
16. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36(1):252–259. https://doi.org/10.1002/1097-0142(197507)36:1<252::aid-cncr2820360128>3.0.co;2-7.
17. Carde P, Karrasch M, Fortpied C, *et al.* Eight Cycles of ABVD Versus Four Cycles of BEACOPPescalated Plus Four Cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score ≥ 3, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial. *J Clin Oncol*. 2016;34(17):2028–2036. https://doi.org/10.1200/JCO.2015.64.5648.
18. Federico M, Luminari S, Iannitto E, *et al.* ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol*. 2009;27(5):805–811. https://doi.org/10.1200/JCO.2008.17.0910.

19. Merli F, Luminari S, Gobbi PG, *et al.* Long-Term Results of the HD2000 Trial Comparing ABVD Versus BEACOPP Versus COPP-EBV-CAD in Untreated Patients With Advanced Hodgkin Lymphoma: A Study by Fondazione Italiana Linfomi. *Journal of Clinical Oncology*. 2015. https://doi.org/10.1200/JCO.2015.62.4817.
20. de Vries S, Schaapveld M, Janus CPM, *et al.* Long-Term Cause-Specific Mortality in Hodgkin Lymphoma Patients. *JNCI: Journal of the National Cancer Institute*. 2021;113(6):760–769. https://doi.org/10.1093/jnci/djaa194.
21. Phillips EH, Kirkwood AA, Hague C, *et al.* Bleomycin Affects Lung Function for at Least 5 Years after Treatment for Hodgkin Lymphoma - Data from the International, Randomised Phase 3 RATHL Trial. *Blood*. 2023;142(Supplement 1):612. https://doi.org/10.1182/blood-2023-185818.
22. Potre O, Pescaru M, Sima A, *et al.* Evaluation of the Relapse Risk and Survival Rate in Patients with Hodgkin Lymphoma: A Monocentric Experience. *Medicina*. 2021;57(10):1026. https://doi.org/10.3390/medicina57101026.
23. Vassilakopoulos TP, Asimakopoulos JV, Konstantopoulos K, Angelopoulou MK. Optimizing outcomes in relapsed/refractory Hodgkin lymphoma: a review of current and forthcoming therapeutic strategies. *Therapeutic Advances in Hematology*. 2020;11:204062072090291. https://doi.org/10.1177/2040620720902911.
24. Ortega JJ, Olivé T, de Heredia CD, Llort A. Secondary malignancies and quality of life after stem cell transplantation. *Bone Marrow Transplant*. 2005;35 Suppl 1:S83-87. https://doi.org/10.1038/sj.bmt.1704854.
25. Danner-Koptik KE, Majhail NS, Brazauskas R, *et al.* SECOND MALIGNANCIES AFTER AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION IN CHILDREN. *Bone Marrow Transplant*. 2013;48(3):363–368. https://doi.org/10.1038/bmt.2012.166.
26. Majhail NS. Long-term complications after hematopoietic cell transplantation. *Hematology/Oncology and Stem Cell Therapy*. 2017;10(4):220–227. https://doi.org/10.1016/j.hemonc.2017.05.009.
27. Lowe T, Bhatia S, Somlo G. Second Malignancies after Allogeneic Hematopoietic Cell Transplantation. *Biology of Blood and Marrow Transplantation*. 2007;13(10):1121–1134. https://doi.org/10.1016/j.bbmt.2007.07.002.
28. Eichenauer DA, Aleman BMP, André M, *et al.* Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv19–iv29. https://doi.org/10.1093/annonc/mdy080.
29. Van Nimwegen FA, Schaapveld M, Janus CPM, *et al.* Cardiovascular Disease After Hodgkin Lymphoma Treatment: 40-Year Disease Risk. *JAMA Intern Med*. 2015;175(6):1007. https://doi.org/10.1001/jamainternmed.2015.1180.
30. Bonafede M, Feliciano J, Cai Q, *et al.* Real-world analysis of cost, health care resource utilization, and supportive care in Hodgkin lymphoma patients with frontline failure. *Clinicoecon Outcomes Res*. 2018;10:629–641. https://doi.org/10.2147/CEOR.S178649.
31. Ansell SM, Radford J, Connors JM, *et al.* Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. *N Engl J Med*. 2022;387(4):310–320. https://doi.org/10.1056/NEJMoa2206125.
32. Lim SH, Johnson PWM. Optimizing therapy in advanced-stage Hodgkin lymphoma. *Blood*. 2018;131(15):1679–1688. https://doi.org/10.1182/blood-2017-09-772640.
33. Abdollahpour-Alitappeh M, Lotfinia M, Gharibi T, *et al.* Antibody-drug conjugates (ADCs) for cancer therapy: Strategies, challenges, and successes. *J Cell Physiol*. 2019;234(5):5628–5642. https://doi.org/10.1002/jcp.27419.
34. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma. 2018.
35. NICE. Health Technology Evaluation | Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including Review of TA594) | Final scope. 2024.
36. Takeda. Data on file: Virtual advisory board. 2024.
37. EMA. Adcetris. 2023. Last accessed: 01/24/2024. https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris#:~:text=As%20for%20all%20medicines%2C%20data,action%20taken%20to%20protect%20patients.&text=Adcetris%20received%20a%20conditional%20marketing,EU%20on%2025%20October%202012.

38. Velasco R, Domingo-Domenech E, Sureda A. Brentuximab-Induced Peripheral Neurotoxicity: A Multidisciplinary Approach to Manage an Emerging Challenge in Hodgkin Lymphoma Therapy. *Cancers*. 2021;13(23):6125. https://doi.org/10.3390/cancers13236125.
39. NICE. TA524: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. Available at: https://www.nice.org.uk/guidance/ta524/resources/brentuximab-vedotin-for-treating-cd30positive-hodgkin-lymphoma-pdf-82606840474309 [last accessed: 21/09/2023]. 2018.
40. NICE. TA641: Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma. 08/12/2020. Last accessed: 04/10/2024. https://www.nice.org.uk/guidance/ta641.
41. NICE. TA478: Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma. 2017. Last accessed: 04/01/2024. https://www.nice.org.uk/guidance/ta478.
42. NICE. TA577: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma. 2019. Last accessed: 04/10/2024. https://www.nice.org.uk/guidance/ta577.
43. EMC. Adcetris 50 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC). 2023. Last accessed: 04/10/2024. https://www.medicines.org.uk/emc/product/2859/smpc.
44. Dumitru AV, Țăpoi DA, Halcu G, *et al.* The Polyvalent Role of CD30 for Cancer Diagnosis and Treatment. *Cells*. 2023;12(13):1783. https://doi.org/10.3390/cells12131783.
45. Cancer Research UK. What is Hodgkin lymphoma? 2020. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/about.
46. Follows GA, Ardeshna KM, Barrington SF, *et al.* Guidelines for the first line management of classical Hodgkin lymphoma. *Br J Haematol*. 2014;166(1):34–49. https://doi.org/10.1111/bjh.12878.
47. NHS. Symptoms | Hodgkin's lymphoma. 2021. Last accessed: 04/10/2024. https://www.nhs.uk/conditions/hodgkin-lymphoma/symptoms/.
48. De Bruin ML, Huisbrink J, Hauptmann M, *et al.* Treatment-related risk factors for premature menopause following Hodgkin lymphoma. *Blood*. 2008;111(1):101–108. https://doi.org/10.1182/blood-2007-05-090225.
49. Van Der Kaaij MAE, Heutte N, Le Stang N, *et al.* Gonadal Function in Males After Chemotherapy for Early-Stage Hodgkin's Lymphoma Treated in Four Subsequent Trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Étude des Lymphomes de l'Adulte. *JCO*. 2007;25(19):2825–2832. https://doi.org/10.1200/JCO.2006.10.2020.
50. Anderson RA, Remedios R, Kirkwood AA, *et al.* Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial. *The Lancet Oncology*. 2018;19(10):1328–1337. https://doi.org/10.1016/S1470-2045(18)30500-X.
51. Cancer Research UK. Hodgkins lymphoma | Chemotherapy treatment. 2020. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/treatment/chemotherapy/chemotherapy-treatment.
52. Fox P, Darley A, Furlong E, *et al.* The assessment and management of chemotherapy-related toxicities in patients with breast cancer, colorectal cancer, and Hodgkin's and non-Hodgkin's lymphomas: A scoping review. *European Journal of Oncology Nursing*. 2017;26:63–82. https://doi.org/10.1016/j.ejon.2016.12.008.
53. Bjerring AW, Smeland KHB, Baerug I, *et al.* Long-term cardiac adverse effects after modern Hodgkins lymphoma treatment. *European Heart Journal*. 2022;43(Supplement_2):ehac544.801. https://doi.org/10.1093/eurheartj/ehac544.801.
54. Böll B, Goergen H, Behringer K, *et al.* Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. *Blood*. 2016;127(18):2189–2192. https://doi.org/10.1182/blood-2015-11-681064.
55. Stamatoullas A, Brice P, Bouabdallah R, *et al.* Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. *Br J Haematol*. 2015;170(2):179–184. https://doi.org/10.1111/bjh.13419.
56. Rueda Domínguez A, Alfaro Lizaso J, De La Cruz Merino L, *et al.* SEOM clinical guidelines for the treatment of Hodgkin's lymphoma. *Clin Transl Oncol*. 2015;17(12):1005–1013. https://doi.org/10.1007/s12094-015-1429-1.
57. Epstein MM, Chang ET, Zhang Y, *et al.* Dietary pattern and risk of hodgkin lymphoma in a population-based case-control study. *Am J Epidemiol*. 2015;182(5):405–416. https://doi.org/10.1093/aje/kwv072.

58. Ansell SM. Hodgkin lymphoma: 2018 update on diagnosis, risk-stratification, and management. *American Journal of Hematology*. 2018;93(5):704–715. https://doi.org/10.1002/ajh.25071.
59. Clifford GM, Polesel J, Rickenbach M, *et al.* Cancer Risk in the Swiss HIV Cohort Study: Associations With Immunodeficiency, Smoking, and Highly Active Antiretroviral Therapy. *JNCI: Journal of the National Cancer Institute*. 2005;97(6):425–432. https://doi.org/10.1093/jnci/dji072.
60. Cancer Research UK. Hodgkin lymphoma risk. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/risk-factors.
61. Cozen W, Hamilton AS, Zhao P, *et al.* A protective role for early oral exposures in the etiology of young adult Hodgkin lymphoma. *Blood*. 2009;114(19):4014–4020. https://doi.org/10.1182/blood-2009-03-209601.
62. Kamper-Jørgensen M, Rostgaard K, Glaser SL, *et al.* Cigarette smoking and risk of Hodgkin lymphoma and its subtypes: a pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph). *Ann Oncol*. 2013;24(9):2245–2255. https://doi.org/10.1093/annonc/mdt218.
63. NHS North London and East Anglia Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines Lymphoid Malignancies Part 1: Hodgkin Lymphoma. Last accessed: 10/24/2023. Available at: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-Hodgkin-Guidelines-Jan-2020.pdf. 2020.
64. Lymphoma Action. Staging of lymphoma. 2022. Last accessed: 04/10/2024. https://lymphoma-action.org.uk/about-lymphoma-tests-diagnosis-and-staging/stages-lymphoma.
65. Hasenclever D, Diehl V, Armitage JO, *et al.* A Prognostic Score for Advanced Hodgkin's Disease. *New England Journal of Medicine*. 1998;339(21):1506–1514. https://doi.org/10.1056/NEJM199811193392104.
66. van Leeuwen FE, Ng AK. Long-term risk of second malignancy and cardiovascular disease after Hodgkin lymphoma treatment. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):323–330.
67. Bröckelmann PJ, Müller H, Gillessen S, *et al.* Clinical outcomes of relapsed and refractory Hodgkin lymphoma patients after contemporary first-line treatment: a German Hodgkin Study Group analysis. *Leukemia*. 2022;36(3):772–780. https://doi.org/10.1038/s41375-021-01442-8.
68. Smith A, Crouch S, Lax S, *et al.* Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer*. 2015;112(9):1575–1584. https://doi.org/10.1038/bjc.2015.94.
69. Rafiq M, Hayward A, Warren-Gash C, *et al.* Socioeconomic deprivation and regional variation in Hodgkin's lymphoma incidence in the UK: a population-based cohort study of 10 million individuals. *BMJ Open*. 2019;9(9):e029228. https://doi.org/10.1136/bmjopen-2019-029228.
70. Takeda. Data on file: Virtual advisory board. 2022.
71. Welsh Cancer Intelligence and Surveillance Unit (WCISU). Cancer Incidence in Wales, 2002-2020. 09/06/2023. Last accessed: 01/24/2024. https://www.gov.wales/cancer-incidence-2002-2020.
72. Lymphoma Action. Classical Hodgkin lymphoma. Last accessed: 09/27/2023. https://lymphoma-action.org.uk/types-lymphoma-hodgkin-lymphoma/classical-hodgkin-lymphoma.
73. Rüffer JU, Flechtner H, Tralls P, *et al.* Fatigue in long-term survivors of Hodgkin's lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). *European Journal of Cancer*. 2003;39(15):2179–2186. https://doi.org/10.1016/S0959-8049(03)00545-8.
74. Kreissl S, Müller H, Goergen H, *et al.* Health-Related Quality of Life in Patients With Hodgkin Lymphoma: A Longitudinal Analysis of the German Hodgkin Study Group. *JCO*. 2020;38(25):2839–2848. https://doi.org/10.1200/JCO.19.03160.
75. Global Cancer Observatory. Hodgkin Lymphoma. 2022.
76. Global Cancer Observatory. United Kingdom. 2022.
77. Johnson P, Federico M, Kirkwood A, *et al.* Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *New England Journal of Medicine*. 2016;374(25):2419–2429. https://doi.org/10.1056/NEJMoa1510093.
78. Viviani S, Zinzani PL, Rambaldi A, *et al.* ABVD versus BEACOPP for Hodgkin's Lymphoma When High-Dose Salvage Is Planned. *N Engl J Med*. 2011;365(3):203–212. https://doi.org/10.1056/NEJMoa1100340.

79. Brandt J, Dietrich S, Meissner J, Neben K, Ho AD, Witzens-Harig M. Quality of life of long-term survivors with Hodgkin lymphoma after high-dose chemotherapy, autologous stem cell transplantation, and conventional chemotherapy. *Leukemia & Lymphoma*. 2010;51(11):2012–2020. https://doi.org/10.3109/10428194.2010.513749.
80. Tian Z, Yang Y, Yang Y, *et al.* High cumulative doxorubicin dose for advanced soft tissue sarcoma. *BMC Cancer*. 2020;20(1):1139. https://doi.org/10.1186/s12885-020-07663-x.
81. Cancer Research UK. Sex, fertility and Hodgkin lymphoma. 2020. Last accessed: 10/24/2023. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/living-with/sex-fertility.
82. Behringer K, Mueller H, Goergen H, *et al.* Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *Journal of clinical oncology*. 2013;31(2):231–9.
83. Taparra K, Liu H, Polley M-Y, Ristow KM, Habermann TM, Ansell SM. Bleomycin Use in the Treatment of Hodgkin Lymphoma (HL): Toxicity and Outcomes in the Modern Era. *Blood*. 2019;134:4038. https://doi.org/10.1182/blood-2019-121488.
84. Evens AM, Carter J, Loh KP, David KA. Management of older Hodgkin lymphoma patients. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):233–242. https://doi.org/10.1182/hematology.2019000028.
85. Shbib Dabaja B, Boyce-Fappiano D, Dong W, *et al.* Second malignancies in patients with Hodgkin's Lymphoma: Half a century of experience. *Clinical and Translational Radiation Oncology*. 2022;35:64–69. https://doi.org/10.1016/j.ctro.2022.04.011.
86. Schaapveld M, Aleman BMP, Van Eggermond AM, *et al.* Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med*. 2015;373(26):2499–2511. https://doi.org/10.1056/NEJMoa1505949.
87. André MPE, Carde P, Viviani S, *et al.* Long-term overall survival and toxicities of ABVD vs BEACOPP in advanced Hodgkin lymphoma: A pooled analysis of four randomized trials. *Cancer Med*. 2020;9(18):6565–6575. https://doi.org/10.1002/cam4.3298.
88. Luminari S, Fossa A, Trotman J, *et al.* Long-Term Follow-Up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma Trial. *JCO*. 2024;42(1):13–18. https://doi.org/10.1200/JCO.23.01177.
89. Cancer.org. Second Cancers Related to Treatment. Last accessed: 02/16/2024. https://www.cancer.org/cancer/survivorship/long-term-health-concerns/second-cancers-in-adults/treatment-risks.html.
90. Cancer Research UK. Living with Hodgkin Lymphoma | Coping. 2020. Last accessed: 04/05/2024. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/living-with/coping.
91. Heutte N, Flechtner HH, Mounier N, *et al.* Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10-year follow-up of the EORTC-GELA H8 randomised controlled trial. *Lancet Oncol*. 2009;10(12):1160–1170. https://doi.org/10.1016/S1470-2045(09)70258-X.
92. Lymphoma Action. Lymphoma action | Paris. Last accessed: 09/28/2023. https://lymphoma-action.org.uk/paris.
93. Lymphoma Action. Lymphoma Action | Faye. Last accessed: 09/28/2023. https://lymphoma-action.org.uk/faye.
94. Vachon H, Mierzynska J, Taye M, *et al.* Reference values for the EORTC QLQ-C30 in patients with advanced stage Hodgkin lymphoma and in Hodgkin lymphoma survivors. *European Journal of Haematology*. 2021;106(5):697–707. https://doi.org/10.1111/ejh.13601.
95. Daniëls LA, Oerlemans S, Krol ADG, Creutzberg CL, van de Poll-Franse LV. Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *Br J Cancer*. 2014;110(4):868–874. https://doi.org/10.1038/bjc.2013.779.
96. Øvlisen AK, Jakobsen LH, Kragholm KH, *et al.* Depression and anxiety in Hodgkin lymphoma patients: A Danish nationwide cohort study of 945 patients. *Cancer Med*. 2020;9(12):4395–4404. https://doi.org/10.1002/cam4.2981.
97. Kreissl S, Goergen H, Müller H, *et al.* Survivors' perspectives on risks and benefits of Hodgkin lymphoma treatment: results of a survey by the German Hodgkin Study Group. *Leukemia & Lymphoma*. 2019;60(6):1389–1398. https://doi.org/10.1080/10428194.2018.1540781.
98. Hjermstad MJ, Knobel H, Brinch L, *et al.* A prospective study of health-related quality of life, fatigue, anxiety and depression 3-5 years after stem cell transplantation. *Bone Marrow Transplant*. 2004;34(3):257–266. https://doi.org/10.1038/sj.bmt.1704561.
99. Blood Cancer UK. Finding hope in the face of infertility. Last accessed: 04/10/2024. https://bloodcancer.org.uk/support-for-you/living-well/stories/hope-in-the-face-of-infertility/.

100. Cancer Research UK. If Hodgkin lymphoma comes back. 2020. Last accessed: 04/05/2024. https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/treatment/if-comes-back.
101. Lymphoma Action. Hannah. Last accessed: 02/13/2024. https://lymphoma-action.org.uk/hannah.
102. Flora DR, Evens AM, Liu N, *et al.* The impact of classic Hodgkin lymphoma on informal caregivers: results from the CONNECT cross-sectional survey. *Support Care Cancer*. 2023;31(12):664. https://doi.org/10.1007/s00520-023-08120-8.
103. Lymphoma Research Foundation. Fallon, Hodgkin Lymphoma Caregiver. Last accessed: 09/27/2023. https://lymphoma.org/storiesofhope/fallon-hodgkin-lymphoma-caregiver/.
104. Flora DR, Evens AM, Liu N, *et al.* The impact of classic Hodgkin lymphoma (cHL) on informal caregivers: Results from the cHL—Real-world observations from physicians, patients, and caregivers on the disease and its treatment (CONNECT) study. *JCO*. 2022;40(16_suppl):e24004–e24004. https://doi.org/10.1200/JCO.2022.40.16_suppl.e24004.
105. The patient story. Carley's Caregiver Story. Last accessed: 09/27/2023. https://thepatientstory.com/caregiver-stories/spouse/carley-g/#:~:text=My%20name%20is%20Carley%20and,on%20the%20role%20almost%20immediately.
106. Burns R, Leal J, Sullivan R, Luengo-Fernandez R. Economic burden of malignant blood disorders across Europe: a population-based cost analysis. *The Lancet Haematology*. 2016;3(8):e362–e370. https://doi.org/10.1016/S2352-3026(16)30062-X.
107. Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: The cost of lost productivity due to premature cancer-related mortality in Europe: Cancer-related Lost Productivity Costs. *Int J Cancer*. 2015;136(4):E136–E145. https://doi.org/10.1002/ijc.29105.
108. Bradley CJ, Yabroff KR, Dahman B, Feuer EJ, Mariotto A, Brown ML. Productivity Costs of Cancer Mortality in the United States: 2000–2020. *JNCI: Journal of the National Cancer Institute*. 2008;100(24):1763–1770. https://doi.org/10.1093/jnci/djn384.
109. Phillips T, Liu N, Bloudek B, Migliaccio-Walle K, Reynolds J, Burke JM. Estimated impact of ECHELON-1 overall survival on productivity costs in stage III/IV classical Hodgkin lymphoma in the United States. *Journal of Managed Care & Specialty Pharmacy*. 2023;29(12):1312–1320.
110. Juul SJ, Rossetti S, Kicinski M, *et al.* Work and education interruption in long-term Hodgkin lymphoma survivors: an analysis among patients from nine EORTC-LYSA trials. *Acta Oncologica*. 2023;62(7):744–752. https://doi.org/10.1080/0284186X.2023.2195561.
111. Radford J, McKay P, Malladi R, *et al.* Treatment pathways and resource use associated with recurrent Hodgkin lymphoma after autologous stem cell transplantation. *Bone Marrow Transplant*. 2017;52(3):452–454. https://doi.org/10.1038/bmt.2016.244.
112. Connors JM, Jurczak W, Straus DJ, *et al.* Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *New England Journal of Medicine*. 2018;378(4):331–344. https://doi.org/10.1056/NEJMoa1708984.
113. Vassilakopoulos TP, Kravvariti E, Panitsas F, *et al.* Very late relapses in Hodgkin lymphoma treated with chemotherapy with or without radiotherapy: linear pattern and distinct prognostic factors. *Blood Cancer J*. 2022;12(7):1–5. https://doi.org/10.1038/s41408-022-00674-w.
114. Andersen MD, Hamilton-Dutoit S, Modvig L, *et al.* Late recurrence of lymphoid malignancies after initial treatment for Hodgkin lymphoma – A study from the Danish Lymphoma Registry. *Br J Haematol*. 2022;198(1):50–61. https://doi.org/10.1111/bjh.18180.
115. Collins GP, Parker AN, Pocock C, *et al.* Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. *British Journal of Haematology*. 2014;164(1):39–52. https://doi.org/10.1111/bjh.12582.
116. NICE. TA462: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. 2017. Last accessed: 10/19/2023. https://www.nice.org.uk/guidance/ta462.
117. NICE. TA524: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 2018. Last accessed: 10/19/2023. https://www.nice.org.uk/guidance/ta524.
118. NICE. TA540: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma. 2018. Last accessed: 04/10/2024. https://www.nice.org.uk/guidance/ta540.
119. NICE. TA772: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies. 2022. Last accessed: 10/19/2023. https://www.nice.org.uk/guidance/ta772.

120. Hoppe RT, Advani RH, Ai WZ, *et al.* Hodgkin Lymphoma, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(6):755–781. https://doi.org/10.6004/jnccn.2020.0026.
121. Kreissl S, Goergen H, Buehnen I, *et al.* PET-guided eBEACOPP treatment of advanced-stage Hodgkin lymphoma (HD18): follow-up analysis of an international, open-label, randomised, phase 3 trial. *The Lancet Haematology*. 2021;8(6):e398–e409. https://doi.org/10.1016/S2352-3026(21)00101-0.
122. NICE. TA772 public committee slides. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies. Available at: https://www.nice.org.uk/guidance/ta772/documents/1 [last accessed: 10/03/2024]. 2021.
123. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma | Addendum 3 - March 2024. 2024.
124. Takeda. Data on file: Table 15.2.5.2 | Summary of Progression-Free Survival (PFS) per Investigator | ITT population. 2023.
125. Takeda. Data on file: Table 15.2.9.1 | Summary of Overall Survival (OS) | ITT Population. 2023.
126. Straus D, Collins G, Walewski J, *et al.* Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy. *Leuk Lymphoma*. 2020;61(12):2931–2938. https://doi.org/10.1080/10428194.2020.1791846.
127. Straus DJ, Długosz-Danecka M, Alekseev S, *et al.* Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. *Blood*. 2020;135(10):735–742. https://doi.org/10.1182/blood.2019003127.
128. Straus DJ, Długosz-Danecka M, Connors JM, *et al.* Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2021;8(6):e410–e421. https://doi.org/10.1016/S2352-3026(21)00102-2.
129. Straus DJ, Dlugosz-Danecka M, Connors JM, *et al.* Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study. *Blood*. 2020;136:26–28. https://doi.org/10.1182/blood-2020-137089.
130. Stephens DM, Li H, Schöder H, *et al.* Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. *Blood*. 2019;134(15):1238–1246. https://doi.org/10.1182/blood.2019000719.
131. Cancer Research UK Cancer Intelligence. Proportion Diagnosed by Stage (stacked chart). 2023. Last accessed: 06/02/2024. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.
132. University of York. CRD's guidance for undertaking reviews in health care | Sytematic reviews. 2009.
133. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *JCO*. 1998;16(1):139–144. https://doi.org/10.1200/JCO.1998.16.1.139.
134. Nolte S, Liegl G, Petersen MA, *et al.* General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *European Journal of Cancer*. 2019;107:153–163. https://doi.org/10.1016/j.ejca.2018.11.024.
135. Sloan J, Cella D, Hays R. Clinical significance of patient-reported questionnaire data: another step toward consensus. *Journal of Clinical Epidemiology*. 2005;58(12):1217–1219. https://doi.org/10.1016/j.jclinepi.2005.07.009.
136. Abramson JS, Arnason JE, LaCasce AS, *et al.* Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma. *Blood*. 2019;134(7):606–613. https://doi.org/10.1182/blood.2019001272.
137. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5(1):70. https://doi.org/10.1186/1477-7525-5-70.
138. Janssen MF, Pickard AS, Shaw JW. General population normative data for the EQ-5D-3L in the five largest European economies. *Eur J Health Econ*. 2021;22(9):1467–1475. https://doi.org/10.1007/s10198-021-01326-9.

139. Takeda. Data on file: Figure 99.3.5.2A | Forest Plot of Hazard Ratio in Progression-Free Survival (PFS) Per Investigator for Subgroup Analyses | ITT Population - Baseline Deauville score < 5 at Cycle 2. 2023.
140. Takeda. Data on file: Figure 99.3.5.2B | Forest Plot of Hazard Ratio in Progression-Free Survival (PFS) Per Investigator for Subgroup Analyses | ITT Population - Baseline Deauville score 5 at Cycle 2. 2023.
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149. Zinzani PL, Viviani S, Anastasia A, *et al.* Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. *Haematologica*. 2013;98(8):1232–1236. https://doi.org/10.3324/haematol.2012.083048.
150. Herrera AF, LeBlanc ML, Castellino SM, *et al.* SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). *JCO*. 2023;41(17_suppl):LBA4–LBA4. https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA4.
151. Luminari S, Fosså A, Trotman J, *et al.* Long Follow-up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma (RATHL) Trial (CRUK/07/033) Confirms the Safety of Both De-Escalation and Intensification of Chemotherapy. *Blood*. 2022;140(Supplement 1):766–767. https://doi.org/10.1182/blood-2022-162780.
152. ClinicalTrials.gov. S0816 Fludeoxyglucose F 18-PET/CT Imaging and combination Chemotherapy With or Without Additional Chemotherapy and G-CSF in Treating Patients With Stage III or Stage IV Hodgkin Lymphoma. 2022. Last accessed: 01/16/2024. https://www.clinicaltrials.gov/study/NCT00822120.
153. ClinicalTrials.gov. Fludeoxyglucose F 18-PET/CT Imaging in Assessing Response to Chemotherapy in Patients With Newly Diagnosed Stage II, Stage III, or Stage IV Hodgkin Lymphoma. 2023. Last accessed: 01/16/2024. https://www.clinicaltrials.gov/study/NCT00678327.
154. Casasnovas R-O, Bouabdallah R, Brice P, *et al.* Positron Emission Tomography–Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study. *Journal of Clinical Oncology*. 2022;40(10):1091–1101. https://doi.org/10.1200/JCO.21.01777.
155. University College London. A Randomised Phase III Trial to Assess Response Adapted Therapy Using FDG-PET Imaging in patients with Newly Diagnosed, Advanced Hodgkin Lymphoma. 2013.
156. Ramchandren R. Advances in the Treatment of Relapsed or Refractory Hodgkin's Lymphoma. *The Oncologist*. 2012;17(3):367–376. https://doi.org/10.1634/theoncologist.2011-0258.
157. Aleman BMP, Van Den Belt-Dusebout AW, Klokman WJ, Van'T Veer MB, Bartelink H, Van Leeuwen FE. Long-Term Cause-Specific Mortality of Patients Treated for Hodgkin's Disease. *JCO*. 2003;21(18):3431–3439. https://doi.org/10.1200/JCO.2003.07.131.
158. Dores GM, Curtis RE, Dalal NH, Linet MS, Morton LM. Cause-Specific Mortality Following Initial Chemotherapy in a Population-Based Cohort of Patients With Classical Hodgkin

Lymphoma, 2000-2016. *J Clin Oncol*. 2020;38(35):4149–4162. https://doi.org/10.1200/JCO.20.00264.
159. Delea TE, Sharma A, Grossman A, *et al.* Cost-effectiveness of brentuximab vedotin plus chemotherapy as frontline treatment of stage III or IV classical Hodgkin lymphoma. *Journal of Medical Economics*. 2019;22(2):117–130.
160. Goenka L, Kumar SM, Essakky S, *et al.* Cost-effectiveness of response-adapted therapy (RAT) for advanced Hodgkin's Lymphoma compared with conventional treatment in India: a Markov-model based analysis. *Leukemia & Lymphoma*. 2023;64(13):2188–2194.
161. Huntington SF, von Keudell G, Davidoff AJ, Gross CP, Prasad SA. Cost-effectiveness analysis of brentuximab vedotin with chemotherapy in newly diagnosed stage III and IV Hodgkin lymphoma. *Journal of Clinical Oncology*. 2018;36(33):3307.
162. Huntington SF, Von Keudell GR, Davidoff AJ, Gross CP, Prasad SA. Cost-effectiveness analysis of brentuximab vedotin with chemotherapy in newly diagnosed stage III/IV Hodgkin lymphoma. *Journal of Clinical Oncology Conference*. 2018;36(15):Supplement 1.
163. Norum J, Angelsen V, Wist E, Olsen J. Treatment costs in Hodgkin's disease: a cost-utility analysis. *European Journal of Cancer*. 1996;32(9):1510–1517.
164. Prica A, Vijenthira A, Chan K, Cheung M. COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF MULTIPLE TREATMENT STRATEGIES USING ABVD AND/OR BEACOPP IN THE TREATMENT OF ADVANCED-STAGE HODGKIN LYMPHOMA. *Hematological Oncology*. 2019;37:148–149.
165. Raymakers A, Costa S, Peacock SJ, Regier D. Brentuximab Vedotin Compared with Standard Therapy for Patients with Advanced-Stage Hodgkin's Lymphoma: A Cost-Effectiveness Analysis. *Value in Health*. n.d.;21(Supplement 3):S44.
166. Raymakers A, Costa S, Cameron D, Regier DA. Cost-effectiveness of brentuximab vedotin in advanced stage Hodgkin's lymphoma: a probabilistic analysis. *BMC cancer*. 2020;20(1):1–9.
167. Vijenthira A, Chan K, Cheung MC, Prica A. Cost-effectiveness of first-line treatment options for patients with advanced-stage Hodgkin lymphoma: a modelling study. *The Lancet Haematology*. 2020;7(2):e146–e156.
168. Vijenthira A, Chan K, Cheung M, Prica A. Cost-Effectiveness and Cost-Utility Analysis of ABVD Versus Beacopp in the treatment of advanced-stage hodgkin lymphoma. *Blood*. 2018;132:2248.
169. pCODR EXPERT REVIEW COMMITTEE. Seattle Genetics Inc submission. For the treatment of previously untreated patients with stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine. FINAL RECOMMENDATION. 2020.
170. NICE. TA874: Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta874/ [last accessed: 09/01/2024]. 2023.
171. Alava MH, Pudney S, Wailoo A. ESTIMATING EQ-5D BY AGE AND SEX FOR THE UK. 2022.
172. NICE. TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta872/ [last accessed: 09/01/2024]. 2023.
173. NICE. TA677: Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta677/ [last accessed: 09/01/2024]. 2021.
174. NICE. TA567: Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta567/ [last accessed: 09/01/2024]. 2019.
175. NICE. NICE health technology evaluations: the manual. 01/31/2022. Last accessed: 04/01/2024. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.
176. Horwitz S, O'Connor OA, Pro B, *et al.* Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *The Lancet*. 2019;393(10168):229–240.
177. Sehn LH, Martelli M, Trněný M, *et al.* Final analysis of GOYA: a randomized, open-label, phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma. *Blood*. 2019;134:4088.
178. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2023.
179. NICE. British National Formulary (BNF). 2023.

180. NHS England. 2021/22 National Cost Collection Data Publication (2023). Accessed at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. Last accessed on: 09/01/2024. 2023. .
181. NICE. TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 02/26/2014. Last accessed: 01/09/2024. https://www.nice.org.uk/guidance/ta306.
182. Jones et al. Unit Costs of Health and Social Care 2022 Manual. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York).
183. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents). *NICE Decision Support Unit*. 2016;18.
184. NHS The Christie. Escalated BEACOPDac in Hodgkin lymphoma. Last accessed: 02/14/2024. https://www.christie.nhs.uk/media/3obncmdr/1420-escalated-beacopdac-in-hodgkin-lymphoma-dec-2020-unlocked.pdf.
185. NHS Thames Valley Strategic Clinical Network. BEACOPDac-Escalated. Available at: https://www.clatterbridgecc.nhs.uk/application/files/2616/7162/2389/Escalated_BEACOPDac_High_Grade_Hodgkin_Lymphoma.pdf. [Last accessed: 18/01/2024]. 2022.
186. NHS South West Clinical Network. BEACOPDac-14/ EscalatedBEACOPDac. Last accessed: 02/14/2024. https://www.swagcanceralliance.nhs.uk/wp-content/uploads/2020/10/BEACOPDac-14-escBEACOPDac-2.pdf.
187. NHS Northern Cancer Alliance. Escalated BEACOPDAC for Hodgkin's lymphoma. Last accessed: 02/14/2024. https://www.northerncanceralliance.nhs.uk/wp-content/uploads/2018/11/Escalated-BEACOPDac-Hodgkins-CRP18-H054.pdf.
188. NHS University Hospital Southampton. BLEOMYCIN-CYCLOPHOSPHAMIDE-DACARBAZINE-DOXORUBICIN-ETOPOSIDEPREDNISOLONE-VINCRISTINE (BEACOPDac Escalated). Last accessed: 02/14/2024. https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Lymphoma/BEACOPDac-escalated.pdf.
189. NHS The Clatterbridge Cancer Centre. Escalated BEACOPDac High Grade Hodgkin Lymphoma. Last accessed: 02/14/2024. https://www.clatterbridgecc.nhs.uk/application/files/2616/7162/2389/Escalated_BEACOPDac_High_Grade_Hodgkin_Lymphoma.pdf.
190. NHS Cumbria, Northumberland, Tyne & Wear Area Team. ABVD (Hodgkin's Lymphoma). 2014. Last accessed: 01/09/2024. https://www.northerncanceralliance.nhs.uk/wp-content/uploads/2018/11/ABVD-Protocol-Lymphomas.pdf.
191. NHS Kent & Medway Cancer Collaborative. ABVD. 04/24/2023. Last accessed: 01/09/2024. https://www.kmcc.nhs.uk/s3/assets/haem-hl-001-abvd-v4.pdf.
192. NHS South West Clinical Network. ABVD. 08/2020. Last accessed: 01/09/2024. https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2018/11/ABVD_.pdf.
193. NHS Thames Valley Strategic Clinical Network. ABVD. Last accessed: 01/09/2024. https://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-chemo-protocols/L-8%20-%20abvd.pdf.
194. NHS The Clatterbridge Cancer Centre. ABVD. Hodgkin's Lymphoma. 05/20/2022. Last accessed: 01/09/2024. https://www.clatterbridgecc.nhs.uk/application/files/5416/5590/6776/ABVD_Hodgkins_Lymphoma_V2.0.pdf.
195. NHS The Royal Marsden. ABVD chemotherapy for Hodgkin lymphoma. 08/2020. Last accessed: 01/09/2024. https://patientinfolibrary.royalmarsden.nhs.uk/document/download/1024.
196. NHS University Hospital Southampton. BLEOMYCIN-DACARBAZINE-DOXORUBICIN-VINBLASTINE (ABVD). 01/2015. Last accessed: 01/18/2024. https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Lymphoma/ABVD-%E2%80%93-Bleomycin-Dacarbazine-Doxorubicin-Vinblastine-Ver-1.2.pdf.
197. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. *Report by the Decision Support Unit*. 2011.
198. Rutherford M, Lambert P, Sweeting M, *et al.* Nice DSU technical support document 21: Flexible methods for survival analysis. *Leicester, UK: Department of Health Sciences, University of Leicester*. 2020;1–97.

199. Palmer S, Borget I, Friede T, *et al.* A guide to selecting flexible survival models to inform economic evaluations of cancer immunotherapies. *Value in Health*. 2023;26(2):185–192.
200. Office for National Statistics (ONS). National life tables: UK. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. [Last accessed: 05/02/3034]. .
201. Dolan P. Modeling valuations for EuroQol health states. *Medical care*. 1997;1095–1108.
202. Brazier J, Longworth L. NICE DSU Technical Support Document 8: an introduction to the measurement and valuation of health for NICE submissions. 2011.
203. Ramchandren R, Ansell SM, Armand P, *et al.* HSR19-107: Nivolumab for Newly Diagnosed Classical Hodgkin Lymphoma: Patient-Reported Outcomes From CheckMate 205 Cohort D. *Journal of the National Comprehensive Cancer Network*. 2019;17(3.5):HSR19-107.
204. Borchmann P, Goergen H, Kobe C, *et al.* PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *The Lancet*. 2017;390(10114):2790–2802.
205. NHS. 2020/21 National Tariff Payment System Annex B: Guidance on currencies with national prices. 2020.
206. NICE. TA446: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 06/28/2017. Last accessed: 04/11/2024. https://www.nice.org.uk/guidance/ta446.
207. NHS Blood and Transplant. Price List 2023/24. NHS. Blood and Components - Contract Equivalent Cost per Item. .
208. Laudicella M, Walsh B, Burns E, Smith PC. Cost of care for cancer patients in England: evidence from population-based patient-level data. *Br J Cancer*. 2016;114(11):1286–1292. https://doi.org/10.1038/bjc.2016.77.
209. Hancock H, Brockbank J, Brodtkorb T, Lucherini S, Russell J. EE469 A Review of Cure Assumptions Implemented in Early-Stage Oncology NICE Appraisals. *Value in Health*. 2022;25(12):S148. https://doi.org/10.1016/j.jval.2022.09.714.
210. Wigfield P, Sillem E, Heeg B. SA15 A Systematic Review to Assess How Cure Is Modelled and Subsequently Evaluated in Health Technology Submissions to the National Institute for Health and Care Excellence (NICE). *Value in Health*. 2023;26(12):S543. https://doi.org/10.1016/j.jval.2023.09.2924.
211. NHS. NHS commercial framework for new medicines. 06/06/2022. Last accessed: 04/12/2024. https://www.england.nhs.uk/wp-content/uploads/2021/02/B1688-nhs-commercial-framework-for-new-medicines-june-22.pdf.
212. Department of Health and Social Care. 2024 Voluntary Scheme for Branded Medicines Pricing, Access and Growth. 2024.
213. Amin MSA, Brunckhorst O, Scott C, *et al.* ABVD and BEACOPP regimens' effects on fertility in young males with Hodgkin lymphoma. *Clin Transl Oncol*. 2021;23(6):1067–1077. https://doi.org/10.1007/s12094-020-02483-8.
214. Bröckelmann PJ, McMullen S, Wilson JB, *et al.* Patient and physician preferences for first-line treatment of classical Hodgkin lymphoma in Germany, France and the United Kingdom. *British Journal of Haematology*. 2019;184(2):202–214. https://doi.org/10.1111/bjh.15566.
215. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ: British Medical Journal*. 1996;313(7052):275.
216. Philips Z, Ginnelly L, Sculpher M, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health technology assessment (Winchester, England)*. 2004;8(36):iii–iv.
217. Bullement A, Cranmer HL, Shields GE. A Review of Recent Decision-Analytic Models Used to Evaluate the Economic Value of Cancer Treatments. *Appl Health Econ Health Policy*. 2019;17(6):771–780. https://doi.org/10.1007/s40258-019-00513-3.
218. Büyükkaramikli NC, Rutten-van Mölken MP, Severens JL, Al M. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. *Pharmacoeconomics*. 2019;37:1391–1408.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

Addendum to Company Submission in response to Evidence Assessment Group report

September 2024

File name	Version	Contains confidential information	Date
ID6334_ brentuximab_ vedotin_uHL_ Addendum_ [redacted]	1.0	No	26 September 2024

Contents

Purpose of addendum

In response to the Company submission for brentuximab vedotin with doxorubicin, dacarbazine and vinblastine (A+AVD) for previously untreated late-stage classical Hodgkin lymphoma, the EAG provided their report, dated 24 June 2024. The report detailed the EAG's five key issues with the submission. The Company subsequently agreed with NICE to provide additional information and points of clarification relating to three key issues (issues 1, 2, and 5) to address residual uncertainty prior to the first Appraisal Committee Meeting.

EAG key issue 1 | Clinical data for ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) not reflective of current standard care in UK clinical practice

As described by the EAG in Table 2 of the EAG report, the Company used clinical efficacy data for six-cycle ABVD from the ECHELON-1 trial to inform ABVD-based treatment in its economic model, and inherently assumed equal efficacy between six-cycle and positron emission tomography (PET)-adapted ABVD. The assumption of equal efficacy between ABVD-based treatments was supported by matching-adjusted indirect comparisons (MAICs), informed by data on PET-adapted ABVD from the Response-Adapted Therapy for advanced Hodgkin Lymphoma (RATHL) trial. In response to the EAG clarification questions, the Company also provided an MAIC comparing A+AVD from ECHELON-1 with PET-adapted ABVD from RATHL. However, the EAG considered "*the results of the MAICs to be unreliable*" due to the following:

- The EAG stated that "*the data from RATHL in the company's MAICs only comprise of patients who are de-escalated following a negative PET2 scan*", and indicated that because the RATHL data "*does not include the outcomes for PET2 positive patients who would receive treatment escalation to escBEACOPDac*", it is not reflective of UK clinical practice (EAG report, pages 39, 63, 64, 68, and 80)

- The EAG considered the results of the fully adjusted MAIC comparing six-cycles of ABVD from ECHELON-1 vs PET-adapted ABVD from RATHL to

"*contradict findings in the RATHL trial*" and suggested that this may impact the "*face validity and generalisability of the findings*" of this analysis (EAG report, pages 39, 64)

- The EAG stated that "*there is evidence to suggest that the proportional hazards assumption is violated*" (EAG report, pages 39, 63, and 80).

The Company have provided further information below with an aim of alleviating these concerns.

Outcomes for PET after cycle 2 (PET2)-positive patients who escalate treatment are captured

The Company would like to clarify that, as per our factual accuracy check (FAC) of the EAG report (FAC; pages 3–5), the RATHL data informing the Company's MAICs included both patients who were PET2 positive and underwent treatment escalation, and those who were PET2 negative and de-escalated treatment.

From the RATHL trial, 702 Stage III and IV patients contributed to the progression-free survival (PFS) and overall survival (OS) data. Of these, 99 (14.1%) patients were PET2 positive and received bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (BEACOPP)-based regimens. For reassurance, the Company used Figure A2 from the supplemental appendix of Luminari et al. 2024, which shows the 702 Stage III and IV patients at risk at time zero.[1] Therefore, the impact of treatment escalation is reflected in the data informing all MAICs presented in the Company's response to the EAG's clarification questions.

The Company notes the opinion of the EAG that "*the clinical efficacy of A+AVD versus PET-adapted ABVD to be uncertain and is concerned that the clinical efficacy data used in the cost effectiveness analyses may not accurately reflect outcomes in UK clinical practice*" (EAG report, pages 39 and 69). However, the Company is concerned that this conclusion is based on the assumption that the RATHL data informing the analyses only includes patients who are de-escalated following a negative PET2 scan, which is an inaccurate interpretation of the data informing the MAICs presented in the Company submission and response to clarification

questions. The Company therefore believes the analyses informed by the RATHL data are reflective of the outcomes associated with PET-adapted ABVD in UK clinical practice.

Face validity of results of the MAIC comparing six cycles of ABVD from ECHELON-1 vs PET-adapted ABVD from RATHL

In the original Company submission, unanchored MAICs comparing six cycles of ABVD and PET-adapted ABVD were presented, adjusting for age, International Prognostic Score (IPS) and Eastern Cooperative Oncology Group (ECOG) score. For OS, the relative efficacy of ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL) was associated with a hazard ratio (HR) of 0.63 (95% confidence interval [CI]: 0.44–0.89, p<0.001). This result was statistically significant and suggested a benefit with ABVD (six cycles) compared to PET-adapted ABVD. However, as stated in Section B.1.3.4.3 of the original Company submission, a survival difference between ABVD (six cycles) and PET-adapted ABVD was not expected based on UK clinical experience.

As discussed in Appendix D.1.7.2 (page 85) of the original Company submission, these results were believed to be driven by matching on the age variable; specifically, the RATHL population is younger than the ABVD (six cycles) arm of ECHELON-1, with a mean age of [redacted] and [redacted] years, respectively. Therefore, the Company presented an additional MAIC in Appendix D.1.7.2, where age was excluded from the adjustment, and these analyses were associated with a non-significant HR of 0.88 (95% CI: 0.62–1.23) for ABVD (six cycles) vs PET-adapted ABVD, supporting the assumption of equivalent efficacy between ABVD (six cycles) and PET-adapted ABVD, and aligning with the results of the RATHL trial and clinical expectations.

The Company consider the results of the fully adjusted, unanchored MAIC comparing six-cycles of ABVD from ECHELON-1 vs PET-adapted ABVD from RATHL (adjusting for age, IPS, ECOG, stage, sex, B-symptoms, bulky disease and presence of extra-nodal sites), as presented in response to the EAG clarification questions, to similarly be driven by matching on the age variable. Therefore, the Company have conducted a further MAIC to explore this, adjusting for IPS, ECOG,

stage, sex, B-symptoms, bulky disease and presence of extra-nodal sites (i.e. adjusting for all available baseline characteristics, excluding age).

Table 1 presents the baseline characteristics before and after matching, adjusting for all reported baseline characteristics, excluding age, for the comparison of the MAIC-weighted ABVD (six cycles) arm from ECHELON-1 and PET-adapted ABVD from the Stage III and IV subgroup in RATHL.

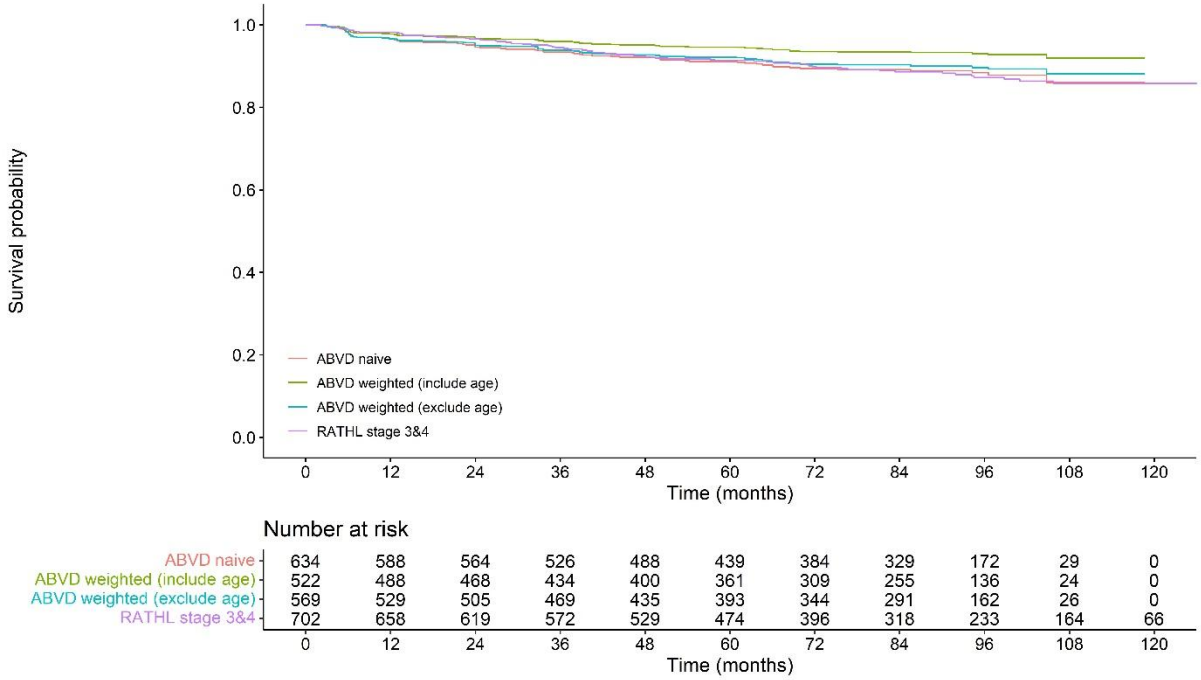
Table 1: Baseline characteristics before and after matching for the MAIC adjusting for all reported baseline characteristics, excluding age | ABVD (six cycles) vs. PET-adapted ABVD

Analysis	Treatment	ESS*	Baseline characteristic						
			IPS 3-7	ECOG ≥1	Stage IV	Male	B symptom present	Bulky present	Extranodal site ≥1
Unweighted	ABVD (six cycles)	634 (100.0%)	52.1%	43.1%	63.1%	59.0%	56.5%	32.0%	65.0%
Weighted	ABVD (six cycles)	512.74 (80.9%)	50.2%	29.6%	48.4%	59.3%	61.7%	27.2%	52.0%
Weighted	PET-adapted ABVD	702	50.2%	29.6%	48.4%	59.3%	61.7%	27.2%	52.0%

*36 patients from ABVD arm of ECHELON-1 who did not have stage, bulky disease, or extranodal site information were excluded from the analysis; therefore, the starting sample for ABVD was 634 instead of 670.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IPS, International Prognostic Score; MAIC, matching-adjusted indirect comparison; PET, positron emission tomography.

Figure 1 presents the unweighted and weighted ABVD (six cycles; ECHELON-1) OS Kaplan-Meier data compared to the PET-adapted ABVD (RATHL Stage III/IV subgroup) OS data when matching on all baseline characteristics reported in the respective studies, including age, alongside the new analysis that matches on all baseline characteristics, excluding age. Critically, the weighted ABVD (six cycles; ECHELON-1) and PET-adapted ABVD (RATHL) Kaplan–Meier curves in the new analysis appear to be similar and overlap at multiple timepoints and, compared to the analysis matching on all baseline characteristics including age, there is no longer a visible difference between treatment arms.

Figure 1: Unweighted and weighted OS data for ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics, and adjusting for all baseline characteristics excluding age, for the MAIC analyses



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matching-adjusted indirect comparison; OS, overall survival; PET, positron emission tomography; RATHL, response-adapted trial.

Table 2 presents the results of all unanchored MAIC analyses for OS, including results of the new analysis that adjusts for all available baseline characteristics, excluding age. Importantly, for OS, the relative efficacy of ABVD (six-cycles) compared to PET-adapted ABVD (RATHL) is associated with a HR of 0.88 (95% CI: 0.61–1.27, p=0.490); this non-significant HR is considerably closer to one than the MAIC where age is adjusted for and aligns with the visual interpretation of the Kaplan–Meier curves (Figure 1).

Table 2: Results of the ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL) MAIC analyses, including analyses previously presented and new analysis matching based on all baseline characteristics, excluding age | OS

Variables matched	Analysis	ESS	HR (95% CI)	Log rank p-value
Age + IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.02 (0.73, 1.42)	0.987
	Weighted	553.22 (82.8%)	0.63 (0.44, 0.89)	0.010
IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.02 (0.73, 1.42)	0.909
	Weighted	619.42 (92.7%)	0.88 (0.62, 1.23)	0.443
All baseline characteristics (response to EAG clarification questions)	Unweighted	634 (100.0%) ‡	1.00 (0.71, 1.40)	0.996
	Weighted	441.72 (69.7%)	0.59 (0.40, 0.85)	0.005
	Unweighted	634 (100.0%) ‡	1.00 (0.71, 1.40)	0.071

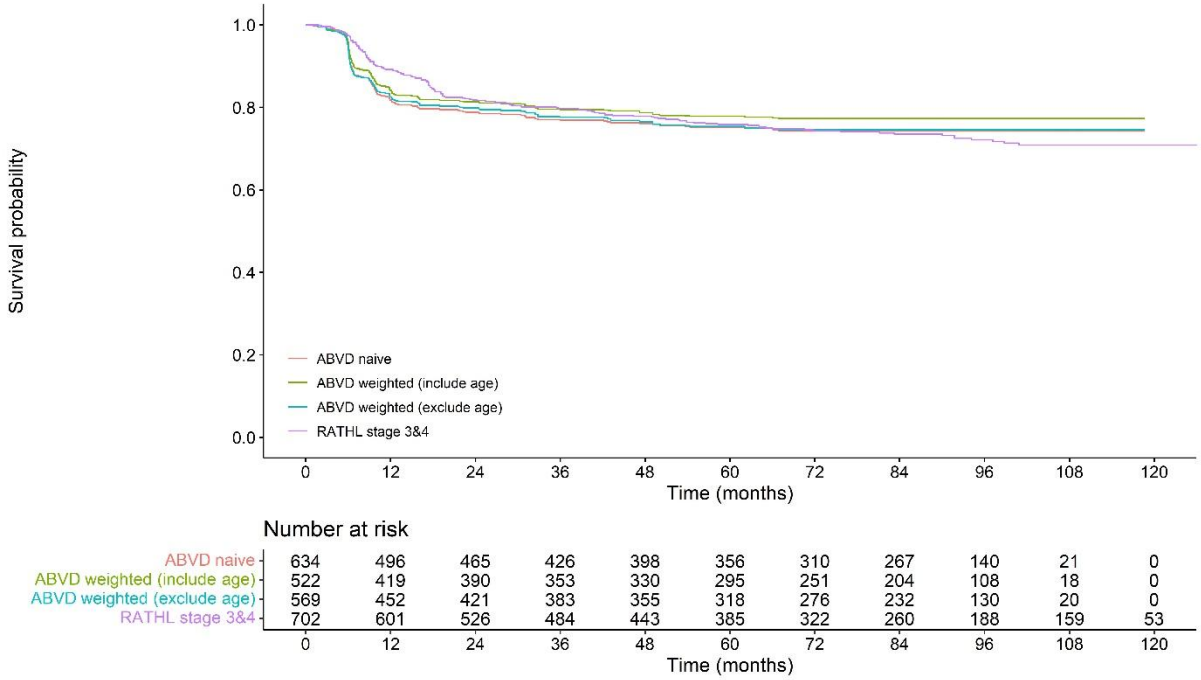
Variables matched	Analysis	ESS	HR (95% CI)	Log rank p-value
All baseline characteristics excluding age (new analysis)	Weighted	512.74 (80.9%)	0.88 (0.61, 1.27)	0.490

‡2 patients from ABVD arm of ECHELON-1 who did not have ECOG information were excluded from the analysis. ‡ 36 patients from ABVD arm of ECHELON-1 who did not have stage, ECOG, bulky disease, or extranodal site information were excluded from the analysis.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IPS, International Prognostic Score; MAIC, matching-adjusted indirect comparison; OS, overall survival; PET, positron emission tomography; RATHL, response-adapted trial.

For completeness, the Company have also presented results of the MAIC for PFS, adjusting for all available baseline characteristics, excluding age. The unweighted and weighted PFS Kaplan–Meier data and results of the MAIC comparing ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL Stage III/IV subgroup), matching on all baseline characteristics, excluding age, are presented in Figure 2 and Table 3, respectively.

Importantly, when age is excluded from the MAIC, the Kaplan–Meier curves appear to be similar and overlap at multiple timepoints, and the PFS HR is even closer to one than the MAIC where age is adjusted for and remains non-significant (1.01 [95% CI: 0.80–1.27, p=0.960]).

Figure 2: Unweighted and weighted PFS data for ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics, and adjusting for all baseline characteristics excluding age, for the MAIC analyses



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matching-adjusted indirect comparison; PET, positron emission tomography; PFS, progression-free survival; RATHL, response-adapted trial.

Table 3: Results of the ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL) MAIC analyses, including analyses previously presented and new analysis matching based on all baseline characteristics, excluding age | PFS

Variables matched	Analysis	ESS	HR (95% CI)	Log rank p-value
Age + IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.03 (0.83, 1.27)	0.818
	Weighted	553.22 (82.8%)	0.92 (0.73, 1.17)	0.505
IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.02 (0.82, 1.26)	0.878
	Weighted	619.42 (92.7%)	0.99 (0.79, 1.24)	0.937
All baseline characteristics (response to EAG clarification questions)	Unweighted	634 (100.0%) ‡	1.03 (0.83, 1.27)	0.818
	Weighted	441.72 (69.7%)	0.89 (0.70, 1.13)	0.342
All baseline characteristics excluding age (new analysis)	Unweighted	634 (100.0%) ‡	1.03 (0.83, 1.27)	0.818
	Weighted	512.74 (80.9%)	1.01 (0.80, 1.27)	0.960

† 2 patients from ABVD arm of ECHELON-1 who did not have ECOG information were excluded from the analysis. ‡ 36 patients from ABVD arm of ECHELON-1 who did not have stage, ECOG, bulky disease, or extranodal site information were excluded from the analysis.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IPS, International Prognostic Score; MAIC, matching-adjusted indirect comparison; PET, positron emission tomography; PFS, progression-free survival; RATHL, response-adapted trial.

In conclusion, the results of the MAIC comparing six-cycles of ABVD versus PET-adapted ABVD adjusting for all available baseline characteristics, excluding age,

demonstrate comparable OS and PFS, with non-significant HRs and similar Kaplan–Meier curves which overlap at multiple timepoints. These results support the findings of the RATHL trial which confirmed non-inferiority of treatment de-escalation in PET-negative patients, and clinical expert opinion that outcomes are not expected to differ between ABVD-based treatments. These results indicate that results of the fully adjusted MAICs presented in the Company's response to EAG clarification questions were driven by matching on the age variable, due to the RATHL population being younger than the ECHELON-1 population. When adjusting for all possible variables, including age, the Company believes that the residual difference between the OS Kaplan-Meier curves for ABVD (six cycles) and PET-adapted ABVD specifically may be due to heterogeneity in treatment practices across regions. The Company believes that the results of the additional analyses have face validity, are generalisable to UK clinical practice, and further support the assumption of equivalent efficacy between ABVD (six cycles) and PET-adapted ABVD applied in the Company's economic analysis.

The proportional hazards assumption

In reference to the MAICs conducted to support equivalent efficacy between ABVD-based treatments, the EAG considered "*the results of the MAICs to be unreliable*", partly due to "*the assumption of proportional hazards was shown not to hold in the MAICs where full adjustment for all baseline characteristics was made*" (EAG report, page 22).

The Company do not believe that violation of the proportional hazards assumption would result in these MAICs being unreliable for the purpose of demonstrating equivalent efficacy between ABVD-based treatments. For clarity, outcomes from these analyses were not used to inform the economic model. The economic model assumes equivalent outcomes for ABVD (six cycles) and PET-adapted ABVD; an assumption validated by the outputs from the MAICs, including both HRs and visual interpretation of the weighted Kaplan–Meiers. The log-cumulative hazard plots, presented in Figures 5 and 6 of the EAG clarification response, support this assumption further by demonstrating a similar hazard profile with lines that repeatedly overlap.

At clarification stage, the EAG requested an MAIC comparing A+AVD from ECHELON-1 with PET-adapted ABVD from RATHL as the EAG considered it "*to be the most appropriate source of data for the comparison of A+AVD versus ABVD*". Similarly to above, the EAG has noted that these analyses are "*likely to also be unreliable*", partly based on "*evidence to suggest the assumption of proportional hazards is violated*" (EAG report, pages 39, 68, and 80).

The Company would like to clarify that in the alternative base case presented in the Company's response to the EAG clarification questions (pages 88–96), where the MAIC comparing A+AVD from ECHELON-1 with PET-adapted ABVD from RATHL was utilised to inform comparative efficacy, outcomes were modelled independently using the weighted A+AVD PFS and OS Kaplan-Meier data from the MAIC and the PET-adapted ABVD digitised data from RATHL (Stage III/IV subgroup). Importantly, this approach does not use HRs and does not assume proportional hazards. Therefore, the Company do not believe that the proportional hazards assumption is relevant to the interpretation of comparative efficacy in the economic model.

EAG key issue 2 | Bimodal age patient population not adequately accounted for in the model

As stated in the original Company submission and EAG report, the incidence of Hodgkin lymphoma (HL) in clinical practice is bimodal, with peaks at ages 20–24 years and 75–79 years (Company submission; Section B.1.3.2).[2, 3]

In the original Company submission, a mean age of 39.53 (95% CI: 38.68–40.39) based on the intention to treat (ITT) population of ECHELON-1 was used to inform the economic model. The Company explored uncertainty in baseline age via the probabilistic sensitivity analyses which randomly sampled age using a normal distribution, and via deterministic and probabilistic scenario analyses which explored the impact of using a median baseline age of [redacted] (95% CI: [redacted]) from the Stage III/IV subgroup of the RATHL trial (Company submission; Section B.3.11). However, the EAG indicated that the "*company's mean age based approach may not be appropriate, given the two patient populations predominantly impacted*" and may be "*overly simplistic*" (EAG report; Section 4.2.3.1, pages 23 and 78).

In the clarification questions, the EAG requested an alternative approach based on age subgroups (<60 years and ≥60 years) to explore the impact of age distribution on the incremental cost-effectiveness ratio (ICER); this approach modelled the <60 years and ≥60 years subgroups independently and then weighted the respective ICERs by the proportion of patients in each subgroup in ECHELON-1 (86.1% <60 years and 13.9% ≥60 years).

Whilst the Company conducted the scenario in response to the EAG's clarification question, the Company disagrees with this approach, as detailed below:

- This approach explores the cost-effectiveness of two age subgroups defined by the pre-specified subgroup analysis for the modified PFS endpoint in the ECHELON-1 clinical study report (CSR). Despite, this clinical expert opinion elicited by the Company indicated that subgroup analyses based on age would not impact the way they would treat previously untreated Stage III or IV HL, and a patient considered suitable for ABVD-based treatment will receive it if they are deemed sufficiently fit to do so, irrespective of age (EAG

clarification response to question B1, page 41). Therefore, assessing the cost-effectiveness of specific age subgroups is not appropriate, nor does it align with UK clinical practice (Company response to EAG clarification questions; question B1; page 32).

- This approach introduces additional, and unnecessary, uncertainty. As the ECHELON-1 trial was not stratified by age (age was only a pre-specified subgroup analysis for the modified PFS endpoint that was not used to inform the economic model), utilising subgroup data based on age breaks randomisation (EAG clarification response to question B1, page 41). A key advantage of the base case submitted by the Company is that the economic model is informed by the ITT population from ECHELON-1, thus preserving the benefits of randomisation and reducing the potential bias between treatment arms. As per the NICE manual, inferences about relative effects drawn from studies without randomisation will be more uncertain than those from randomised controlled trials (RCTs).[4] The Company therefore consider it fundamentally inappropriate to utilise these subgroup data to inform outcomes and associated quality-adjusted life years (QALYs) in the economic model.

- In addition, there are considerably fewer patients informing the subgroup analyses versus the ITT analyses (1,334 patients; A+AVD, 664; ABVD, 670), and lower numbers of PFS and OS events. [5] For the age ≥60 years subgroup in particular, data are only available for 84 and 102 patients in the A+AVD and ABVD arms, respectively (Company response to the EAG clarification questions; question B1, page 41).

- The EAG's proposed method for capturing the bimodal nature of HL still utilises a mean age-based approach; the mean age of patients in each subgroup is used to inform age in the economic model. The Company therefore believe the EAG's proposed approach does not fully address the EAG's issue that the "*mean age-based approach may not be appropriate*".

- The EAG states that "*the populations are not considered separately and so there is no negative impact to health inequities*". The Company acknowledge that the EAG presents one weighted ICER in their preferred base case.

However, the approach in the EAG preferred base case models the two subgroups separately (i.e., adopting different modelling approaches to inform efficacy and updated subgroup-specific inputs); this is further demonstrated in Section 6.3.1 in the EAG report where the uncertainty within each age-specific subgroup is explored separately. Therefore, the Company want to highlight that this approach does consider the populations separately and so there remains a risk of a potentially negative impact on health inequities.

- In addition, the presentation of separate sets of sensitivity analysis results for each modelled subgroup (EAG report Section 6.3.1) indicates that uncertainty around the weighted base case ICER has not been fully characterised and quantified, as specified in the NICE manual. The NICE manual also stipulates that “the committee's preferred cost-effectiveness estimate should be derived from a probabilistic analysis”; this is not possible given the EAG only presents a deterministic weighted base case ICER for decision making.

To support the response to this issue, the Company conducted a targeted review of NICE technology appraisals (TAs) published in the last three years in disease areas cited to have a bimodal age distribution based on Desai et al. (2022): acute lymphoblastic leukaemia, osteosarcoma, Hodgkin lymphoma, germ cell tumours, and breast cancer.[6] A search was conducted for technology appraisal guidance in these therapy areas that was published in the last three years and mentioned “age” in their final appraisal determination and “bimodal” or “peak” in their committee papers in relation to this issue were considered in this review. Six prior TAs were identified: two in acute lymphoblastic leukaemia (TA893 and TA975), two in Hodgkin lymphoma (TA540 and TA967) and two in breast cancer (TA952 and TA992).[7–12] Importantly, none of the identified appraisals modelled subgroups independently based on age, and the bimodal age distribution was only discussed in the context of equity issues. This was similarly the case in the prior NICE TA assessing brentuximab vedotin for the treatment of CD30-positive Hodgkin lymphoma (TA524).[13] Therefore, there is no precedence for the EAG’s approach in prior NICE appraisals.

The Company acknowledges the bimodal incidence of HL in UK clinical practice. However, the Company believes that the most robust approach to assess the impact of the distribution of age is through an appropriately parameterised probabilistic

sensitivity analysis and the associated probabilistic ICER. Therefore, the Company has explored an alternative approach to exploring the impact of the age distribution on the probabilistic ICER. Aligning with the efficacy data informing the economic model, the probabilistic analysis now randomly samples age from the individual patient data from ECHELON-1 with replacement across 1,000 iterations. This approach ensures that the distribution of age observed in ECHELON-1 is accounted for in the probabilistic analysis.

Based on the updated cost-effectiveness results presented in the Company's response to EAG clarification questions, and the updated probabilistic analysis that randomly sampled age from the ECHELON-1 data, the probabilistic ICER was £39,079. This is congruent with the deterministic ICER of £37,355, as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 3). The proportions of simulations considered cost-effective at a threshold of £20,000 and £30,000 per QALY are [redacted]% and [redacted]% when using the ECHELON-1 data, respectively (Figure 4).

Table 4: Probabilistic sensitivity analysis results | Sampling age from the ECHELON-1 individual patient level data

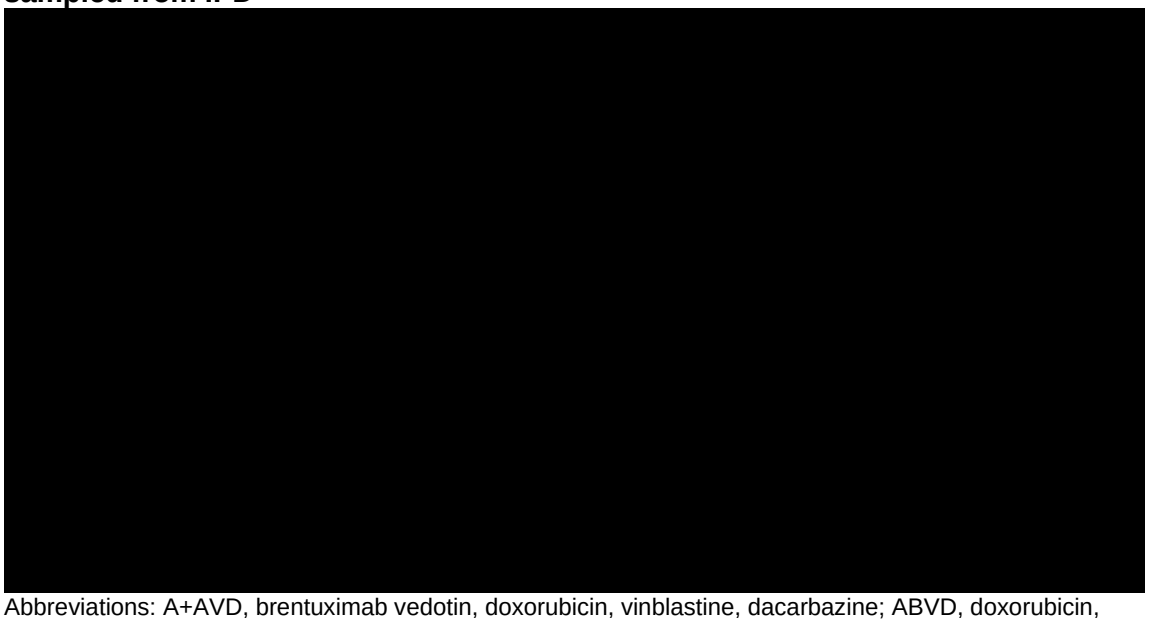
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	£[redacted]	[redacted]	[redacted]				
ABVD-based treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALY, quality adjusted life year.

Figure 3: Cost-effectiveness plane | 1,000 iterations | ECHELON-1 data | Baseline age sampled from the IPD

Abbreviations: IPD, individual patient data; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 4: Cost-effectiveness acceptability curve | ECHELON-1 data | Baseline age sampled from IPD



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; IPD, individual patient data.

EAG key issue 5 | Life-long peripheral neuropathy not included in the model

In the original Company submission, the model included Grade ≥3 drug-related treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients from ECHELON-1, which corresponds to Table 12.k in the CSR. Note that, as per the Company response to Question A8, peripheral neuropathy was a standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) that grouped multiple peripheral neuropathy preferred terms. As no single preferred term relating to neuropathy was reported in ≥5% of patients at the March 2023 data cut-off, peripheral neuropathy (PN) was not captured in the Company economic model.

Following the EAG's request in their clarification questions, the Company provided a scenario where peripheral neuropathy was added to the economic model based on Grade ≥3 events under the SMQ of Peripheral Neuropathy. As per Question A7, 68 patients (10.3%) in the A+AVD arm and 11 patients (1.7%) in the ABVD arm reported one or more Grade ≥3 PN events. In this scenario, the impact of PN on health-related quality of life (HRQoL) was assumed to be captured by the AE coefficient included in the utility regression model (−0.03), and the duration of PN was based on average mean time to resolution of resolved PN from ECHELON-1 ([redacted] and [redacted] weeks for A+AVD and ABVD, respectively). The utility decrement was multiplied by the proportion of patients experiencing PN and the mean duration of PN from ECHELON-1, equating to a QALY loss of −0.0018 and −0.0003 for A+AVD and ABVD, respectively, which was applied in the first cycle of the model.

However, in the EAG report, the EAG noted that 16 (2.4%) and 4 (0.6%) of A+AVD and ABVD patients had "*unresolved"* Grade ≥3 PN at last follow up (March 2023 DCO), respectively. The EAG's preferred base case includes an assumption that patients with "*unresolved"* Grade ≥3 PN at the end of follow up experience "lifelong" Grade ≥3 PN, which has been modelled across the model time horizon, incurring a utility decrement of −0.33, informed by Swinburn *at al*. 2015.

The Company have provided further information regarding the following:

- Further clarity on the ECHELON-1 data on ongoing Grade ≥3 PN at last follow up
- Potential errors in the EAGs method of modelling lifelong PN
- The EAG's base case assumption regarding the HRQoL impact of PN is considered inappropriate
- Further analyses exploring the impact of Grade ≥3 PN on HRQoL in ECHELON-1
- Precedence for the EAG's approach to modelling lifelong PN in prior NICE appraisals
- An alternative approach to modelling PN

Further clarity on the ECHELON-1 data on ongoing Grade ≥3 PN at last follow up

The Company would like to provide clarity regarding the data reported by the EAG on ongoing Grade ≥3 PN at last follow up (16 [2.4%] and 4 [0.6%] of A+AVD and ABVD patients, respectively). Of the 16 patients in the A+AVD arm who had ongoing Grade ≥3 PN at last follow up (March 2023), [redacted] previously died on-study, [redacted] were lost to follow up, and [redacted] had withdrawn from the study. Of the 4 patients in the ABVD arm who had ongoing Grade ≥3 PN at last follow up, [redacted] previously died and [redacted] were lost to follow up. Therefore, assuming 2.4% and 0.6% of patients experience "lifelong" PN is likely to be an overestimate and the assumption that all these patients have lifelong Grade ≥3 PN is inappropriate.

Two clinical experts consulted by the Company advised that treatment-related PN resolves in most patients, as observed in ECHELON-1 where 86% of patients with a treatment-emergent all-grade PN SMQ event (N=381/443) in the A+AVD arm experienced resolution or improvement (Table 6 of the Company response to EAG clarification questions). They also indicated that lifelong PN is rare but would be expected in a very small proportion of patients whose PN remains at the same Grade for 3 years or more. Therefore, only patients who had at least 3 years of

unresolved Grade ≥3 at their last follow-up were considered at risk of having lifelong PN.

Table 5 summarises patient numbers from ECHELON-1 who had ongoing Grade ≥3 PN at the end of trial follow up, were alive at the end of follow-up, and had at least 3 years of unresolved Grade ≥3 PN at their last follow-up ([redacted] [redacted%] and [redacted] [redacted%] of A+AVD and ABVD patients, respectively). Importantly, without long-term follow up, data on the duration of PN in these patients is limited, especially for those who were lost to follow up or withdrew from the study, and so there remains uncertainty regarding whether these patients go on to have lifelong Grade ≥3 PN. Therefore, these data may in fact overestimate the proportion of patients who have lifelong Grade ≥3 PN post-treatment, as only [redacted] patients in the A+AVD arm are still active in study and known to have Grade ≥3 PN at the end of trial follow-up.

Table 5: Ongoing Grade ≥3 peripheral neuropathy at last follow-up (March 2023) | ECHELON-1

	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing Grade ≥3 PN at last follow-up, n (%)	16 (2.4%)	4 (0.6%)
Patients with ongoing Grade ≥3 PN at last follow-up, who were alive at end of follow-up, n (%)	13 (2.0%)	2 (0.3%)
Patients with ongoing Grade ≥3 PN at last follow-up, who were alive at end of follow-up and had Grade ≥3 PN for at least 3 years prior to their last follow-up date, n (%)	[redacted] ([redacted%])	[redacted] ([redacted%])
End of study status of patients with ongoing Grade ≥3 PN at last follow up, who were alive at end of follow-up and had at least 3 years of unresolved Grade ≥3 at their last follow-up		
Lost to follow-up, n (%)	[redacted] ([redacted%])	[redacted] ([redacted%])
Withdrawal by subject, n (%)	[redacted] ([redacted%])	[redacted] ([redacted%])
Still active, n (%)	[redacted] ([redacted%])	[redacted] ([redacted%])

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PN, peripheral neuropathy.

Potential errors in the EAG's method of modelling lifelong PN

In the EAG's proposed approach, the disutility associated with lifelong PN is divided by the number of weeks in a year and multiplied by the proportion of patients who have ongoing Grade ≥3 PN at last follow up (16 [2.4%] and 4 [0.6%] of A+AVD and ABVD patients, respectively). This is then added to the total undiscounted QALYs per health state in the "Trace" sheet (columns AU and BG) and applied across the entire model time horizon. Whilst this approach transforms the utility decrement to a QALY decrement, this decrement is then applied at a constant rate throughout the

model time horizon without accounting for mortality. The Company have proposed a correction to ensure that patients who have died are not accruing this decrement. The Company have included an option on the "User" sheet defined as "Correct EAG application of lifelong PN". When this is set to equal 1, the utility decrement for lifelong PN is multiplied by the proportion of patients with "lifelong" PN and the total life years in each model cycle; this correction is made in columns AU and BG in the "Trace" sheet. Under the EAG's base case assumptions, this correction results in a change in the deterministic ICER from £[redacted] to £[redacted] (−4.95%).

Table 6: EAG base case results including the correction for the application of lifelong PN

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	£[redacted]	[redacted]	[redacted]				
ABVD-based treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; PN, peripheral neuropathy; QALY, quality adjusted life year.

In addition, a potential error has been identified in the model adapted by the EAG relating to the "HRQoL" sheet BJ14 for the duration of neutrophil count decreased. It appears the formula relevant for duration of neutropenia (BJ13) has been incorrectly copied to BJ14. The Company believes the formula in BJ14 should be corrected from *"=IF(User!O37=1,HRQoL!BD35,AVERAGE(11.1,15))"* to *"=IF(User!O37=1,HRQoL!BD35,AVERAGE(0,15))"*. This does not impact the EAG's base case ICER.

The EAG's base case assumption regarding the HRQoL impact of PN is inappropriate

Regardless of the potential errors identified, the Company does not consider the approach presented by the EAG to be appropriate based on the discussion below.

Importantly, while the Company acknowledges that Grade ≥3 PN has a severe impact on a patient's HRQoL, the assumption that Grade ≥3 PN is associated with a utility decrement of −0.33 is considered implausible. For example, under this assumption, a patient who is progression-free, off treatment and with PN, has a

lower quality of life (utility value of 0.531) than a patient with progressed disease (utility value of 0.791). The Company sought further clinical feedback on the impact of PN on quality of life (QoL), and they advised that patients who had progressed disease would have a worse QoL than patients who are progression-free with PN, as they would move on to stem cell transplant, further toxic treatments and have an increased risk of death. This therefore supports the Company's position that a utility decrement of −0.33 is implausibly high for lifelong Grade ≥3 PN.

Furthermore, the Company consider it implausible to assume a utility decrement as high as −0.33 would remain constant for the entire lifetime of a patient if they go on to have lifelong Grade ≥3 PN. Clinical feedback indicated that the management of PN with analgesics and other symptom controlling therapies has improved over recent years, and it is likely that the QoL of the small proportion of patients who have persistent, permanent PN may improve over time as they manage and better tolerate their symptoms. Assuming a constant utility decrement over a patients' lifetime may therefore overestimate the QALY loss associated with lifelong Grade ≥3 PN.

The utility decrement of −0.33 utilised in the EAG base case assumptions was sourced from Swinburn et al. 2015.[14] While the research presented by Swinburn et al. 2015 supports the Company's position and elicited clinical expert opinion that the HRQoL of a patient who has complete response and Grade 3 PN (mean utility score of 0.56 for the UK population) would be better than a patient with progressed disease (mean utility score of 0.38 for the UK population), the Company believes this study is an inappropriate source of data based on the following:[14]

- The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 11 states that "*vignettes and patient own health state valuation do not meet the NICE Methods Guidance for alternatives to EQ-5D. These only have a role where there are no data from validated HRQL measures*".[15] The EAG's base case approach is therefore considered a departure from the reference case. Further analysis on the impact of Grade ≥3 PN on HRQoL, as measured via EQ-5D-3L in ECHELON-1, is presented in the next subsection.

- Swinburn et al., (2015) is a vignette study which elicited time trade-off (TTO) valuations from members of the general public across seven countries

(including 100 members of the UK general public), developed to represent health states associated with a pooled population of relapsed/refractory (R/R) systemic anaplastic large cell lymphoma (sALCL) and R/R HL patients. These data were therefore intended to represent different populations, comprising relapsed/refractory lymphoma patients, rather than the frontline HL population relevant to this appraisal.

- Vignette studies are subject to bias in the definition of health state descriptions, which is particularly pertinent due to the methodology of eliciting health state descriptions in Swinburn et al 2015; vignettes were developed based on a review of the literature, consultation with clinical specialists and interviews with patients. Importantly, the NICE manual stipulates that "*health-related quality of life, or changes in health-related quality of life, should be measured directly by patients*". However, only five patients with R/R HL and one patient with sALCL were interviewed and hence contributed to the definition of vignettes and the associated health states, alongside supplementary input from the literature and clinical specialists. Furthermore, the NICE DSU TSD11 states that "*the validity of vignettes depends on the rigour with which they are designed", recommending "extensive qualitative work [to be] undertaken with patients to construct the vignettes*".[15] The small number of patients informing the study is therefore a limitation, and the Company has concerns about its validity and generalisability of the utility estimates in this patient population.

- The utility values presented in Swinburn et al. 2015 demonstrate that it is inappropriate to apply these data directly to the population of interest for this appraisal.[14] Specifically, the mean utility score associated with progressed disease is 0.38 (SD:0.28) for the UK population. This is considerably lower than the mean utility value estimated for progressed disease from ECHELON-1 (0.791; 95% CI 0.755, 0.828).

- The health states explored in Swinburn et al. 2015 included complete response (CR) alone and CR with peripheral sensory neuropathy (PSN) Grade 3.[14] This study therefore does not investigate the impact of PSN on QoL independently to the impact of CR.

Further analysis on the impact of Grade ≥3 PN on HRQoL in ECHELON-1

As discussed, the EAG base case approach applies a utility decrement of −0.33 to Grade ≥3 PN sourced from the Swinburn et al. 2015 publication, a vignette study that intended to represent a patient population with R/R sALCL and R/R HL. However, the NICE manual stipulates that "*health-related quality of life, or changes in health-related quality of life, should be measured directly by patients*", and that "*the EQ-5D measurement method is preferred to measure health-related quality of life in adults*" over sources from the literature or vignettes, as listed in the hierarchy of preferred HRQoL methods.[16] The EAG's base case approach is therefore considered a departure from the reference case.

As EQ-5D-3L data were collected in ECHELON-1, the Company conducted a further multivariate utility analysis of the ECHELON-1 data to better understand the impact of Grade ≥3 PN on HRQoL, specifically in patients with previously untreated Stage III and IV HL who have been treated with either A+AVD or ABVD. As this analysis is informed by ECHELON-1, utilising EQ-5D-3L in the patient population of interest, outputs are considered more relevant to this appraisal than the data presented by Swinburn et al. 2015.

The saturated model presented in the original company submission (Section B.3.4; from page 126) was adapted; the predictor for Grade ≥3 AEs was replaced by two PN-related predictors, "Grade ≥3 AEs that are not PN-related" and "Grade ≥3 AEs that are PN-related". A summary of the output from this model is presented in Table 7 and demonstrate that both AE-related terms were statistically significant ($p<0.05$) predictors of change in HRQoL over time. Specifically, Grade ≥3 PN AEs were associated with a utility decrement of −0.0836 (standard error [SE], 0.0141; $p<0.001$).

Table 7: Output from the saturated regression model including predictors for PN

Factor	Estimate	SE	t-value	p-value
(Intercept)	0.739	0.0251	29.4846	<0.001
Treatment status (ref=Off treatment) On treatment	-0.0813	0.0028	-29.4059	<0.001
Age (years)	-0.0028	0.0003	-10.3419	<0.001
Sex (ref=Female) Male	0.0084	0.0089	0.9444	0.3452

Factor	Estimate	SE	t-value	p-value
Baseline utility score	0.2851	0.0172	16.5964	<0.001
Receipt of G-CSF (ref=No) Yes	-0.0106	0.0138	-0.7706	0.4411
IPS risk factors (ref=0)				
1	0.0056	0.0221	0.2544	0.7992
2	0.0073	0.0219	0.3334	0.7389
3	0.0091	0.0222	0.4118	0.6805
4	0.017	0.0235	0.7222	0.4703
5	0.0417	0.0264	1.5827	0.1137
6	0.0832	0.0404	2.0575	0.0398
7	0.0182	0.0686	0.2659	0.7904
Grade 3+ non-PN AE (ref= no)	-0.0221	0.0045	-4.8746	<0.001
Grade 3+ PN AE (ref= no)	-0.0836	0.0141	-5.9383	<0.001
Progression status (ref=PF) PD	-0.0697	0.0088	-7.8797	<0.001

Abbreviations: AE, adverse event; G-CSF, granulocyte colony stimulating factor; IPS, International Prognostic Score; PD, progressive disease; PF, progression-free; ref, reference; SE, standard error.

While there are limited additional data in the literature, the Company identified a study (Hirose et al. 2020) which assessed the impact of serious adverse events on the QoL of patients in an outpatient cancer chemotherapy setting in Japan, utilising the EQ-5D-5L QoL measure.[17] Hirose et al. 2020 demonstrated that peripheral sensory neuropathy had a significant impact on HRQoL, reducing the EQ-5D-5L utility value by −0.06 (prior to peripheral sensory neuropathy, 0.807; during the development of peripheral sensory neuropathy, 0.747; P <0.001). The Company acknowledges the limitations associated with this study; for example, it was conducted in a Japanese patient population with a variety of cancers, of which "malignant lymphoma" only accounted for 6.7% of the population. However, in the absence of alternative data, the relative difference in utilities reported supports that the utility decrement of −0.0836 estimated by the Company's additional HRQoL analysis is more plausible than the −0.33 estimated by Swinburn et al. 2015.

Furthermore, Hirose et al 2020 also demonstrated that a disutility of −0.06 may be an overestimate of the utility impact of PN, as the EQ-5D-5L utility value associated with peripheral sensory neuropathy significantly improved after pharmaceutical intervention with treatments that aimed to alleviate neuropathy and general pain (pre-intervention, 0.747; post-intervention, 0.776; P = 0.015), which we know to be well established in UK clinical practice based on clinical expert feedback.

Precedence for the EAG's approach to modelling PN in prior NICE appraisals

To further support the response to this issue, the Company conducted a review of all published NICE TAs assessing brentuximab vedotin (BV; TA641, TA478, TA524, TA577).[13, 18–20] While it was widely acknowledged that Grade ≥3 PN is a known class effect of agents with an anti-microtubule mechanism of action, such as BV, only a small proportion of patients treated with BV experienced a Grade ≥3 PN across these appraisals. Furthermore, PN was widely considered manageable, with high rates of resolution or improvement. Several of these appraisals cited Swinburn et al. 2015 as the source of PN disutility data, however it was evident that this was only due to a lack of clinical trial data on the impact of PN on HRQoL, for example:

- In TA641, the impact of PN on HRQoL was not estimated in the regression analysis based on the key clinical trial, ECHELON-2, due to lack of observations.[18] Although the broader impact of AEs was captured in the HRQoL analysis based on ECHELON-2, the Company sourced an additional utility decrement of −0.33 from TA478 to account for Grade 3–4 PN in the absence of trial data in the population of interest. This approach was criticised by the EAG, who considered that the impact of Grade 3–4 PN would be captured in the Company's utility analyses and presented a scenario without this additional utility decrement applied.[18]

- In TA478, HRQoL data was not collected in the key clinical trial (Study SG035-0004) for the R/R sALCL indication.[19] In the absence of trial data, Swinburn et al. 2015 was considered appropriate as it was the only study identified by the SLR which reported utilities in sALCL.[19]

- In TA577, while the HRQoL analysis based on the ALCANZA data demonstrated that no difference in EQ-5D scores was observed between patients with and without peripheral neuropathy, it was noted that the full QoL impact was not captured in the ALCANZA trial due to low completion rates (69% for the BV arm) and small number of Grade ≥3 PN events (8% Grade ≥3 peripheral sensory neuropathy occurring in two or more patients treated with BV).[20] In the absence of robust data on the impact of PN on QoL from the ALCANZA trial, Swinburn et al. 2015 was cited as the source for the disutility

associated with Grade 1/2 PN (−0.11). A disutility associated with Grade ≥3 PN was not applied in the economic model.[20]

- In TA446/TA524, HRQoL data were not collected in the relevant clinical trial (0003) to inform utility analyses in the population of interest.[20, 21] Therefore, the Company sourced utility data from the literature, including Swinburn et al 2015 to inform disutilities associated with Grade 3+ peripheral neuropathy. However, the Company detailed the limitations of Swinburn et al. 2015 within their submission; Swinburn et al was a vignette study so does not meet the NICE reference case, and is subject to bias in the health state descriptions.[14, 21]

Further information on the approach to modelling PN in TA641, TA478, TA446/TA524, and TA577 is summarised in Table 9.

Importantly, despite acknowledging that PN can, in a small proportion of cases, be irreversible, none of the prior appraisals assessing brentuximab vedotin modelled the HRQoL impact of lifelong PN. Of note, in TA641, there were two patients in the BV+CHP arm of the ECHELON-2 trial that had ongoing Grade ≥3 peripheral neuropathy at the end of follow up; no discussion was had during the NICE appraisal regarding whether these patients were at risk of developing lifelong PN, and QALY losses associated with Grade 3–4 PN were only applied in the first model cycle for a duration of 127.4 days (as per ECHELON-2).[18]

Therefore, there is no precedence for the EAG's approach to model lifelong PN in prior NICE appraisals, and the Company maintains that sourcing disutility data from Swinburn et al. 2015 is inappropriate and that data derived directly from ECHELON-1 is preferable.

An alternative approach to modelling PN

As described above, the Company maintains that the EAG's approach to modelling PN is inappropriate and, given the uncertainty in the numbers of patients from ECHELON-1 who have ongoing Grade ≥3 PN, that modelling lifelong PN introduces unnecessary decision uncertainty in the analysis. However, the Company have conducted a scenario which explores an alternative approach to modelling PN that is

considered more appropriate. This scenario is based on the Company's updated base case assumptions that were presented in response to EAG clarification questions, with the addition of the EAG's approach to modelling PN assuming the below changes:

- The proportion of patients assumed to have lifelong Grade ≥3 PN has been updated to reflect the number of patients in ECHELON-1 who had ongoing Grade ≥3 PN at the end of trial follow up, were alive at the end of follow-up, and had at least 3 years of unresolved Grade ≥3 PN at their last follow-up ([redacted] [redacted%] and [redacted] [redacted%] of A+AVD and ABVD patients, respectively). Note that the Company maintain that these data still likely overestimate the proportion of patients who may go on to have lifelong Grade ≥3 PN in clinical practice.

- The potential errors in the EAG's method of modelling lifelong PN have been corrected to ensure that patients who have died are not accruing the utility decrement associated with Grade ≥3 PN, as previously detailed in this response.

- The utility analysis informing the economic model has been updated to reflect the Company's revised multivariate utility analysis based on ECHELON-1, with predictors for "Grade ≥3 AEs that are not PN-related" and "Grade ≥3 AEs that are PN-related". This attributes a utility decrement of −0.0836 to Grade ≥3 PN in the economic model.

Table 8 presents the results of this scenario, which demonstrated a minor increase in the Company's updated base case ICER from £[redacted] to £[redacted] (+2.39%).

Table 8: Scenario results based on the Company's updated base case assumptions, with the Company's alternative approach to modelling PN

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	£[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD-based treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALY, quality adjusted life year.

Table 9: Summary of prior brentuximab vedotin appraisals approach to modelling PN

Prior NICE TA	Approach to modelling PN	Approach to modelling lifelong PN
Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma (TA641)	• A small proportion of patients (4%, N=6) treated with BV+CHP in ECHELON-2 experienced Grade ≥3 peripheral sensory neuropathy, resulting in a low average rate of 0.04 events per patient. At the last follow up among the patients with ongoing events, two patients in the BV+CHP group had ongoing Grade 3 peripheral neuropathy events; treatment emergent PN generally resolved or improved following treatment (62% of all treatment emergent PN events). • Grade 3-4 PN was included in the model as it was acknowledged as a known class effect of agents such as BV with an anti-microtubule mechanism of action – assumptions of PN-related resource use and utility decrements were taken from TA478. • AEs were not extrapolated beyond the safety period and all costs/QALY losses were assumed to occur in the first model cycle. Grade 3-4 peripheral neuropathy was assumed to have an average duration of 127.4 days (sourced from ECHELON-2). • An additional disutility of -0.33 was applied to the number of Grade 3-4 PN events. This disutility was assumed identical to that applied in TA478; this effect was not estimated in the regression analysis based on ECHELON-2 due to lack of observations. The duration of Grade 3-4 PN was assumed to be 80.53 days in the BV+CHP arm, based on the ECHELON-2 data. • The Company applied an additional disutility for Grade 3-4 PN based on clinical opinion regarding the severity of episodes of Grade 3-4 PN, however the EAG noted that there was no justification as to why this AE would not have been captured in the HRQoL data which were assumed to cover all other AEs experienced. The EAG commented that "*assuming an additional substantial decrement for this AE could overestimate the impact of AEs*", and presented a scenario where this additional decrement was removed and the impact of this AE was assumed to be captured in the AE model coefficient.	No mention of modelling the utility impact of lifelong PN throughout appraisal documents.
Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma (TA478)	• In Study SG035-0004, AEs that occurred in ≥20% of patients included peripheral sensory neuropathy (41%, N=24/58), which were predominantly low in grade, sensory in nature and largely reversible. Of those treated with brentuximab vedotin, only seven had treatment emergent grade ≥3 peripheral sensory neuropathy. • Resolution or improvement in some or all events of peripheral neuropathy was noted in 81% of patients; they were sensory in nature and grade 1 or 2 in severity, and the median time to improvement or resolution was 13.4 weeks. The Company commented that these data demonstrated that peripheral neuropathy events with brentuximab vedotin were generally manageable, with high rates of resolution or improvement. • No HRQoL data were collected in the Study SG035-0004 for R/R sALCL indication. In the absence of trial data, other sources of utility data identified in the SLR were used. The Company presented the UK data from Swinburn et al. 2015, which was the only study identified by the SLR investigating utilities in sALCL. o Grade 1-2 peripheral sensory neuropathy: utility decrement of 0.10 o Grade 3-4 peripheral sensory neuropathy: utility decrement of 0.331 o The utility impact of AEs was applied in the first model cycle only	No mention of modelling the utility impact of lifelong PN throughout appraisal documents, nor any committee discussion in the ACD or FAD.

Prior NICE TA	Approach to modelling PN	Approach to modelling lifelong PN
Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (TA446/TA524)	• Although limited information is published regarding the Company's approach to modelling peripheral neuropathy (detail is in the original company submission TA446 that is not published on the NICE website), a comment from a UK clinician states that "*Although there are no comparative trials looking a QoL with brentuximab, it is a well tolerated agent and centres are very used to managing the well know side effect of peripheral neuropathy. Peripheral neuropathy is a common side effect. This can be severe. However brentuximab has been used now for some years and centres are well used to monitoring for it. Sometimes dose reductions and delays are required. Sometimes treatment needs to be discontinued. Thankfully it is reversible on stopping treatment in the majority of patients".* • HRQoL data were not collected in the relevant clinical trial to inform utility analyses in the population of interest. Therefore, the Company sourced utility data from the literature, including Swinburn et al 2015 to inform disutilities associated with Grade 3+ peripheral neuropathy (a disutility of -0.33). However, the Company detailed the limitations of Swinburn et al. 2015 within their submission; Swinburn et al was a vignette study so does not meet the NICE reference case, and is subject to bias in the definition of health state descriptions.	No mention of modelling the utility impact of lifelong PN throughout appraisal documents, nor any committee discussion in the FAD.
Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma (TA577)	• The most common Grade ≥3 TRAE observed with brentuximab vedotin in the ALCANZA trial was peripheral neuropathy, based on the peripheral sensory neuropathy SMQ definition (n=7 events at a median of 33.9 months follow up); 86% had improvement or resolution. While there were patients with ongoing grade 1/2 PN (41%), there were no patients with ongoing grade 3/4 PN at the end of trial follow up. The median time to resolution of peripheral neuropathy was 30.0 weeks. • The HRQoL analysis based on the ALCANZA data demonstrated that no difference in EQ-5D scores were observed between patients with and without peripheral neuropathy. However, it was noted that the full QoL impact was not captured in the ALCANZA trial due to low completion rates (69% for BV) and small number of Grade ≥3 events (8% Grade ≥3 peripheral sensory neuropathy occurring in two or more patients treated with BV). • The Company used a disutility of -0.11 for peripheral neuropathy, assumed to be equal to the Grade I/II peripheral sensory neuropathy utility value reported by Swinburn et al 2015, which was identified in a targeted review of previous NICE submissions focusing on lymphoma indications. The Company considered the Swinburn study to be a "*often cited representation of highly progressed lymphoma patients*" specifically.	No mention of modelling the utility impact of lifelong PN throughout appraisal documents, nor any committee discussion in the ACD or FAD.

Abbreviations: ACD, appraisal consultation document; AE, adverse event; BV, brentuximab vedotin; BV-CHP, brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisolone; EAG, external assessment group; FAD, final appraisal determination/document; PN, peripheral neuropathy; QALY, quality-adjusted life year; QoL, quality of life; sALCL, systemic anaplastic large cell lymphoma; SLR, systematic literature review; SMQ, standardised MedDRA query; TA, technology appraisal; TRAE, treatment-related adverse event.

References

1. Luminari S, Fossa A, Trotman J, *et al.* Long-Term Follow-Up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma Trial. *JCO*. 2024;42(1):13–18. https://doi.org/10.1200/JCO.23.01177.
2. Cancer Research UK. Hodgkin lymphoma statistics. Last accessed: 04/10/2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma.
3. Rafiq M, Hayward A, Warren-Gash C, *et al.* Socioeconomic deprivation and regional variation in Hodgkin's lymphoma incidence in the UK: a population-based cohort study of 10 million individuals. *BMJ Open*. 2019;9(9):e029228. https://doi.org/10.1136/bmjopen-2019-029228.
4. NICE. NICE health technology evaluations: the manual (Section 3.3.9). 01/31/2022. Last accessed: 04/01/2024. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.
5. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma | Addendum 3 - March 2024. 2024.
6. Desai S, Guddati AK. Bimodal Age Distribution in Cancer Incidence. *World J Oncol*. 2022;13(6):329–336. https://doi.org/10.14740/wjon1424.
7. NICE. TA893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. Available at: https://www.nice.org.uk/guidance/ta893. [Last accessed: 12/09/2024]. 2023.
8. NICE. TA975: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under. Available at: https://www.nice.org.uk/guidance/ta975. [Last accessed: 12/09/2024]. 2024.
9. NICE. TA967: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma in people 3 years and over. Available at: https://www.nice.org.uk/guidance/ta967. [Last accessed: 12/09/2024]. 2024.
10. NICE. TA952: Talazoparib for treating HER2-negative advanced breast cancer with germline BRCA mutations . Available at: https://www.nice.org.uk/guidance/ta952. [Last accessed: 12/09/2024]. 2024.
11. NICE. TA992: Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy. Available at: https://www.nice.org.uk/guidance/ta992. [Last accessed: 12/09/2024]. 2024.
12. NICE. TA540: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma. Available at: https://www.nice.org.uk/guidance/ta540. [Last accessed: 12/09/2024]. 2024.
13. NICE. TA524: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 2018. Last accessed: 10/19/2023. https://www.nice.org.uk/guidance/ta524.
14. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leukemia & Lymphoma*. 2015.
15. Brazier J, Rowen D. NICE DSU Technical Support Document 11: Alternatives to EQ-5D for Generating Health State Utility Values. London: National Institute for Health and Care Excellence (NICE); 2011.

16. NICE. NICE health technology evaluations: the manual. 01/31/2022. Last accessed: 04/01/2024. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.
17. Hirose C, Fujii H, Iihara H, *et al.* Real-world data of the association between quality of life using the EuroQol 5 Dimension 5 Level utility value and adverse events for outpatient cancer chemotherapy. *Support Care Cancer*. 2020;28(12):5943–5952. https://doi.org/10.1007/s00520-020-05443-8.
18. NICE. TA641: Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma. 08/12/2020. Last accessed: 04/10/2024. https://www.nice.org.uk/guidance/ta641.
19. NICE. TA478: Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma. 2017. Last accessed: 04/01/2024. https://www.nice.org.uk/guidance/ta478.
20. NICE. TA577: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma. 2019. Last accessed: 04/10/2024. https://www.nice.org.uk/guidance/ta577.
21. NICE. TA446: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 06/28/2017. Last accessed: 04/11/2024. https://www.nice.org.uk/guidance/ta446.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
ID6334_brentuximab_vedotin_uHL_SIP	1.0	No	12 April 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Brentuximab vedotin Brand name: Adcetris®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (AVD) is intended to be used as treatment for adult patients with previously untreated CD30+ (classical) Stage III or IV Hodgkin lymphoma (HL). Patients who are expected to receive brentuximab vedotin would have advanced- or late-stage (i.e. Stage III or IV) disease, where their lymphoma has spread to lymph nodes on both sides of the diaphragm (Stage III) or to other organs outside of the lymphatic system (Stage IV) (1,2). Patients who are diagnosed with Stage III or IV HL typically receive first-line treatment that aims to cure the disease and achieve long-term remission, while minimising the complications of treatment (3). The combination regimen of brentuximab vedotin with AVD (A+AVD) is intended to be used to treat patients who would otherwise be suitable for treatment with combination chemotherapy with doxorubicin (also called Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) (2).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Brentuximab vedotin currently has a marketing authorisation in Great Britain for the treatment of previously untreated CD30+ Stage IV HL, which was issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 06 February 2019. Brentuximab vedotin does not currently have a marketing authorisation in Great Britain for previously untreated CD30+ Stage III HL. The regulatory process for this revised indication is ongoing and a decision is expected later in 2024.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Takeda provides hands-off financial grants to Lymphoma Action, Leukaemia Care and Anthony Nolan, in response to annual requests to provide funding to support their core operations. Takeda also sponsors meetings between healthcare professionals where Lymphoma Action acts as secretariat.

Takeda provides financial support for Blood Cancer UK's Blood Cancer Action Plan. Takeda is a member of the Blood Cancer Alliance Industry Forum and provides financial support for the Forum.

No other collaborations exist that could be considered a potential conflict of interest.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained

CD30+ Stage III or IV HL

HL is a type of lymphoma, a blood cancer that affects white blood cells called lymphocytes (4,5). Lymphocytes are part of the immune system and help fight infections; they travel around the body through small tissue vessels called lymph vessels, which are part of the lymphatic system (a network of tubes, tissues, and organs that include lymph nodes, the spleen and thymus) (6).

HL severity is described by the disease stage, which depends on how advanced the lymphoma is (1). There are four stages of HL, characterised by the number and location of the affected lymph nodes. Stages I and II HL affect one or more groups of lymph nodes that are restricted to one side of the diaphragm. Stage III HL affects lymph nodes on both sides of the diaphragm, and in Stage IV HL, the lymphoma has spread to ≥1 body organ outside the lymphatic system (1).

The most common symptom of HL is swollen lymph nodes or lumps that do not go down after a few weeks, usually in the neck, armpit, or groin (7). Swollen lymph nodes can lead to pain from nerve compression, cause swelling in the arms or legs, and cause yellowing of the skin and eyes (jaundice) (3,7). Patients with Stage III or IV HL also experience burdensome symptoms that substantially impair their quality of life, such as fatigue (exhaustion that can be physical, emotional, or mental), coughing or shortness of breath, abdominal pain, and vomiting after drinking alcohol (3,7,8).

In most people, the cause of HL is unknown; however, HL affects slightly more men than women (6). Other factors which may increase a person's risk of developing HL include family history of lymphoma, advanced age, and a weak immune system (9,10).

Classical HL is characterised by the presence of the protein (antigen) CD30 on the cell surface of the cancerous lymphoma cells; as such, classical HL is also referred to as CD30-positive (CD30+) HL (11).

Number of patients with CD30+ Stage III or IV HL

While HL is a rare cancer, with around 2,100 patients diagnosed in the UK every year, it is the most common cancer in teenagers and young adults globally (12,13).
In 2021, 822 patients were diagnosed with Stage III or IV HL in England, while in

Wales, 40 patients were diagnosed in 2020 (14,15). Approximately 95% of patients with HL are CD30+, and therefore approximately 781 and 38 patients of those diagnosed with Stage III or IV in England and Wales, respectively, were CD30+ (16).

Impact of CD30+ Stage III or IV HL on patients

HL is a curable disease, and it often responds well to treatment, with many patients going into long-term remission (no signs or symptoms of lymphoma in tests or scans) (17). However, patients with Stage III or IV HL[a] are less likely to be cured by first-line treatment compared with earlier stages, with 20–30% experiencing disease that either comes back after first-line treatment (relapses) or does not respond to ongoing treatment (refractory) (19,20). Patients not achieving initial cure require subsequent treatment, including further chemotherapy and/or stem cell transplantation (SCT), a procedure that replaces damaged stem cells (the undeveloped cells in the bone marrow that go on to become mature blood cells) (17,21,22). SCTs are invasive and burdensome, and patients are more likely to develop second cancers (i.e. a new cancer unrelated to the initial HL) compared with those cured after first-line treatment. Only approximately 50% of patients who receive SCT achieve cure (17,22,23).

Patients with HL also experience side effects from their treatment, including sickness, loss of appetite, higher susceptibility to infections, and diarrhoea, all of which can be highly burdensome (24). Fatigue is a common side effect of chemotherapy and has a considerable negative impact on a patient's ability to do routine daily activities (8). The specific drugs used to treat HL – in particular, bleomycin (Section 2c) – are associated with further clinical and quality of life burden for patients. Current chemotherapies are associated with high rates of [1] heart disease or heart failure, [2] long-term lung damage (whereby the lungs' ability to transfer oxygen to the blood is reduced), [3] infertility, and [4] developing a second cancer (25–30). This means that patients with HL who are considered cured can still experience residual negative impacts of treatment after treatment has finished and are more likely to die due to chemotherapy-associated toxicities compared with healthy individuals (2,30).

All of these treatment- and disease-related toxicities negatively impact patients' quality of life. In particular, patients with HL experience higher rates of anxiety (23% vs. 13%) and depression (18% vs. 12%) compared with healthy individuals, and are more likely to have a higher incidence of mental health problems (31,32). Aspects of patients' lives can be affected even after treatment, particularly in the first 2 years after the end of treatment, such as persistent fatigue, the inability to sleep, and financial problems (33).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosis

Patients with HL typically present with swollen lymph nodes, as described in Section 2a. Some patients may also present with burdensome symptoms such as unexplained profound weight loss (>10% of body weight over six months or less), high fevers, and drenching night sweats; these are called B symptoms and are more common in patients with advanced-stage disease (Stage III or IV) compared with patients with early-stage HL (Stage I or II) (3,11).

If a General Practitioner (GP) or a specialist suspects lymphoma, especially in the presence of B symptoms, they refer the patient to a specialist for further tests, usually a haematologist who specialises in treating blood conditions (34).

[a] Note: published data refer to 'advanced-stage' HL. This is predominantly patients with Stage III or IV HL, but may also include a small proportion of patients with high-risk Stage II disease, who are typically managed as per Stage III or IV disease (2,18).

To confirm a diagnosis of HL, patients have a biopsy; this is done by taking cells from an affected lymph node using a needle, or by removing a whole lymph node if it is near the skin. The sample is evaluated to determine the type of cancer and confirm whether the CD30 protein is present (35). If a biopsy confirms a diagnosis of HL, further testing takes place including:

- Blood tests to check general health and levels of blood cells
- Bone marrow biopsy, chest X-ray, computerised tomography (CT) scan, magnetic resonance imaging (MRI) scan, and/or positron emission tomography (PET) scan, which produces detailed 3D images of the inside of the body, to assess the location and extent of spread of the lymphoma.

Staging and prognostic scoring

In Stages I and II, the lymphoma is restricted to the lymphatic system on one side of the diaphragm; in Stage III, the disease has spread within the lymphatic system to both sides of the diaphragm, and in Stage IV, the disease has spread to ≥1 body organ outside the lymphatic system (Section 2a) (1). Staging a patient's HL is important because it influences treatment choices (see Section 2c): Stages III or IV, which the current submission focuses on, are treated as "advanced-stage" disease (2).

Following the tests outlined above, if a patient has Stage III or IV HL, their International Prognostic Score (IPS) is assessed – a tool used to identify those patients at high risk of treatment failure based on seven criteria: stage of disease, age, gender, white blood cell count, lymphocyte count, liver function via albumin count assessment, and red blood cell level via haemoglobin count assessment (2). Based on the patients' risk profile, the IPS is one aspect used to guide choice of first-line treatment in this patient population (2).

No additional testing is required prior to treatment with A+AVD.

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The goal of first-line treatment for patients with Stage III or IV HL is to cure the disease and achieve long-term remission while minimising complications of treatment (3). The most relevant UK treatment guideline for previously untreated HL was published by the British Society for Haematology (BSH) in 2022 (2).

For patients with CD30+ Stage III or IV HL, the BSH guidelines recommend chemotherapy. Options for initial treatment are (2):

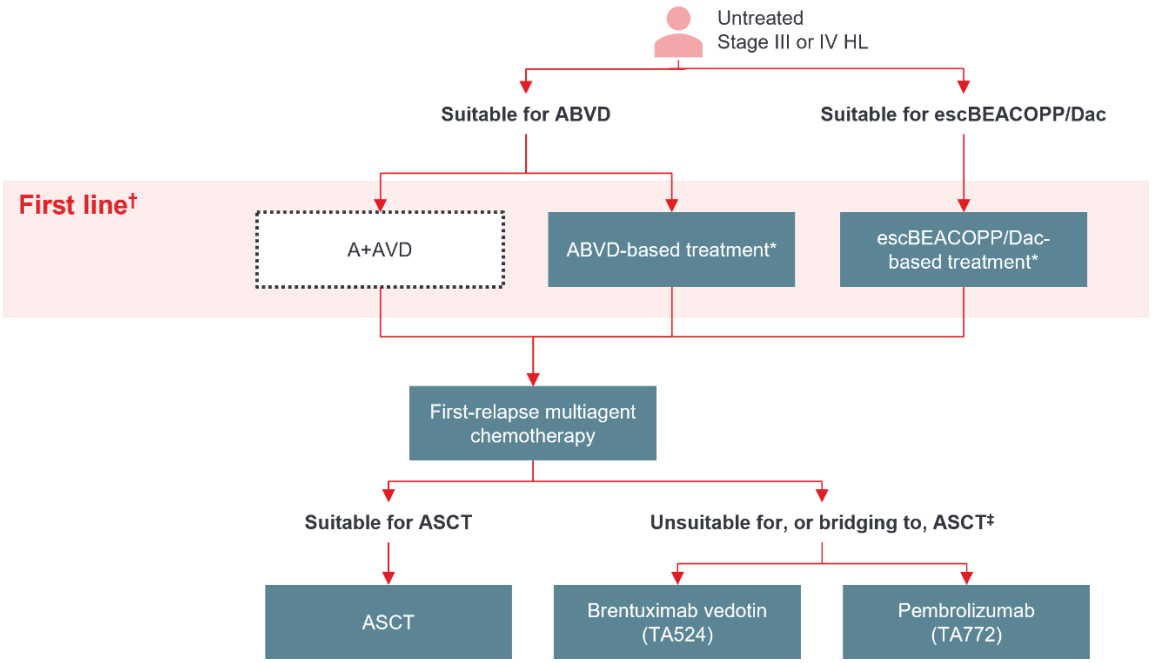
1. An ABVD-based regimen (comprising doxorubicin [Adriamycin; A], bleomycin [B], vincristine [V] and dacarbazine [D]) or;
2. For patients who can tolerate a more intensive treatment, an escBEACOPP/Dac-based regimen, which includes bleomycin (B), etoposide (E), doxorubicin (Adriamycin [A]), cyclophosphamide (C), vincristine (also called Oncovin [O]), prednisolone (P), and either procarbazine (P) or dacarbazine (Dac). In current UK clinical practice, escBEACOPDac, which uses dacarbazine instead of procarbazine, is usually preferred to escBEACOPP, due to fertility toxicities that are more pronounced with procarbazine than dacarbazine (2).

Choice of initial treatment varies across the UK based on regional or centre-based preferences and is influenced by other factors, including a patient's risk profile, the balance between toxicity and efficacy of available treatment regimens, and patient preference (2,36). escBEACOPDac may be offered to patients who are able to tolerate a heavier toxicity burden and those considered to need a more intensive treatment option to control their disease (2). Patients who do not require such an intense regimen or are unable to tolerate the increased toxicity that comes with escBEACOPDac are typically treated initially with ABVD (2).

Following the first two cycles of ABVD treatment, some patients in the UK may have a PET scan to check if their lymphoma has responded to initial treatment. The result of this scan is based on Deauville score (a tool used to determine response to treatment during a PET scan), which then informs whether treatment needs to be escalated to enhance disease response or de-escalated for better tolerability. If there has been no response (i.e. the patient's disease is 'PET positive', defined as a Deauville score 4–5), treatment is escalated to a more intensive, though more toxic, regimen, such as escBEACOPDac; otherwise (i.e. in patients with a 'PET-negative' disease, defined as Deauville score 1–3), treatment is de-escalated to a less intensive regimen, such as AVD (2). However, not all patients receive PET-adapted treatment, and some may receive six cycles of ABVD.

There remains an unmet need for a treatment option with the potential to improve survival outcomes while minimising toxicities, particularly in patients who are currently treated with ABVD. Of importance to both patients and clinicians is the lung damage associated with the use of bleomycin (the B in ABVD), which is likely to persist long term and have negative consequences in lung function capacity in later years for cured patients (30). If approved, A+AVD is expected to be used in previously untreated patients with CD30+ Stage III or IV HL who would otherwise be suitable for ABVD (Figure 1) (37).

Figure 1: Current treatment pathway for untreated Stage III or IV HL in England and Wales, and proposed positioning of A+AVD



Dashed box shows the proposed place of A+AVD in the treatment pathway.
*Treatment may be PET guided (e.g. RATHL) or not PET directed. †Alternative treatment options (e.g. AVD, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone [ACOPP]) may be used in some patients where age or frailty precludes standard treatment options. ‡In transplant-naïve patients, treatment with pembrolizumab or brentuximab vedotin may be used as a bridge to ASCT.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplantation; CD30, cell membrane

receptor 30; escBEACOPP/Dac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, prednisolone, procarbazine or dacarbazine; HL, Hodgkin lymphoma; PET, positron emission tomography; RATHL, response-adapted therapy for advanced Hodgkin lymphoma; TA, technology appraisal.
Sources: NICE 2021 (TA772 public committee slides) (38); British Society for Haematology guidelines (2); Takeda, Medical Advisory Board (2023) (39).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Evidence from patients with HL treated with current first-line SoC

Patients who are diagnosed with HL talk about it having a huge impact on their mental health and wellbeing (33). Receiving a diagnosis of HL can be shocking, upsetting, and frightening (40). Even HL survivors, who are cured from the disease, have a substantial emotional burden, reporting high levels of anxiety, depression, and fatigue, which can impact on daily activities (31). In some cases, patients with HL are particularly emotionally affected by their disease and treatment (41). The potential impact of chemotherapy on fertility can be a major worry, causing substantial distress to patients (26,42).

Examples of published quotes from patients with HL illustrate the negative impact that diagnosis and treatment of HL can have on their daily lives and emotional wellbeing:

- *"When I first received my diagnosis, it was very overwhelming. I felt frightened about what would happen to me, and anxious at the thought of starting treatment".* Paris, diagnosed with HL at age 28 years (43).
- *"Hearing the words 'you have cancer' is the most terrifying thing anyone can ever say to you, and not something you expect to hear at the age of 21. Asking a doctor if I'm going to die was the most frightening thing".* Faye, diagnosed with HL at age 21 years (43).
- "*Sadly, relationships I've been in have fallen apart as a result of having that conversation about my fertility".* Federica, diagnosed with HL at age 20 years (44).

Evidence from patients with Stage III or IV HL treated with A+AVD

Patient-reported outcomes for A+AVD were collected in the ECHELON-1 trial (Section 3d) for patients with CD30+ Stage III or IV HL based on questionnaires designed to capture the impact of treatment on patients' quality of life (9,45,46).

In ECHELON-1, patient outcomes were collected via four different instruments before and during treatment, and two instruments during post-treatment follow-up (see Section 3f for details). As these are all patient-reported measures, they help to assess the impact of HL on patients and whether treatments improve patients' health-related quality of life (HRQoL) (45,47).

Additionally, safety data were collected to ensure the safety profile of A+AVD is well-understood and manageable for patients with CD30+ Stage III or IV HL (see Section 3g for more details) (45,47).

SECTION 3: The treatment

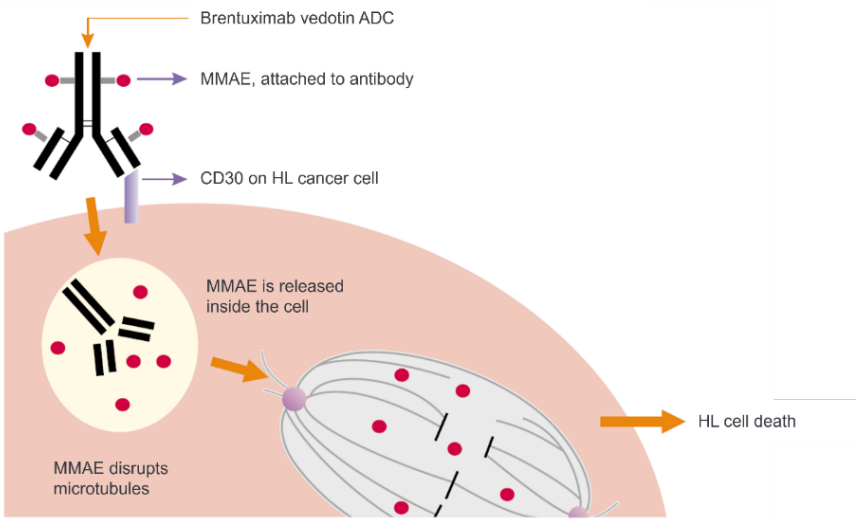
3a) How does the new treatment work?

What are the important features of this treatment?
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How does brentuximab vedotin work?

Brentuximab vedotin is an antibody–drug conjugate (ADC), where a cytotoxic anticancer drug (a drug that can damage cells or cause them to die) is linked to an antibody (a protein that can recognise and bind to specific molecules on a cancer cell surface). For brentuximab vedotin, the antibody binds to a specific molecule on the cancer cell surface, called antigen CD30, allowing the cytotoxic drug (called monomethyl auristatin E [MMAE]) to be directly delivered inside the cell. Once MMAE is inside the cell, it disrupts microtubules (required for cell movement and division), causing death of the cancer cell (Figure 2) (48–50).

Figure 2: Brentuximab vedotin mode of action



Abbreviations: ADC, antibody–drug conjugate; CD30, cell membrane antigen 30; HL, Hodgkin lymphoma; MMAE, monomethyl auristatin E.
Source: Adapted from Currin *et al* (2012) (51).

Why is brentuximab vedotin innovative?

Current first-line treatment for patients with previously untreated CD30+ Stage III or IV HL is systemic chemotherapy regimens, which have remained largely unchanged since the development of ABVD nearly 50 years ago (2,52). In the UK, only chemotherapy-based regimens are used for first-line treatment in HL, and targeted treatments, such as brentuximab vedotin, are only available for the treatment of patients whose lymphoma has returned or not responded to first-line treatment (2,17,22).

If recommended, A+AVD would represent the first targeted treatment to be used at first line for adult patients with CD30+ Stage III or IV HL and the first regimen to provide a significant benefit in overall survival (OS) when compared head-to-head with ABVD regimens (PET-adapted or six cycles) in this patient population (Section 3e). Unlike other current treatments for previously untreated HL, A+AVD omits bleomycin, which is associated with long-term lung damage (see Section 2c) (2,30). Finally, brentuximab vedotin is intended to be used with AVD, which has a known efficacy profile in the first-line treatment of HL, providing both a targeted and a systemic mode of cancer cell killing. As a

targeted treatment, brentuximab vedotin's ability to specifically target cancerous cells and spare healthy ones means it has a manageable safety profile. Therefore, A+AVD has the potential to provide improved efficacy vs. ABVD while minimising toxicities associated with current first-line treatments, particularly bleomycin-related lung damage (2,30,53).

Please refer to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet for more details about the way this treatment works.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?
- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.
If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.
If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Brentuximab vedotin is intended to be used in combination with AVD chemotherapy, based on the ECHELON-1 trial (45). Brentuximab vedotin binds to CD30 on the HL cancer cell surface and delivers the cytotoxic drug, MMAE, which kills the cancer cell via microtubule disruption (see Section 3a) (48–50). Vinblastine (the V in AVD) also targets microtubules, which means that the A+AVD regimen includes two components that target microtubules (54). Doxorubicin (the A in AVD) slows or stops the growth of cancer cells by blocking an enzyme, isomerase 2, which is needed for cell growth and division (55). Dacarbazine (the D in AVD) binds to the cancer cell's DNA causing DNA damage, meaning the cancer cell can no longer divide (56).

Both brentuximab vedotin and AVD have a well-known and manageable side effect profile. For brentuximab vedotin, side effects include infection, low number of white blood cells called neutrophils (neutropenia – symptoms include nausea, fatigue, and long-term infections), peripheral neuropathy (a type of nerve damage that can cause pain, numbness, or weakness in the extremities, such as hands and feet), cough, and shortness of breath (dyspnoea). For AVD, side effects include nausea, vomiting, skin rashes, hair loss, decreased appetite, and sore mouth (57,58).

For adult patients with previously untreated HL receiving A+AVD, primary prophylaxis with growth factor support (G-CSF) is recommended (58). Treatment with G-CSF helps the white blood cells recover after treatment, since neutropenia is a common side effect with brentuximab vedotin (see above) (58,59). Common side effects with G-CSF include headaches, bone or muscle pain, fatigue, nosebleeds, and diarrhoea (59).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.
How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Brentuximab vedotin, A, V and D are administered on days 1 and 15 of each 28-day treatment cycle – meaning that the patient has treatment every 2 weeks, followed by 2 weeks of rest – for a total of six cycles. The treatments are administered in a hospital outpatient clinic on the same day, under the supervision of a physician experienced in the use of anti-cancer treatments. AVD is administered first, followed by brentuximab vedotin within approximately one hour after dacarbazine administration. AVD is administered at a recommended dose of 25 mg/m^2 for doxorubicin (intravenous bolus), 6 mg/m^2 for vinblastine (intravenous infusion over 10 mins), and 375 mg/m^2 for dacarbazine (intravenous infusion over 1−2 hours) (60). Brentuximab vedotin is administered via intravenous infusion at a recommended dose of 1.2 mg/kg over approximately 30 minutes (45,58).

Primary prophylaxis with G-CSF (see Section 3b) is given as an injection under the skin (subcutaneous) in most cases from the first day of treatment (58,61,62).

ABVD, the current standard of care for the proposed patient population for A+AVD, is also administered in a hospital outpatient clinic on days 1 and 15 of each 28-day treatment cycle. Doxorubicin, vinblastine, and dacarbazine are administered as described above (60). Bleomycin is administered at a recommended dose of 10,000 units/m^2, via intravenous infusion over >1 hour or as an intravenous bolus (57,60).

Since ABVD is already administered via infusion in an outpatient setting, the impact of introducing brentuximab vedotin for patients and their caregivers is not expected to substantially differ, for example due to travel associated with attending hospital appointments.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Evidence for A+AVD for the first-line treatment of CD30+ Stage III or IV HL comes from the phase III ECHELON-1 clinical trial, which assessed patients for more than 7 years. ECHELON-1 was a randomised trial that included 1,334 adult patients with previously untreated CD30+ Stage III or IV HL in 21 countries, of whom 154 patients were treated at 23 sites in Great Britain. The full inclusion and exclusion criteria have been published and can be found in Connors *et al* (2018) (45). In total, 664 patients in ECHELON-1 were randomly assigned to A+AVD treatment and 670 patients to ABVD treatment. A PET scan, which helps to assess the spread of cancer (Section 2b), was conducted at the end of the second treatment cycle, the results of which were primarily for disease assessment (45).

The study was open-label, meaning each patient and their physician knew which treatment they were being given. However, patients, physicians, and the study coordinator were not aware of the results from the trial until after their analysis and publication (45). An open-label design is common across clinical trials in untreated HL, as it ensures that treating physicians are aware of potential side effects of the treatment administered and are able to treat them appropriately if they arise (63–65).

Use of G-CSF primary prophylaxis is recommended in adult patients with previously untreated HL receiving A+AVD to help the white blood cells recover after treatment (Section 3b) (58,59). In ECHELON-1, primary prophylaxis with G-CSF was defined as G-CSF given by day 5 of study treatment (45). Though not mandated at the start of ECHELON-1, the trial protocol was amended after enrolment of approximately 70% of patients, recommending the use of G-CSF prophylaxis in patients treated with A+AVD, as per brentuximab vedotin's SmPC (Section 3a) (45,58). In total, primary prophylaxis with G-CSF was given to 83 patients treated with A+AVD and 43 patients treated with ABVD[b] (45).

The 7-year, long-term follow-up in ECHELON-1 provides robust evidence of the survival benefits of A+AVD and reduces uncertainty on the long-term benefits of treatment with this regimen. There were five data cuts in ECHELON-1, data from which have been published in peer-reviewed journals. The trial data cuts from which efficacy and safety data are presented in this document are: [1] in 2017, when all patients who were going to finish their course of treatment in the trial had done so – the data cut date for this was 20th April 2017 (median follow-up of progression-free survival [PFS]: 24.6 months); [2] in 2018 – the data cut date for this was 15th October 2018 – for which safety data after

[b] Primary prophylaxis with G-CSF was not mandated in patients treated with ABVD, but was given to some patients at the treating physician's choice (47).

introduction of G-CSF treatment are reported (median follow-up: 30.6 months); and [3] at the end of trial – the data cut date for this was 11th March 2023 (45,46,66).

Key endpoints from ECHELON-1 included PFS (i.e. how long patients lived before their disease worsened) defined as the time from randomisation to the time of first documentation of disease progression or death due to any cause, whichever occurred first, and OS (i.e. how long patients lived for) defined as the time from the date of randomisation to the date of death (45). An endpoint called 'modified PFS' was also explored in ECHELON-1; this looked at progressive disease and death (as for PFS previously) and also looked at whether patients who did not have complete response (i.e. Deauville score ≥3) had received any subsequent anticancer treatment for HL. This outcome, though not typical for clinical trials in HL, has the advantage of identifying patients for whom first-line chemotherapy failed and have received subsequent treatment, even though no progression nor death has occurred (45). Of note, PFS is the most relevant endpoint for assessment of cost-effectiveness analysis of brentuximab vedotin (Section 3j), as it is the most widely recognised and accepted endpoint for assessment of HL treatments, allows for comparisons across trials and the literature, and has a long, 7-year follow-up available (67–72). Patient-reported outcomes were also assessed; these outcomes subjectively measured patients' HRQoL and relied on information from questionnaires that patients themselves had answered. Finally, safety outcomes were reported, including overall and treatment-related adverse reactions (45).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Progression-free survival

(See company submission, Document B, Section B.2.6.1.2)

A+AVD showed improvements in how long patients lived before their disease worsened compared with ABVD. After 6 years of follow-up, A+AVD was associated with a notable improvement in PFS compared with ABVD, with a 32% reduction in risk of disease progression or death; the treatment benefit with A+AVD remained consistent at the 7-year follow-up (46,53). Approximately 83% of patients treated with A+AVD were alive and without disease progression at 2 years, the time when clinicians usually discharge disease-free patients on the assumption that they are cured (36,46). The benefit in PFS for A+AVD compared with ABVD was sustained across multiple analysis points, demonstrating a robust and durable improvement in PFS vs. ABVD for at least 7 years (45,46,53).

Overall survival

(See company submission, Document B, Section B.2.6.2)

A+AVD resulted in a statistically significant, 41% lower risk of dying compared with ABVD after 6 years of follow-up, which remained consistent at the 7-year follow-up (46,53). This is an important result because historically it has been difficult to show an OS benefit following first-line treatment in HL (53). This clinically meaningful improvement in OS with A+AVD in first-line HL is unprecedented in recent clinical trials in untreated HL (36).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?
Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).** Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient quality of life was measured in ECHELON-1 using the following patient-reported questionnaires, where higher scores signify better quality of life than lower scores:

- EORTC QLQ-C30, a 30-item cancer-specific questionnaire designed to measure physical health, psychological function, and social function in cancer patients (73).
- EQ-5D-3L, a questionnaire used to describe a patient's health state by looking at five areas relating to health: how easily you move around, take care of yourself, handle daily activities, deal with pain or discomfort, and manage feelings of anxiety or depression. It helps to assess how the treatment influences different parts of patients' daily lives (74).
- FACIT-Dyspnea 10 assesses difficulty breathing (dyspnoea) in adult patients (75).
- FACT/GOG-Ntx neurotoxicity scale provides a targeted assessment of peripheral neuropathy, a type of nerve damage which includes sensory, motor, and auditory problems and cold sensitivity (76).

EORTC QLQ-C30 and EQ-5D-3L were assessed at baseline, at the end of each treatment cycle during treatment, and for up to 3 years after the end of treatment.
FACIT-Dyspnea 10 and FACT/GOG-Ntx scales were only assessed at baseline and at the end of each treatment cycle (45).

Across both treatment arms, mean scores for EORTC QLQ-C30 and EQ-5D-3L decreased during treatment; however they quickly recovered to similar levels to before treatment (47). Moreover, EQ-5D-3L and EORTC QLQ-C30 scores after treatment were similar to scores reported for the general, healthy population, suggesting that treatment may restore patient HRQoL without a long-term impact, supporting the positive impact of successful treatment on long-term quality of life for patients (77,78).

Trends observed with the FACIT-Dyspnea 10 questionnaire in both treatment arms were not clinically meaningful. Mean FACT/GOG-Ntx scores were lower in patients who received A+AVD compared with ABVD; this is consistent with the known side effect profile of brentuximab vedotin, which includes peripheral neuropathy, a type of nerve damage (Sections 3b and 3g) (46,54,79). However, symptoms of peripheral neuropathy continued to improve or resolve over time after the end of treatment, and any events of worsening neuropathy could have been managed by dose delay (see Section 3g) (47).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer. Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In ECHELON-1, A+AVD was well tolerated and side effects were manageable (53). Brentuximab vedotin is used for a number of other lymphomas, both as combination therapy and as monotherapy (58). The side effects reported in ECHELON-1 were consistent with those observed for these other indications and no new safety concerns were identified (53,58).

A+AVD was associated with a higher rate of neutropenia (Section 3c) compared with ABVD (69% vs. 55%) (66). As this is a known side effect of brentuximab vedotin, this was managed by G-CSF administration and dose modifications (dose delays and/or reductions), as per SmPC recommendations (Section 3b) (45,58,66). In patients treated with A+AVD who received G-CSF primary prophylaxis, the incidence of neutropenia was lower compared with those who did not receive G-CSF prophylaxis (35% vs. 73%) (66).

Another side effect that occurs in some patients treated with brentuximab vedotin is peripheral neuropathy (58). Higher rates of peripheral neuropathy were reported in patients treated with A+AVD compared with ABVD at the end of treatment (67% vs. 43%); this was considered to be due to the combination of brentuximab vedotin with vinblastine (the V in AVD), as they have a similar mechanism of action (see Section 3b) (46,54,79). However, symptoms of peripheral neuropathy can be managed by clinicians by delaying or reducing the dose of brentuximab vedotin (58). Symptoms of peripheral neuropathy also continued to improve or completely resolve over time after the end of treatment in the majority of patients treated with either A+AVD or ABVD (46).

As mentioned above, current treatments for previously untreated CD30+ Stage III or IV HL contain bleomycin, a drug associated with high rates of lung damage (see Section 2c) (30). During treatment, a lower incidence of lung damage was observed in patients receiving A+AVD compared with ABVD (2% vs. 7%, respectively). Importantly, there were no deaths caused by lung damage in patients treated with A+AVD, whereas three patients treated with ABVD had a fatal lung damage event (46,53,80).

Finally, a lower numerical incidence of second cancers was reported in patients treated with A+AVD compared with those treated with ABVD (53).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:
- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Improvement in progression-free survival and overall survival

The use of ABVD for patients with previously untreated CD30+ Stage III or IV HL was first described nearly 50 years ago (see Sections 2c and 3b for details) (2,52). In ECHELON-1, A+AVD demonstrated a notable treatment benefit in PFS and a statistically significant treatment benefit in OS compared with ABVD, which represents the first significant improvement in OS seen in clinical trials of CD30+ Stage III or IV HL for many years; this result was widely welcomed by the clinical community in a recent (2024) clinical expert advisory board (36,53).

Bleomycin-free regimen

Another benefit of the A+AVD regimen is that it avoids use of bleomycin. Lung damage due to bleomycin occurs with ABVD, the current standard of care, and can be severe and long lasting, reducing lung function capacity and being only partially reversible 5 years after end of treatment (30). The use of a bleomycin-containing regimen is therefore a key treatment consideration for patients and clinicians (30,37). In ECHELON-1, fewer patients treated with A+AVD had lung damage compared with those treated with ABVD, and no deaths were caused by lung damage in patients treated with A+AVD compared with three deaths in those treated with ABVD (30,47).

Lower rates of second cancers

A lower incidence of second cancers was observed with A+AVD compared with ABVD (53). Second cancers can cause a substantial burden for patients, including impacting survival outcomes, HRQoL, and exposure to potentially aggressive subsequent

treatments. These findings can therefore be reassuring for patients and clinicians that A+AVD is associated with a numerically lower rate of second cancers than ABVD (36,46).

Fertility benefits

Current HL treatment options can, in some cases, result in infertility in both men and women; this is therefore a key consideration for choosing treatment for patients of child-bearing age (25,26,37). In ECHELON-1, there were a higher number of pregnancies and live births in the patients or patients' partners treated with A+AVD compared with those treated with ABVD (46). Even though fertility outcomes between the two groups were not assessed statistically, clinical expert feedback highlighted that the clinical community were reassured by the reported pregnancies and live births in patients/patients' partners treated with A+AVD (37). Therefore, treatment with A+AVD has the potential to relieve patients and their families from a significant psychological load caused by fertility concerns.

No additional administration burden

A+AVD is not expected to create any substantial additional administration burden for patients or the NHS compared with ABVD, as all treatment components are given on the same day intravenously in an outpatient setting (Section 3c) (58,60). G-CSF prophylaxis, part of standard practice with brentuximab vedotin administration and, therefore, expected to be given to all patients treated with A+AVD, is simple to administer and is usually done by an injection below the skin (subcutaneously; Section 3c) (58,61,62).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with most cancer treatments, treatment with A+AVD is associated with side effects (Section 3g). In patients treated with A+AVD, rates of peripheral neuropathy were higher compared with those treated with ABVD, consistent with the known safety profile of brentuximab vedotin (46,58). However, most events of peripheral neuropathy had resolved or ameliorated within the study follow-up time (46,53). Peripheral neuropathy can be routinely managed by clinicians by reducing dosing or by pausing or completely stopping administration of brentuximab vedotin, according to severity (58).

Additionally, there was a higher rate of neutropenia in patients treated with A+AVD compared with those treated with ABVD, which is again consistent with the known safety profile of brentuximab vedotin (46,58). As per recommendations for the use of brentuximab vedotin from the SmPC and ECHELON-1 protocol, neutropenia was managed with administration of G-CSF and dose modifications in ECHELON-1, which reduced the rate of neutropenia in patients treated with A+AVD (58,66).

3j) Value and economic considerations

Introduction for patients:
Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness assessment of new medicines

In assessing whether a medicine represents a cost-effective use of NHS resources, NICE refers to a measure called the incremental cost-effectiveness ratio (ICER) (81). This looks at the cost-effectiveness of the product in question – in this case, A+AVD – against other treatments currently used to treat the condition – in this case, ABVD-based treatment.

The ICER is measured in terms of what needs to be spent to gain one additional quality-adjusted life year (QALY), equivalent to a person living for 1 year in "perfect health". Such costs include direct costs, such as drug and administration costs, and indirect costs, if relevant, such as work productivity loss. The QALY is a measure of disease burden and includes both the quality and quantity of life lived. A treatment can increase the number of QALYs a patient experiences by extending life, increasing the quality of life, or both.

NICE has introduced a tool called the severity modifier, to formally consider disease severity in decision making. For severe diseases which meet the eligibility criteria, NICE applies a severity weighting (a "boost") to QALYs for drugs used to treat such diseases. Since the aim of current treatments is cure, A+AVD does not meet the criteria for additional severity weighting in adult patients with previously untreated CD30+ Stage III or IV HL (3).

How the economic assessment of A+AVD in HL was conducted

The cost-effectiveness model looks at the benefits and costs of A+AVD against NICE-selected comparator treatments, over what is called a lifetime horizon. This means that all the QALY gains a patient might expect from being treated with A+AVD are added up over the patient's lifetime, as are all the costs that would be incurred treating the patient. This is the commonly accepted method for calculating cost effectiveness of oncology medicines and is consistent with the clinical pathway of care in HL.

The patient population evaluated by the model is those with previously untreated CD30+ Stage III or IV HL, which aligns with the ECHELON-1 trial (Section 3d). This corresponds to the expected marketing authorisation for A+AVD. The costs captured within the analysis include all important aspects of the disease and treatment pathway, such as drug costs, administration costs, medications given alongside A+AVD or ABVD, costs associated with managing adverse events, and costs of subsequent treatments in patients with progressive disease. Information on the quality of life captured in the model comes from the EQ-5D-3L data captured in ECHELON-1 (Section 3f).

HL health states

The economic model used was a partitioned survival model, a type of model commonly used for cancer appraisals, which models costs and benefits over a patient's lifetime (70,71,82,83). In the economic model, patients are assumed to be in one of several "health states" that reflect the progressive nature of HL: [1] progression free, where patients are alive without disease worsening; [2] progressed disease, where the

patients' disease has come back or did not respond to treatment or; [3] death. In the model, patients who remain in the progression-free health state are considered cured 2 years after the end of treatment and are assumed to be comparable to the general population with respect to HRQoL. Each of these health states is associated with a different level of costs and quality of life over a lifetime period. Data for how patients are expected to move between the health states come from ECHELON-1.

Assumptions and limitations

Economic modelling can be uncertain. One limitation with this type of model is that, while data come from a study with a 7-year follow-up period, they have to be extrapolated over a longer period. There are several accepted statistical techniques for handling this difficulty, which have been followed, and several assumptions have been made. For each health state, data for PFS and OS were extrapolated from ECHELON-1. Multiple methods were used to explore uncertainty within the model, including sensitivity and scenario analyses. Such methods were used to explore assumptions including the timepoint patients are considered cured, progression-free and survival assumptions, and resource use (for example, follow-up care frequencies) captured. Of note, it was not possible to capture any impact of the trend in higher pregnancy and live birth rates with A+AVD in the economic model, meaning any fertility impact is not considered (Section 3k).

Cost-effectiveness analysis for brentuximab vedotin

In line with the improved PFS and OS seen with A+AVD compared with ABVD (Section 3e), the model demonstrates that A+AVD provides additional QALYs compared with ABVD at an additional cost. Key drivers for this ICER are: [1] how well patients on A+AVD and ABVD-based treatment do in the long term; specifically, the ratio of the number of deaths observed in patients with previously untreated CD30+ Stage III or IV HL treated with either A+AVD or ABVD over the number of deaths expected in healthy individuals of the same age (called the standardised mortality rate, or SMR); [2] the costs associated with the use of G-CSF in HL (Section 3c); and [3] the long-term survival extrapolations for PFS and OS used for the economic modelling.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

In patients with CD30+ Stage III or IV HL, the key issue associated with ABVD use at first line is the unmet need for improved cure rates while minimising associated toxicities, especially bleomycin-associated long-term lung damage (see Section 2c) (30,52). A+AVD is a step change in this patient population in that it is the first targeted treatment to demonstrate an advantage in both PFS and OS for many years, and the first treatment to show a significant OS benefit when compared head-to-head with ABVD regimen. Specifically, 83% of patients treated with A+AVD were alive without progression of disease at 2 years, the time when clinicians usually discharge patients on the assumption that they are cured (36,46). Importantly, A+AVD showed a significant improvement in OS compared with ABVD, which has been difficult to show in previously untreated HL (46,53). A+AVD is the only approved, targeted treatment for previously untreated HL that omits bleomycin, which is associated with long-lasting lung damage, and treatment with A+AVD resulted in a lower incidence of second cancers compared with ABVD (see Section 2c) (28,30,46,84). A+AVD represents the first regimen to show an OS advantage compared with ABVD regimen (PET-adapted or six cycles) in patients with previously untreated Stage III or IV HL, whilst also providing improved PFS and an acceptable tolerability profile.

Benefits not captured in the QALY

In ECHELON-1, there were a higher number of pregnancies and live births in patients or patients' partners treated with A+AVD arm compared with those treated with ABVD (Section 3h) (46). Even though fertility outcomes between A+AVD and ABVD were not statistically assessed, they indicate that A+AVD may be a suitable option in patients where maintenance of fertility influences treatment choice (25,26,36). The potential cost and HRQoL impact of fertility has not been explored in prior NICE appraisals, and it is unclear whether it is possible to capture the health-related benefits of this within the QALY framework. In addition, the economic model does not capture the potential societal costs saved through the introduction of A+AVD. HL is a cancer commonly diagnosed in young, working adults (Section 2a), and patients who are cured will be able to continue working, leading to an increase in lifetime earnings and contribution to the economy (14,85). Finally, a lower numerical incidence of second cancers was reported in patients treated with A+AVD compared with those treated with ABVD (Section 3g); however, this was only considered as a scenario analysis in the economic modelling (Section 3j) as the HRQoL and cost impact of second cancers is uncertain (46). Given all of the above, the resulting ICER may represent a conservative estimate of the cost-effectiveness of A+AVD.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics
More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

No equality issues were identified for this patient population.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Information related to HL:

- Cancer research UK
- Macmillan cancer support
- Lymphoma action
- Blood cancer UK
- NHS

British Society for Haematology resources:

- Guideline for first-line management of classical Hodgkin lymphoma – A British Society for Haematology guideline (2022)

Key published ECHELON-1 clinical trial data:

- 6-year update of ECHELON-1, reporting overall survival outcomes and adverse events (2022)
- 5-year update of ECHELON-1, reporting progression-free survival outcomes in patients and adverse events (2021)
- Subgroup analysis of patients treated with primary prophylaxis with G-CSF in ECHELON-1, reporting adverse events and modified progression-free survival (2020)
- End of treatment, 2-year update of ECHELON-1, reporting key efficacy and safety outcomes (2018)

Brentuximab vedotin (including the combination with AVD)

- Summary of product characteristics

Further information:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

A+AVD – brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine.

ABVD – doxorubicin, bleomycin, vinblastine, and dacarbazine.

Antibody–drug conjugate – a type of targeted treatment for cancer, consisting of an antibody (protein) linked to a cytotoxic drug.

CD30+ – presence of the cell membrane protein called CD30.

escBEACOPP/Dac – an escalated dosing regimen of combination chemotherapy consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and procarbazine or dacarbazine.

Hodgkin lymphoma – a blood cancer that affects white blood cells called lymphocytes.

ICER – incremental cost-effectiveness ratio. Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition.

Intravenous – administration of medications directly via a person's vein.

Licensed medicine – a drug that has been assessed for efficacy, safety, and quality, has been manufactured to appropriate quality standards, and, when placed on the market, is accompanied by appropriate product information and labelling, that is, it has been authorised for marketing.

Marketing authorisation – permission to sell a medicine after the evidence around it (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS.

Neutropenia – a condition where there is a low number of white blood cells, called neutrophils, in the blood.

Open-label trial – a trial where patients and physicians have knowledge of the assigned treatment.

Peripheral neuropathy – a type of nerve damage that develops in the body's extremities, such as the hands, feet, and arms, that can cause pain, numbness or.

Phase III – a clinical study that investigates how safe and efficacious a medicine is. The medicine will previously have been tested in Phase I–II studies, which test whether the medicine is safe enough to use in humans and has an effect on the disease.

QALY – quality-adjusted life year. A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines.

Randomised trial – a study in which a number of similar patients are randomly assigned to two (or more) groups to test a specific drug or other intervention (e.g., a group being given the medicine or a group being given a comparator).

Second cancer – a cancer that occurs in a person who has had cancer in the past.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Lymphoma Action. Staging of lymphoma [Internet]. 2022 [cited 2024 Apr 10]. Available from: https://lymphoma-action.org.uk/about-lymphoma-tests-diagnosis-and-staging/stages-lymphoma
2. Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop-Evans E, et al. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. British Journal of Haematology. 2022;197(5):558–72.
3. Kaseb H, Babiker H M. Hodgkin Lymphoma. In: Hodgkin Lymphoma [Internet]. StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499969/; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499969/
4. Cancer Research UK. What is Hodgkin lymphoma? [Internet]. 2020 [cited 2024 Apr 10]. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/about
5. Singh D, Vaccarella S, Gini A, De Paula Silva N, Steliarova-Foucher E, Bray F. Global patterns of Hodgkin lymphoma incidence and mortality in 2020 and a prediction of the future burden in 2040. International Journal of Cancer. 2022;150(12):1941–7.
6. Lymphoma Action. Hodgkin Lymphoma [Internet]. [cited 2024 Apr 10]. Available from: https://lymphoma-action.org.uk/types-lymphoma/hodgkin-lymphoma
7. Cancer Research UK. Hodgkin Lymphoma | Symptoms [Internet]. 2020 [cited 2024 Apr 10]. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/symptoms
8. Rüffer JU, Flechtner H, Tralls P, Josting A, Sieber M, Lathan B, et al. Fatigue in long-term survivors of Hodgkin's lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). European Journal of Cancer. 2003 Oct;39(15):2179–86.
9. Ansell SM. Hodgkin lymphoma: 2018 update on diagnosis, risk-stratification, and management. American Journal of Hematology. 2018;93(5):704–15.
10. Cancer Research UK. Hodgkin lymphoma risk [Internet]. [cited 2024 Apr 10]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/risk-factors
11. Shanbhag S, Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. CA Cancer J Clin. 2018 Mar;68(2):116–32.
12. Cancer Research UK. Hodgkin lymphoma statistics [Internet]. [cited 2024 Apr 10]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma
13. Rafiq M, Hayward A, Warren-Gash C, Denaxas S, Gonzalez-Izquierdo A, Lyratzopoulos G, et al. Socioeconomic deprivation and regional variation in Hodgkin's lymphoma incidence in the UK: a population-based cohort study of 10 million individuals. BMJ Open. 2019 Sep 20;9(9):e029228.
14. NHS England, National Disease Registration Service. Cancer Registration Statistics, England 2021 - first release, counts only [Internet]. 2023 [cited 2024 Apr 10]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only
15. Welsh Cancer Intelligence and Surveillance Unit (WCISU). Cancer Incidence in Wales, 2002-2020 [Internet]. 2023 [cited 2024 Jan 24]. Available from: https://www.gov.wales/cancer-incidence-2002-2020
16. Rueda Domínguez A, Alfaro Lizaso J, De La Cruz Merino L, Gumá I Padró J, Quero Blanco C, Gómez Codina J, et al. SEOM clinical guidelines for the treatment of Hodgkin's lymphoma. Clin Transl Oncol. 2015 Dec;17(12):1005–13.
17. Mina A, Vakkalagadda C, Pro B. Novel Therapies and Approaches to Relapsed/Refractory HL Beyond Chemotherapy. Cancers. 2019 Mar 25;11(3):421.
18. Ramchandren R. Advances in the Treatment of Relapsed or Refractory Hodgkin's Lymphoma. The Oncologist. 2012 Mar 1;17(3):367–76.
19. Vassilakopoulos TP, Asimakopoulos JV, Konstantopoulos K, Angelopoulou MK. Optimizing outcomes in relapsed/refractory Hodgkin lymphoma: a review of current and forthcoming therapeutic strategies. Therapeutic Advances in Hematology. 2020 Jan;11:204062072090291.
20. Potre O, Pescaru M, Sima A, Ionita I, Tudor R, Borsi E, et al. Evaluation of the Relapse Risk and Survival Rate in Patients with Hodgkin Lymphoma: A Monocentric Experience. Medicina. 2021 Sep 27;57(10):1026.

21. Lymphoma Action. Stem cell transplants [Internet]. [cited 2024 Apr 10]. Available from: https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma/stem-cell-transplants
22. Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv19–29.
23. Ortega JJ, Olivé T, de Heredia CD, Llort A. Secondary malignancies and quality of life after stem cell transplantation. Bone Marrow Transplant. 2005 Mar;35 Suppl 1:S83-87.
24. Cancer Research UK. Hodgkins lymphoma | Chemotherapy treatment [Internet]. 2020 [cited 2024 Apr 10]. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/treatment/chemotherapy/chemotherapy-treatment
25. Van Der Kaaij MAE, Heutte N, Le Stang N, Raemaekers JMM, Simons AHM, Carde P, et al. Gonadal Function in Males After Chemotherapy for Early-Stage Hodgkin's Lymphoma Treated in Four Subsequent Trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Étude des Lymphomes de l'Adulte. JCO. 2007 Jul 1;25(19):2825–32.
26. Anderson RA, Remedios R, Kirkwood AA, Patrick P, Stevens L, Clifton-Hadley L, et al. Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial. The Lancet Oncology. 2018 Oct;19(10):1328–37.
27. Bjerring AW, Smeland KHB, Baerug I, Haugaa KH, Kiserud CE, Edvardsen T, et al. Long-term cardiac adverse effects after modern Hodgkins lymphoma treatment. European Heart Journal. 2022 Oct 3;43(Supplement_2):ehac544.801.
28. Van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Petersen EJ, Raemaekers JMM, et al. Cardiovascular Disease After Hodgkin Lymphoma Treatment: 40-Year Disease Risk. JAMA Intern Med. 2015 Jun 1;175(6):1007.
29. Stamatoullas A, Brice P, Bouabdallah R, Mareschal S, Camus V, Rahal I, et al. Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. Br J Haematol. 2015 Jul;170(2):179–84.
30. Phillips EH, Kirkwood AA, Hague C, Vestbo J, Federico M, D'Amore F, et al. Bleomycin Affects Lung Function for at Least 5 Years after Treatment for Hodgkin Lymphoma - Data from the International, Randomised Phase 3 RATHL Trial. Blood. 2023 Nov 28;142(Supplement 1):612.
31. Daniëls LA, Oerlemans S, Krol ADG, Creutzberg CL, van de Poll-Franse LV. Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. Br J Cancer. 2014 Feb 18;110(4):868–74.
32. Øvlisen AK, Jakobsen LH, Kragholm KH, Nielsen RE, Hutchings M, Dahl-Sørensen RB, et al. Depression and anxiety in Hodgkin lymphoma patients: A Danish nationwide cohort study of 945 patients. Cancer Med. 2020 Jun;9(12):4395–404.
33. Kreissl S, Müller H, Goergen H, Meissner J, Topp M, Sökler M, et al. Health-Related Quality of Life in Patients With Hodgkin Lymphoma: A Longitudinal Analysis of the German Hodgkin Study Group. JCO. 2020 Sep 1;38(25):2839–48.
34. Cancer Research UK. Referral to a specialist [Internet]. 2020 [cited 2024 Apr 10]. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/getting-diagnosed/referral-specialist
35. NHS North London and East Anglia Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines Lymphoid Malignancies Part 1: Hodgkin Lymphoma. [Internet]. 2020 Jan [cited 2023 Oct 24]. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-Hodgkin-Guidelines-Jan-2020.pdf
36. Takeda. Data on file: Virtual advisory board. 2024 Jan.
37. Takeda. Data on file: Virtual advisory board. 2022 Aug.
38. NICE. TA772 public committee slides. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies. Available at: https://www.nice.org.uk/guidance/ta772/documents/1 [last accessed: 10/03/2024]. 2021.
39. Takeda. Data on file: medical advisory board. 2023 Dec.
40. Cancer Research UK. Living with Hodgkin Lymphoma | Coping [Internet]. 2020 [cited 2024 Apr 5]. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/living-with/coping
41. Heutte N, Flechtner HH, Mounier N, Mellink WAM, Meerwaldt JH, Eghbali H, et al. Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10-year follow-up of the EORTC-GELA H8 randomised controlled trial. Lancet Oncol. 2009 Dec;10(12):1160–70.
42. Cancer Research UK. Sex, fertility and Hodgkin lymphoma [Internet]. 2020 [cited 2023 Oct 24]. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/living-with/sex-fertility
43. Lymphoma Action. Patient stories [Internet]. [cited 2024 Apr 9]. Available from: https://lymphoma-action.org.uk/stories
44. Blood Cancer UK. Finding hope in the face of infertility [Internet]. [cited 2024 Apr 10]. Available from: https://bloodcancer.org.uk/support-for-you/living-well/stories/hope-in-the-face-of-infertility/
45. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. New England Journal of Medicine. 2018 Jan 25;378(4):331–44.

46. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma | Addendum 3 - March 2024. 2024;
47. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma. 2018;
48. Abdollahpour-Alitappeh M, Lotfinia M, Gharibi T, Mardaneh J, Farhadihosseinabadi B, Larki P, et al. Antibody-drug conjugates (ADCs) for cancer therapy: Strategies, challenges, and successes. J Cell Physiol. 2019 May;234(5):5628–42.
49. Donato EM, Fernández-Zarzoso M, Hueso JA, de la Rubia J. Brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma: an evidence-based review. Onco Targets Ther. 2018;11:4583–90.
50. Schönberger S, van Beekum C, Götz B, Nettersheim D, Schorle H, Schneider DT, et al. Brentuximab vedotin exerts profound antiproliferative and pro-apoptotic efficacy in CD30-positive as well as cocultured CD30-negative germ cell tumour cell lines. J Cell Mol Med. 2018 Jan;22(1):568–75.
51. Currin ESR, Gopal AK. Treatment strategies for Hodgkin lymphoma recurring following autologous hematopoietic stem cell transplantation. Korean J Hematol. 2012;47(1):8.
52. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer. 1975 Jul;36(1):252–9.
53. Ansell SM, Radford J, Connors JM, Długosz-Danecka M, Kim WS, Gallamini A, et al. Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2022 Jul 28;387(4):310–20.
54. Abramson JS, Arnason JE, LaCasce AS, Redd R, Barnes JA, Sokol L, et al. Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma. Blood. 2019 Aug 15;134(7):606–13.
55. Cancer Research UK. Doxorubicin [Internet]. 2023 [cited 2024 Apr 5]. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/doxorubicin
56. Cancer Research UK. Dacarbazine [Internet]. [cited 2024 Apr 5]. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/dacarbazine
57. NHS The Royal Marsden. ABVD chemotherapy for Hodgkin lymphoma [Internet]. 2020 [cited 2024 Jan 9]. Available from: https://patientinfolibrary.royalmarsden.nhs.uk/document/download/1024
58. EMC. Adcetris 50 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) [Internet]. 2023 [cited 2024 Apr 10]. Available from: https://www.medicines.org.uk/emc/product/2859/smpc
59. Cancer Research UK. Granulocyte colony stimulating factor (G-CSF) [Internet]. 2023 [cited 2024 Apr 5]. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/g-csf
60. NHS South West Clinical Network. ABVD [Internet]. 2020 [cited 2024 Jan 9]. Available from: https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2018/11/ABVD_.pdf
61. NHS Thames Valley Strategic Clinical Network. Brentuximab vedotin in combination with CHP [Internet]. [cited 2024 Feb 4]. Available from: https://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-chemo-protocols/L-127-brentuximab-with-chp.pdf
62. Cancer Research UK & UCL Trials Centre. RADAR [Internet]. [cited 2024 Feb 4]. Available from: https://www.ctc.ucl.ac.uk/TrialDetails.aspx?Trial=172&TherA=4
63. ClinicalTrials.gov. S0816 Fludeoxyglucose F 18-PET/CT Imaging and combination Chemotherapy With or Without Additional Chemotherapy and G-CSF in Treating Patients With Stage III or Stage IV Hodgkin Lymphoma [Internet]. 2022 [cited 2024 Jan 16]. Available from: https://www.clinicaltrials.gov/study/NCT00822120
64. ClinicalTrials.gov. Fludeoxyglucose F 18-PET/CT Imaging in Assessing Response to Chemotherapy in Patients With Newly Diagnosed Stage II, Stage III, or Stage IV Hodgkin Lymphoma [Internet]. 2023 [cited 2024 Jan 16]. Available from: https://www.clinicaltrials.gov/study/NCT00678327
65. Casasnovas RO, Bouabdallah R, Brice P, Lazarovici J, Ghesquieres H, Stamatoullas A, et al. Positron Emission Tomography–Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study. Journal of Clinical Oncology. 2022 Apr 1;40(10):1091–101.
66. Straus D, Collins G, Walewski J, Zinzani PL, Grigg A, Sureda A, et al. Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy. Leuk Lymphoma. 2020 Dec;61(12):2931–8.
67. Carde P, Karrasch M, Fortpied C, Brice P, Khaled H, Casasnovas O, et al. Eight Cycles of ABVD Versus Four Cycles of BEACOPPescalated Plus Four Cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score ≥ 3, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial. J Clin Oncol. 2016 Jun 10;34(17):2028–36.
68. Merli F, Luminari S, Gobbi PG, Cascavilla N, Mammi C, Ilariucci F, et al. Long-Term Results of the HD2000 Trial Comparing ABVD Versus BEACOPP Versus COPP-EBV-CAD in Untreated Patients With Advanced Hodgkin Lymphoma: A Study by Fondazione Italiana Linfomi. Journal of Clinical Oncology [Internet]. 2015 Dec 28 [cited 2023 Sep 26]; Available from: https://ascopubs.org/doi/full/10.1200/JCO.2015.62.4817

69. Stephens DM, Li H, Schöder H, Straus DJ, Moskowitz CH, LeBlanc M, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. Blood. 2019 Oct 10;134(15):1238–46.
70. NICE. TA641: Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma [Internet]. 2020 [cited 2024 Apr 10]. Available from: https://www.nice.org.uk/guidance/ta641
71. NICE. TA577: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [Internet]. 2019 [cited 2024 Apr 10]. Available from: https://www.nice.org.uk/guidance/ta577
72. NICE. TA540 | Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [Internet]. 2018 [cited 2024 Apr 10]. Available from: https://www.nice.org.uk/guidance/ta540
73. EORTC. Questionnaires [Internet]. [cited 2024 Apr 9]. Available from: https://qol.eortc.org/questionnaires/
74. Euroqol. EQ-5D-3L [Internet]. [cited 2024 Apr 9]. Available from: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-3l/
75. FACIT.org. FACIT-Dyspnea [Internet]. [cited 2024 Apr 9]. Available from: https://www.facit.org/measures/facit-dyspnea
76. FACIT.org. FACT-GOG-NTX [Internet]. [cited 2024 Apr 9]. Available from: https://www.facit.org/measures/fact-gog-ntx
77. Janssen MF, Pickard AS, Shaw JW. General population normative data for the EQ-5D-3L in the five largest European economies. Eur J Health Econ. 2021 Dec 1;22(9):1467–75.
78. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. European Journal of Cancer. 2019 Jan;107:153–63.
79. Velasco R, Domingo-Domenech E, Sureda A. Brentuximab-Induced Peripheral Neurotoxicity: A Multidisciplinary Approach to Manage an Emerging Challenge in Hodgkin Lymphoma Therapy. Cancers. 2021 Jan;13(23):6125.
80. Straus DJ, Długosz-Danecka M, Alekseev S, Illés Á, Picardi M, Lech-Maranda E, et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. Blood. 2020 Mar 5;135(10):735–42.
81. NICE. Guide to the methods of technology appraisal. Available at: https://www.nice.org.uk/process/pmg36/ [last accessed: 01/04/2022]. 2022;
82. NICE. TA478: Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma. [Internet]. 2017 [cited 2024 Apr 1]. Available from: https://www.nice.org.uk/guidance/ta478
83. Bullement A, Cranmer HL, Shields GE. A Review of Recent Decision-Analytic Models Used to Evaluate the Economic Value of Cancer Treatments. Appl Health Econ Health Policy. 2019 Dec;17(6):771–80.
84. de Vries S, Schaapveld M, Janus CPM, Daniëls LA, Petersen EJ, van der Maazen RWM, et al. Long-Term Cause-Specific Mortality in Hodgkin Lymphoma Patients. JNCI: Journal of the National Cancer Institute. 2021 Jun 1;113(6):760–9.
85. Phillips T, Liu N, Bloudek B, Migliaccio-Walle K, Reynolds J, Burke JM. Estimated impact of ECHELON-1 overall survival on productivity costs in stage III/IV classical Hodgkin lymphoma in the United States. Journal of Managed Care & Specialty Pharmacy. 2023;29(12):1312–20.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

Response to clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID6334 brentuximab EAG CQs 28th May 2024 [redacted]	1.0	No	28 May 2024

Section A: Clarification on effectiveness data

Population

A1. Please confirm when marketing authorisation is anticipated to be received from the Medicines and Healthcare products Regulatory Agency (MHRA) for the anticipated marketing authorisation: brentuximab vedotin for adult patients with previously untreated CD30+ Stage III Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).

Response: The Company expects to receive marketing authorisation for this indication later in 2024 and will share relevant updates with the NICE team as appropriate.

MAICs

A2. Priority question. The External Assessment Group (EAG) notes that for unanchored matching-adjusted indirect comparisons (MAICs), it is critical that attempts to adjust for all potential prognostic factors and treatment effect modifiers that are in imbalance between arms are made, as outlined in NICE decision support unit technical support document (DSU TSD) 18. Given the difficulty in confirming which factors are prognostic/effect modifying, the EAG considers it best practice to adjust for all baseline characteristics reported in the relevant studies.

a) **Please clarify whether the MAIC with the Response-Adapted Therapy for advanced Hodgkin Lymphoma (RATHL) study reported in company submission appendix D.1.7.2 has been fully adjusted for all baseline characteristics reported in the relevant studies.**
b) **Please conduct a fully adjusted MAIC and ensure all reported baseline characteristics are balanced between the studies, if not already provided, for the comparison of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) from ECHELON-1 and positron emission**

tomography (PET) adapted ABVD (RATHL) from the stage III and IV subgroup of the RATHL study, and provide the following:

i) the baseline characteristics after matching;

ii) the resulting hazard ratio (HR) and 95% confidence interval (95%CI) for progression-free survival (PFS);

iii) the resulting HR and 95%CI for overall survival (OS).

iv) Please comment on any factors that could not be adjusted for and the impact this lack of adjustment is expected to have on the results.

Response (a): The MAIC reported in the original Company submission (Appendix D.1.7.2) did not fully adjust for all baseline characteristics reported in the relevant studies. The approach to identify prognostic factors and treatment effect modifiers to adjust for in the Company's MAIC is described in Appendix D.1.7.2; specifically, statistical analyses were conducted on the ECHELON-1 data which identified age, international prognostic score (IPS), B symptoms, and ECOG performance score as prognostic factors and extranodal site as an effect modifier. In addition, whilst not specified in the Company submission, the Company elicited feedback from clinical experts at the market access advisory board (January 2024) which supported the selection of these variables. A comparison of baseline characteristics between ECHELON-1 and the RATHL Stage III/IV subgroup indicated potential imbalances in age, IPS, and ECOG performance score. Of note, the presence of B symptoms was similar across the studies and extranodal site was unavailable in the RATHL study. Therefore, age, IPS, and ECOG performance score were included as potential prognostic factors and/or treatment effect modifiers in the Company's unanchored MAICs. However, as per the EAG's request in Question A2b, a scenario has been conducted adjusting for all baseline characteristics reported in the relevant studies (including data on extranodal sites which were later obtained directly from the RATHL study team following the Company submission).

Response (b): In response to the EAG's question, the Company's unanchored MAICs have been updated to adjust for all reported baseline characteristics across the relevant studies. Therefore, age, IPS, ECOG, stage, gender, B-symptoms, bulky

disease and presence of extra-nodal sites were included in the updated MAIC analyses.

Response (bi): Table 1 presents the baseline characteristics before and after matching for the MAIC adjusting for all reported baseline characteristics for the comparison of the MAIC-weighted ABVD (six cycles) arm from ECHELON-1 and PET-adapted ABVD from RATHL (Stage III/IV subgroup). Of note, matching the ABVD arm of ECHELON-1 to RATHL based on age reduces the mean age in the ECHELON-1 arm from 40.25 to [redacted], which aligns with the younger population in the RATHL study.

Table 1: Baseline characteristics before and after matching for the MAIC adjusting for all reported baseline characteristics | ABVD (six cycles) vs. PET-adapted ABVD

Comparison	Treatment	ESS*	Baseline characteristics							
			Mean age	IPS 3-7	ECOG ≥1	Stage IV	Male	B symptom present	Bulky present	Extranodal site ≥1
Unweighted	ABVD (six cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	ABVD (six cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	PET-adapted ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*36 patients from ABVD arm of ECHELON-1 who did not have stage, bulky disease, or extranodal site information were excluded from the analysis; therefore, the starting sample for ABVD was 634 instead of 670

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

Response (bii): Figure 1 presents the unweighted and weighted ABVD (six cycles; ECHELON-1) PFS data compared to the PET-adapted ABVD (RATHL Stage III/IV subgroup) PFS data when matching on all baseline characteristics reported in the relevant studies. Weighting for all baseline characteristics slightly improves outcomes in the ABVD (six cycles; ECHELON-1) arm. The weighted ABVD (six cycles; ECHELON-1) and PET-adapted ABVD (RATHL) Kaplan–Meier curves appear to be similar and overlap at multiple timepoints.

Figure 1: Unweighted and weighted PFS data for ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics for the MAIC analyses

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched-adjusted indirect comparison; PET, positron emission tomography; PFS, progression-free survival; RATHL, Response-Adapted Therapy for advanced-stage Hodgkin lymphoma.

Table 2 presents the results of the unanchored MAIC analyses adjusted for all reported baseline characteristics. For PFS, the relative efficacy of the ABVD (six cycles; ECHELON-1) compared to the PET-adapted ABVD (RATHL) is associated with a HR of [redacted] (95% CI: [redacted]; [redacted]); the non-significant difference aligns with the visual interpretation of the weighted ABVD (six cycles) and PET-adapted ABVD (RATHL) Kaplan–Meier curves (Figure 1). In addition, this HR estimate is comparable to that presented in the Company submission in the

unanchored MAIC adjusting for age, IPS score, and ECOG (HR: [redacted]; 95% CI: [redacted]; p=[redacted]). The PFS hazard ratio remains insignificant and supports equivalent PFS between ABVD (six cycles) and PET-adapted ABVD.

Response (biii): Figure 2 presents the unweighted and weighted ABVD (six cycles; ECHELON-1) OS data compared to the PET-adapted ABVD (RATHL Stage III/IV subgroup) OS data when matching on all baseline characteristics reported in the relevant studies. In line with PFS, weighting for all baseline characteristics improves outcomes in the ABVD (six cycles) arm.

Figure 2: Unweighted and weighted OS data for ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics for the MAIC analyses

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched-adjusted indirect comparison; PET, positron emission tomography; OS, overall survival; RATHL, Response-Adapted Therapy for advanced-stage Hodgkin lymphoma.

Table 2 presents the results of the unanchored MAIC analyses. For OS, the relative efficacy of ABVD (six-cycles) compared to PET-adapted ABVD (RATHL) is associated with a HR of [redacted] (95% CI: [redacted], [redacted]). This result is statistically significant which indicates a benefit with ABVD (six cycles) compared to PET-adapted ABVD (RATHL) and is comparable to the results estimated in the

unanchored MAIC adjusting for age, IPS score, and ECOG presented in the Company submission (HR: [redacted]; 95% CI: [redacted], [redacted]).

However, as described in the Company Appendix D.1.7.2, based on UK clinical experience with both ABVD approaches, the efficacy of ABVD (six cycles) and PET-adapted ABVD are expected to be equivalent. Therefore, these results should be interpreted with caution. The suggested survival benefit with ABVD (six cycles) compared to PET-adapted ABVD is likely driven by matching on age, given the RATHL population is younger than the ECHELON-1 population. Scenario analyses were conducted in the Company submission removing age as a matching factor, where the hazard ratios moved closer to one and, importantly, the OS hazard ratio was not significant when removing age as a factor ([redacted]; 95% CI: [redacted], p=[redacted]).

Results of all MAIC scenarios highlight that the assumption of equivalent efficacy between ABVD (six cycles) and a PET-adapted ABVD approach may be conservative. However, the MAICs use an unanchored approach which requires strong assumptions i.e., the absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables, and all effect modifiers and prognostic variables are required to be known. Therefore, the limitations of the MAICs must be considered and results be interpreted with caution. Additionally, these MAICs are reliant on digitised published data for PET-adapted ABVD from RATHL, which adds uncertainty to the analyses.

Table 2: Results of the ABVD (six cycles; ECHELON-1) vs. PET-adapted ABVD (RATHL) MAIC analyses adjusting for all baseline characteristics

Outcome	Analysis	Treatment	ESS	HR (95% CI)	Log rank p-value
PFS	Unweighted	ABVD (six cycles)	[redacted]	[redacted]	[redacted]
	Weighted	ABVD (six cycles)	[redacted]	[redacted]	[redacted]
	Weighted	PET-adapted ABVD	[redacted]	Reference	
OS	Unweighted	ABVD (six cycles)	[redacted]	[redacted]	[redacted]
	Weighted	ABVD (six cycles)	[redacted]	[redacted]	[redacted]

Outcome	Analysis	Treatment	ESS	HR (95% CI)	Log rank p-value
	Weighted	PET-adapted ABVD	[redacted]	Reference	

* 36 patients from ABVD arm of E1 who did not have stage, bulky disease, or extranodal site information were excluded from the analysis; therefore, the starting sample for ABVD was 634 instead of 670
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RATHL, Response-Adapted Therapy for advanced-stage Hodgkin lymphoma.

Response (biv): In response to A2, the Company has adjusted for all variables that were reported and available for both ECHELON-1 and the Stage III/IV subgroup of RATHL, including age, IPS, ECOG, stage, gender, B-symptoms, bulky disease and presence of extra-nodal sites. The only variables reported in ECHELON-1 that the Company could not adjust for were race and country, as these data were unavailable for the Stage III/IV subgroup of RATHL. Importantly, neither race or country were considered prognostic factors or treatment effect modifiers based on statistical analyses (Company submission, Appendix D.1.7.2) and feedback from clinical experts at the market access advisory board (January 2024), so the impact of not adjusting for these variables on outcomes is expected to be minimal. Therefore, the Company does not expect this lack of adjustment to have a material impact on the results.

A3. Priority question. Based on advice received from clinical experts, the EAG considers the population and treatment regimen used in the RATHL study to more closely reflect current clinical practice in England compared to the ABVD arm in ECHELON-1. The EAG therefore considers a MAIC comparing brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine (A+AVD) from ECHELON-1 with PET-adapted ABVD (RATHL) to be the most appropriate source of data for the comparison of A+AVD versus ABVD.

Please conduct a fully adjusted MAIC and ensure all reported characteristics are balanced between the studies, for the comparison of A+AVD from

ECHELON-1 and PET-adapted ABVD (RATHL) from the stage III and IV subgroup of the RATHL study, and provide the following:

a) the baseline characteristics after matching;

b) the resulting HR and 95%CI for PFS;

c) the resulting HR and 95%CI for OS.

Response: While the Company appreciates the EAG's position that RATHL is the most appropriate source of data to inform the comparison of A+AVD vs PET-adapted ABVD, the Company maintains that use of ECHELON-1 to inform clinical outcomes for ABVD-based treatment is the most robust method, and that the MAIC comparing A+AVD to PET-adapted ABVD in RATHL should be used as evidence to support and reinforce the PFS and OS benefits observed with A+AVD based on:

- Methodological best practice is to use individual patient data (IPD) from randomised trials to estimate relative effectiveness, and the company's base case reflects this by using IPD from a large, head-to-head trial with an unprecedented length of follow up (median follow-up of [redacted] months for PFS and [redacted] months for OS) in the relevant patient population.

- The Company elicited extensive feedback from clinical experts at the market access advisory board (January 2024) to confirm the generalisability of the ABVD arm in ECHELON-1 to clinical practice in England and Wales. Section B.3.2.3.2 in the Company submission provides strong supportive evidence for the equivalence of efficacy outcomes for patients receiving six cycles of ABVD (per ECHELON-1) compared with the PET-adapted ABVD strategy followed in the RATHL trial.

- The unanchored, unadjusted, and adjusted indirect treatment comparisons (ITCs) previously provided for ABVD-based regimens, as reported in the Company submission Section B.3.2.3.2. and Appendix D, together provide supportive evidence for the equivalence of ABVD (six-cycles) in ECHELON-1 compared with PET-adapted ABVD (RATHL) and support the use of the IPD from ECHELON-1 for Committee decision-making.

- The NICE health technology evaluations manual states that there is a "*strong preference for randomised controlled trials (RCTs) to inform relative treatment effects",* and that *"it is not acceptable to compare results from single treatment arms from different randomised trials. If this type of comparison is presented, the data will be treated as observational in nature and associated with increased uncertainty*."

For completeness, and in response to the EAG's question, unanchored MAICs have been conducted to estimate the relative efficacy of A+AVD from ECHELON-1 compared to PET-adapted ABVD from the Stage III and IV subgroup of the RATHL study, adjusting for all reported baseline characteristics across the relevant studies. Therefore, age, IPS, ECOG, stage, gender, B-symptoms, bulky disease and presence of extra-nodal sites were included in the updated MAIC analyses as per PFS.

Response (a): Table 3 presents the baseline characteristics before and after matching for the MAIC adjusting for all reported baseline characteristics for the comparison of A+AVD from ECHELON-1 and PET-adapted ABVD from RATHL. Of note, matching the A+AVD arm of ECHELON-1 to RATHL based on age reduces the mean age in the ECHELON-1 arm from 38.90 to [redacted], which aligns with the younger population in the RATHL study.

Table 3: Baseline characteristics before and after matching for the MAIC adjusting for all reported baseline characteristics | A+AVD (ECHELON-1) vs. PET-adapted ABVD (RATHL)

Comparison	Treatments	ESS	Baseline characteristics							
			Mean age	IPS 3-7	ECOG ≥1	Stage IV	Male	B symptom present	Bulky present	Extranodal site ≥1
Unweighted	A+AVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	A+AVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	PET-adapted ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 40 patients from A+AVD arm of E1 who did not have stage, bulky disease, or extranodal site information were excluded from the analysis; therefore, the starting sample for A+AVD of E1 was 624 instead of 664

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

Response (b): Figure 3 presents the unweighted and weighted A+AVD (ECHELON-1) PFS data compared to the PET-adapted ABVD (RATHL Stage III/IV subgroup) PFS data when matching on all baseline characteristics reported in the relevant studies. Weighting for all baseline characteristics slightly improves outcomes in the A+AVD (ECHELON-1) arm vs the unweighted data.

Figure 3: Unweighted and weighted PFS data for A+AVD (ECHELON-1) vs. PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics for the MAIC analyses

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched-adjusted indirect comparison; PET, positron emission tomography; PFS, progression-free survival; RATHL, Response-Adapted Therapy for advanced-stage Hodgkin lymphoma.

Table 4 presents the results of the unanchored MAIC analyses when matching on all baseline characteristics reported in the relevant studies. For PFS, the relative efficacy of the MAIC-weighted A+AVD compared to PET-adapted ABVD (RATHL) is associated with a HR of [redacted] (95% CI: [redacted]; p[redacted]).

Response (c): Figure 4 presents the unweighted and weighted A+AVD (ECHELON-1) OS data compared to the PET-adapted ABVD (RATHL Stage III/IV subgroup) OS data when matching on all baseline characteristics reported in the relevant studies.

Weighting for all baseline characteristics slightly improves outcomes in the A+AVD (ECHELON-1) arm vs the unweighted data.

Figure 4: Unweighted and weighted OS data for A+AVD (ECHELON-1) vs. PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics for the MAIC analyses

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched-adjusted indirect comparison; PET, positron emission tomography; OS, overall survival; RATHL, Response-Adapted Therapy for advanced-stage Hodgkin lymphoma.

For OS, the relative efficacy of the MAIC-weighted A+AVD compared to PET-adapted ABVD (RATHL) is associated with a HR of [redacted] (95% CI: [redacted], p[redacted]).

The head-to-head comparison of A+AVD compared to ABVD from ECHELON-1, based on the March 2023 data cut, was associated with a hazard ratio of [redacted] (95% CI: [redacted]; p[redacted]) for PFS and [redacted] (95% CI: [redacted]; p[redacted]) for OS. The relative efficacy estimates indicate an increased benefit of A+AVD vs. ABVD-based treatment when adjusted to the RATHL population vs the observed data in ECHELON-1([redacted] vs. [redacted] for PFS and [redacted] vs. [redacted] for OS, respectively), with overlap observed across the confidence intervals.

These results highlight that use of IPD from ECHELON-1, and the associated ICER estimates may therefore be conservative. However, there are limitations with the

MAICs which the EAG should be mindful of (see response to A2biii). Additionally, these MAICs are reliant on digitised published data for PET-adapted ABVD from RATHL, which induces further uncertainty in the analyses.

The CEM includes the option to model outcomes using the weighted A+AVD PFS and OS data from the MAICs and the PET-adapted ABVD digitised data from RATHL (Stage III/IV subgroup) in response to B2. This analysis has been presented as an alternative base case to the use of ECHELON-1 directly.

Table 4: Results of the A+AVD (ECHELON-1) vs. PET-adapted ABVD (RATHL) MAIC analyses adjusting for all baseline characteristics

Outcome	Analysis	Treatment	ESS	HR (95% CI)	Log rank p-value
PFS	Unweighted	A+AVD	[redacted]	[redacted]	[redacted]
	Weighted	A+AVD	[redacted]	[redacted]	[redacted]
	Weighted	PET-adapted ABVD	[redacted]	Reference	
OS	Unweighted	A+AVD	[redacted]	[redacted]	[redacted]
	Weighted	A+AVD	[redacted]	[redacted]	[redacted]
	Weighted	PET-adapted ABVD	[redacted]	Reference	

* 40 patients from A+AVD arm of E1 who did not have stage, bulky disease, or extranodal site information were excluded from the analysis; therefore, the starting sample for A+AVD of E1 was 624 instead of 664
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RATHL, Response-Adapted Therapy for advanced-stage Hodgkin lymphoma.

A4. Priority question. Please provide an assessment of proportional hazards for PFS and OS for:

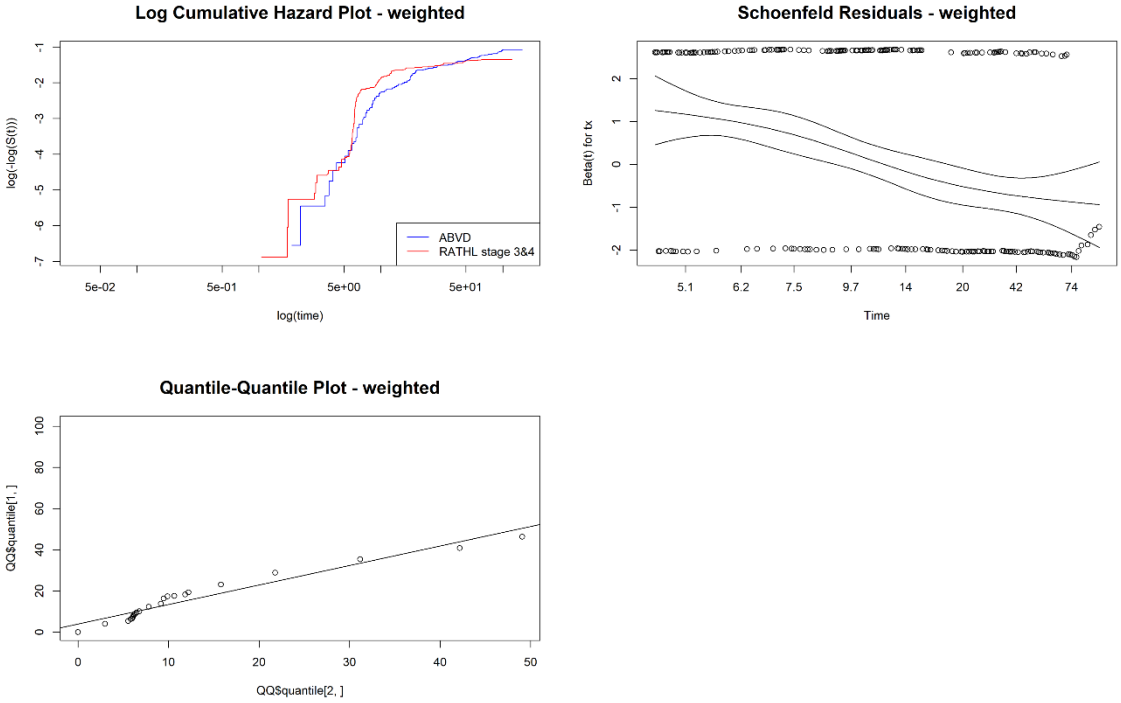
a) **the MAIC requested in question A2, using the adjusted curve for ABVD from ECHELON-1 and the (unadjusted) PET-adapted ABVD from the stage III and IV subgroup of the RATHL study;**
b) **the MAIC requested in question A3, using the adjusted curve for A+AVD from ECHELON-1 and the (unadjusted) PET-adapted ABVD from the stage III and IV subgroup of the RATHL study; and**
c) **the MAIC conducted in the company submission appendix D.1.7.2, using the adjusted curve for ABVD from ECHELON-1 and the (unadjusted) PET-adapted ABVD from the stage III and IV subgroup of the RATHL study.**

Response (a): Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for the MAICs estimating the relative efficacy of ABVD (six cycles) from ECHELON-1 compared to the unadjusted PET-adapted ABVD from the Stage III/IV subgroup of the RATHL study by adjusting for all reported baseline characteristics (see response to A2) are presented in Figure 5 and Figure 6 for PFS and OS, respectively.

For PFS, the Schoenfeld residuals and the Grambsch–Therneau test indicate a p-value of <0.001, the log-cumulative hazard plots demonstrate clear crossings of curves, and there is a clear slope observed in the Schoenfeld residuals plot. Therefore, the assumption of proportional hazards was not considered to hold. The accelerated failure time assumption may hold with the quantile-quantile plot approximating well to the straight line from the origin.

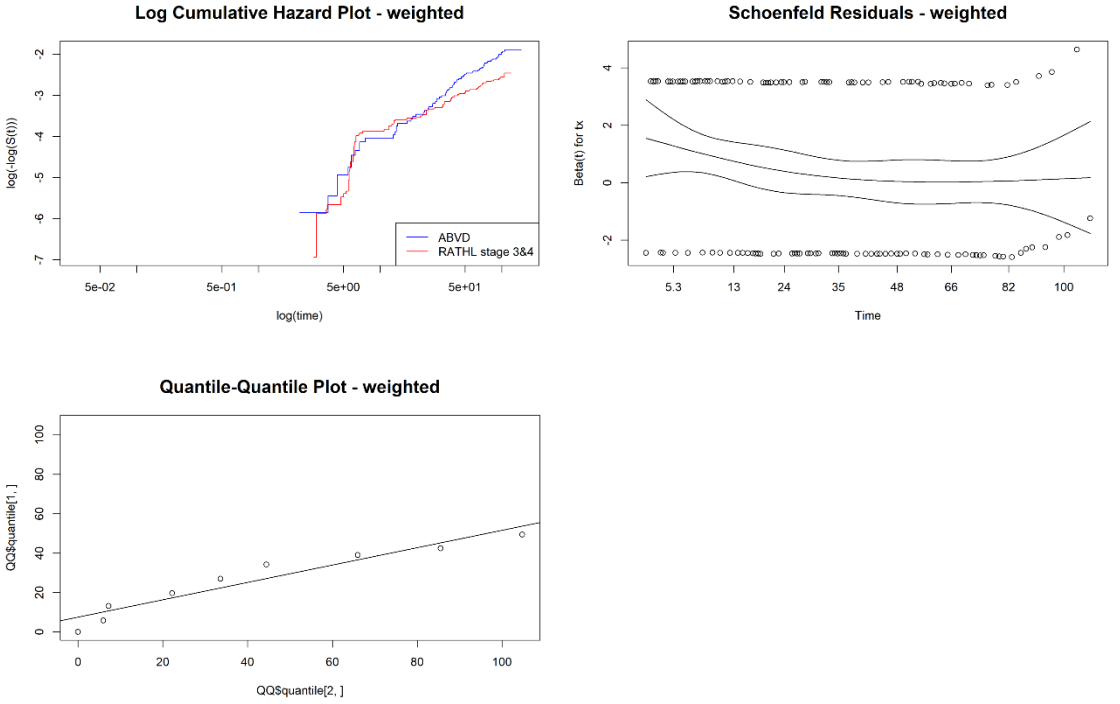
For OS, the Schoenfeld residuals and the Grambsch–Therneau test indicate a p-value of 0.075, the log-cumulative hazard plots demonstrate clear crossings of curves, and there is a slope observed in the Schoenfeld residuals plot. Therefore, the assumption of proportional hazards was not considered to hold. The accelerated failure time assumption may hold with the quantile-quantile plot approximating well to the straight line from the origin.

Figure 5: PFS assessment of proportional hazards and accelerated failure time assumptions | MAIC-weighted ABVD (six cycles) vs. PET-adapted ABVD



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival.

Figure 6: OS assessment of proportional hazards and accelerated failure time assumptions | MAIC-weighted ABVD (six cycles) vs. PET-adapted ABVD



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival.

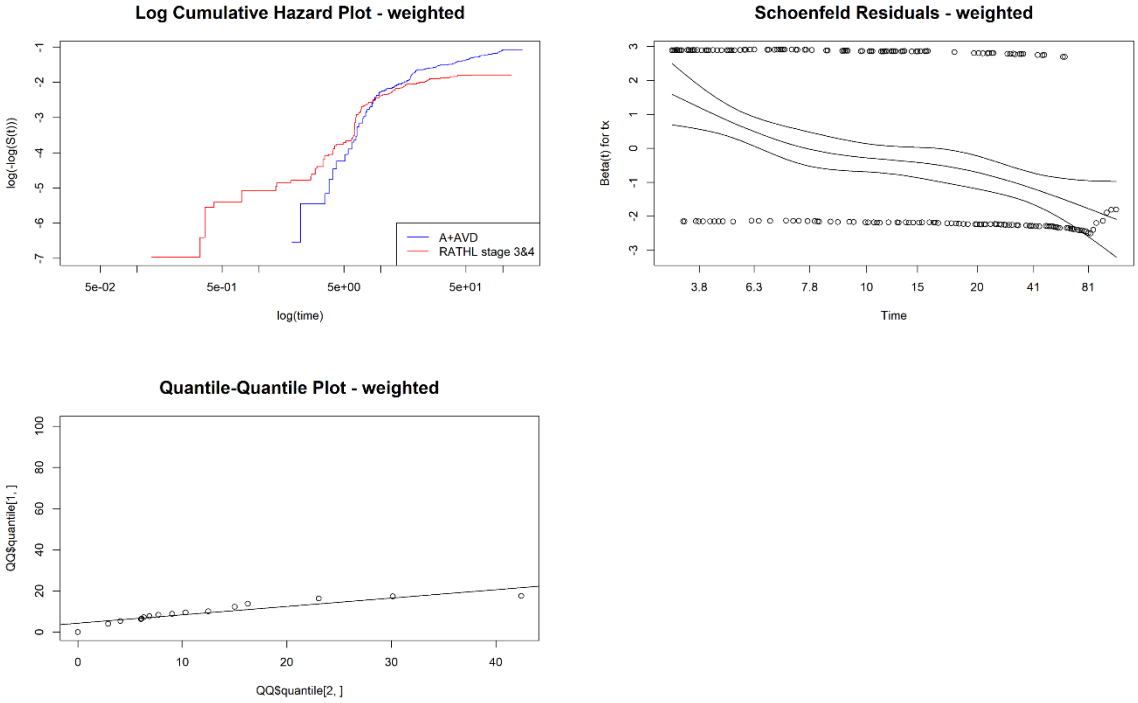
Response (b): Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for the MAICs estimating the relative efficacy of A+AVD from ECHELON-1 compared to the unadjusted PET-adapted ABVD from the Stage III/IV subgroup of the RATHL study by adjusting for all reported baseline characteristics (see response to A3) are presented in Figure 7 and Figure 8 for PFS and OS, respectively.

For PFS, the Schoenfeld residuals and the Grambsch–Therneau test indicate a p-value of <0.001, the log-cumulative hazard plots demonstrate a clear crossing of curves, and there is a clear slope observed in the Schoenfeld residuals plot. Therefore, the assumption of proportional hazards was not considered to hold. The accelerated failure time assumption may hold with the quantile-quantile plot approximating well to the straight line from the origin.

For OS, the Schoenfeld residuals and the Grambsch–Therneau test indicate a p-value of 0.180, which indicate that the proportional hazards assumption may hold; however, the log-cumulative hazard plots demonstrate a clear crossing of curves, and the Schoenfeld residuals plot does not resemble a flat line. Therefore, the assumption of proportional hazards was not considered to hold. The accelerated failure time assumption may be violated with the quantile-quantile plot not approximating to the straight line from the origin.

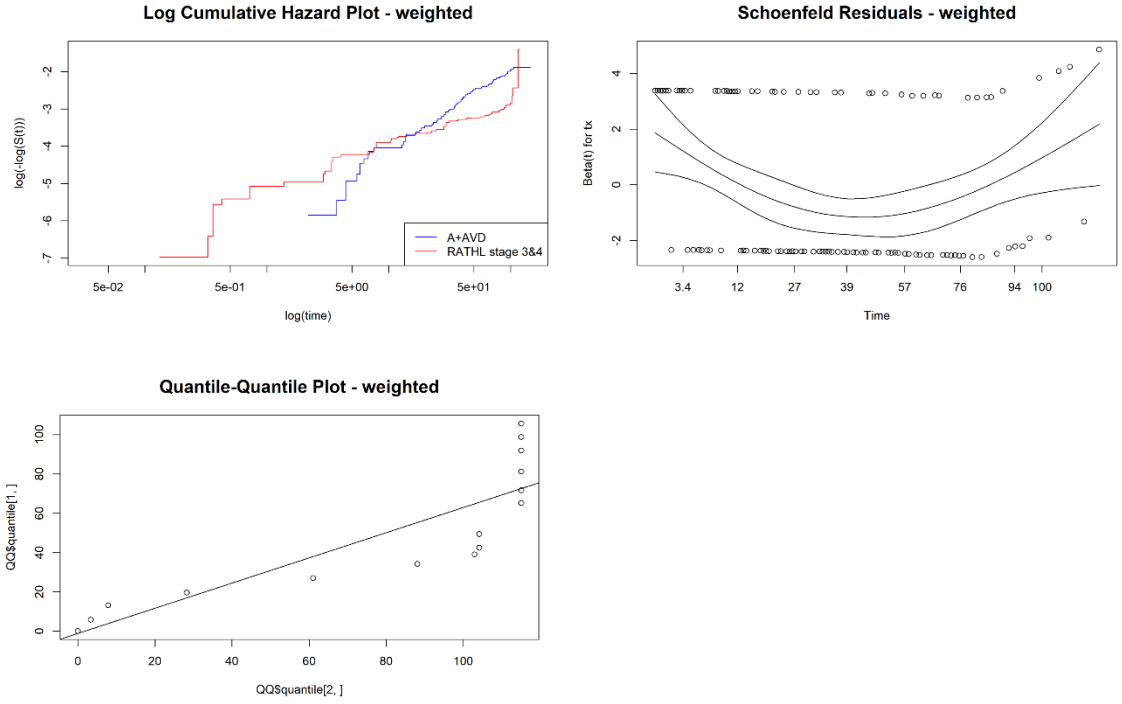
Figure 7 and Figure 8 support using independent flexible parametric models when extrapolating these data; the proportional hazards assumption is likely violated, the accelerated failure time assumption may be violated for OS, and the log-cumulative hazard plots are not straight lines, indicating that flexible parametric models may be most appropriate. The use of independent modelling aligns with the approach used in the Company submission.

Figure 7: PFS assessment of proportional hazards and accelerated failure time assumptions | MAIC-weighted A+AVD vs. PET-adapted ABVD



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival.

Figure 8: OS assessment of proportional hazards and accelerated failure time assumptions | MAIC-weighted A+AVD vs. PET-adapted ABVD



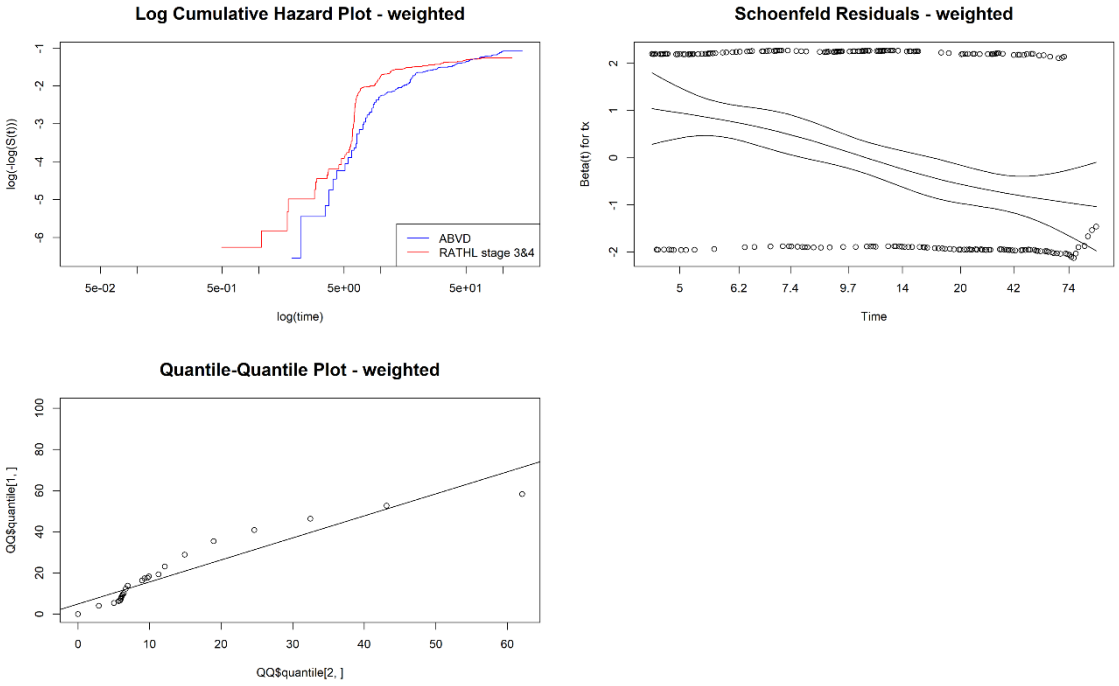
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival.

Response (c): Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for the MAICs estimating the relative efficacy of ABVD from ECHELON-1 compared to the unadjusted PET-adapted ABVD from the Stage III/IV subgroup of the RATHL study by adjusting for age, IPS, and ECOG (see Company appendix D.1.7.2) are presented in Figure 9 and Figure 10 for PFS and OS, respectively.

For PFS, the Schoenfeld residuals and the Grambsch–Therneau test indicate a p-value of <0.001, the log-cumulative hazard plots demonstrate a clear crossing of curves and are not parallel, and there is a clear slope observed in the Schoenfeld residuals plot. Therefore, the assumption of proportional hazards was not considered to hold. The accelerated failure time assumption may hold with the quantile-quantile plot approximating well to the straight line from the origin.

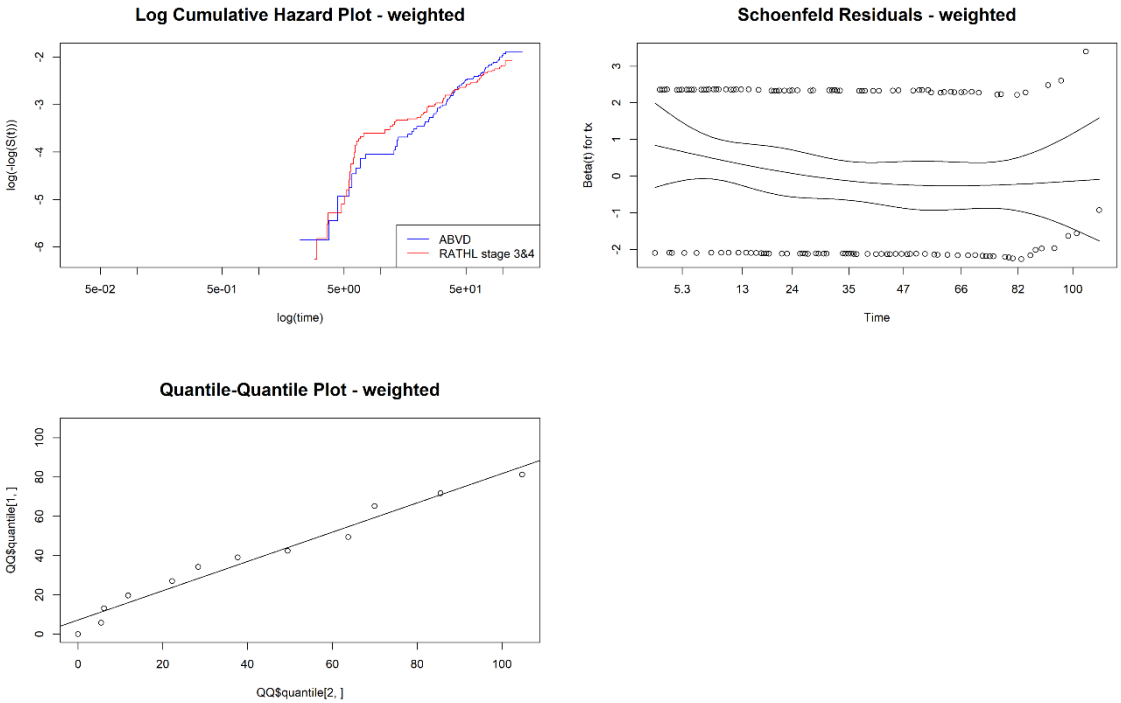
For OS, the Schoenfeld residuals and the Grambsch–Therneau test indicate a p-value of 0.112, which indicate that the proportional hazards assumption may hold; however, the log-cumulative hazard plots demonstrate multiple crossings of curves, and there is a slope observed in the Schoenfeld residuals plot. Therefore, the assumption of proportional hazards was not considered to hold. The accelerated failure time assumption may hold with the quantile-quantile plot approximating well to the straight line from the origin.

Figure 9: PFS assessment of proportional hazards and accelerated failure time assumptions | MAIC-weighted ABVD (six cycles) vs. PET-adapted ABVD | Company submission appendix D.1.7.2



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival.

Figure 10: OS assessment of proportional hazards and accelerated failure time assumptions | MAIC-weighted ABVD (six cycles) vs. PET-adapted ABVD | Company submission appendix D.1.7.2



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival.

A5. Priority question. Please provide the baseline characteristics after matching for the MAIC currently used in the company submission appendix D.1.7.2 for the comparison of ABVD from ECHELON-1 and PET-adapted ABVD from RATHL.

Response: Table 1 presents the baseline characteristics before and after matching for the MAIC presented in the Company submission Appendix D.1.7.2 for the comparison of ABVD from ECHELON-1 and PET-adapted ABVD from RATHL. Of note, matching the ABVD arm of ECHELON-1 to RATHL based on age reduces the mean age in the ECHELON-1 cohort from 40.15 to [redacted], which aligns with the younger population in the RATHL study.

Table 5: Baseline characteristics before and after matching for the MAIC presented in the Company submission | ABVD (six cycles) vs. PET-adapted ABVD

Comparison	MAIC variables	ESS	Baseline characteristics			
			Mean age	IPS 3-7	ECOG ≥1	Stage IV
Unweighted	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	Age + IPS + ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	IPS + ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Four patients in ABVD arm (E1) did not have ECOG or cancer stage data
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

Adverse events

A6. Priority question. Please provide a results table detailing separately for the safety population of each trial arm of ECHELON-1 using the 11 March 2023 data cut:

a) **the total number of patients with a peripheral neuropathy (PN) adverse event (AE);**
b) **the number of patients and proportion who suffered with a PN AE for each AE Grade (1 to 4);**
c) **the mean (SD) of time to resolution for patients with resolved PN AEs from start of treatment;**
d) **the number and proportion of patients with unresolved PN events;**
e) **the number and proportion of patients requiring dose modifications due to PN AEs; and**
f) **the number and proportion of patients discontinuing treatment due to PN AEs.**

Response: Please see Table 6 for a summary of these data.

Table 6: Summary of peripheral neuropathy adverse events in ECHELON-1 | Safety population | March 2023 DCO

	A+AVD (n=662)	ABVD (n=659)
Patients with treatment-emergent PN SMQ event, n (%)*	[redacted]	[redacted]
CTCAE severity of PN SMQ AEs, n (%)*	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Mean time to resolution† of resolved PN events from onset, weeks (SD)	[redacted]	[redacted]
Status of PN AEs at last follow-up, n (%)	[redacted]	[redacted]
Resolution† of all events	[redacted]	[redacted]
Resolution† or improvement in events	[redacted]	[redacted]
Improvement in events	[redacted]	[redacted]

	A+AVD (n=662)	ABVD (n=659)
No resolution† of improvement of any events	[redacted]	[redacted]
Ongoing events	[redacted]	[redacted]
Patients with ≥1 PN (SMQ) TEAE resulting in study drug or dose modification, n (%)‡	[redacted]	[redacted]
Dose interrupted	[redacted]	[redacted]
Dose reduced	[redacted]	[redacted]
Dose delayed	[redacted]	[redacted]
Patients with ≥1 PN (SMQ) TEAE resulting in study drug or dose discontinuation, n (%)‡	[redacted]	[redacted]

Event severity based on National Cancer Institute CTCAE Version 4.03.
*Corresponds to Table 12.aa in 2018 CSR (20 April 2017 data cut). Please note the overall rate of PN SMQ events has increased by one in the A+AVD arm due to subsequent updates after the 2018 CSR. †Resolution defined as resolved or resolved with sequelae. ‡Corresponds to page 278 in 2018 CSR (20 April 2017 data cut). Please note the rate of dose reductions has increased by one in the A+AVD arm and discontinuations has decreased by one in the A+AVD arm and one in the ABVD arm, due to subsequent updates after the 2018 CSR.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse event; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; PN, peripheral neuropathy; SD, standard deviation; SMQ, standardised MedDRA query.

A7. Priority question. From the 2018 clinical study report (CSR, Table 12.j), the EAG is concerned that there may be some overlap between Grade 3 adverse event categories reported in ECHELON-1. Please can the company:

a) explain how [redacted] and

b) provide the total number of patients experiencing any Grade 3 peripheral neuropathy adverse event for each trial arm.

Response (a): Neuropathy peripheral, peripheral sensory neuropathy, and peripheral motor neuropathy are different adverse events, coded under distinct MedDRA codes, and as such are distinct events that are counted separately under each preferred term. While individual events would be expected to be coded separately by study investigators, a patient may have reported more than one event. For example, instances of muscle weakness due to nerve damage would be considered as 'peripheral motor neuropathy', whereas numbness or tingling would be classed as 'peripheral sensory neuropathy'. Where specific events have been

presented (e.g. Company submission Section B.2.10.2.1) these are by preferred term.

For analysis of all events falling under the umbrella of peripheral neuropathy, an AE of special interest for patients treated with brentuximab vedotin, a comprehensive review of MedDRA preferred terms was conducted under the Peripheral Neuropathy (Standardised MedDRA Query [SMQ]) broad definition, which included all relevant preferred terms reported by patients in ECHELON-1. Importantly, the peripheral neuropathy events reported in Section B.2.10.4.3 of the original Company submission are those collected under the Peripheral Neuropathy SMQ, and reflect the total number of patients experiencing any PN adverse event. This provides a more complete picture of PN than analysis of individual preferred terms.

Response (b): In total, 68 patients (10%) in the A+AVD arm, and 11 patients (2%) in the ABVD arm reported one or more Grade ≥3 event under the SMQ of Peripheral Neuropathy[a] by end of treatment. Please note that this is lower than the number of patients reporting each preferred term in either arm, due to some patients reporting more than one PN event (Table 7).

Table 7: Summary of CTCAE Grade ≥3 peripheral neuropathy TEAEs in ECHELON-1 by SMQ or preferred term | Safety population | March 2023 DCO

	A+AVD (n=662)	ABVD (n=659)
Patients reporting PN according to standardised MedDRA query, n (%)		
Patients with ≥1 treatment-emergent Grade ≥3 PN event, n (%)	68 (10)	11 (2)
Patients reporting PN by preferred term, n (%)		
Peripheral sensory neuropathy	32* (5)	3 (<1)
Neuropathy peripheral	28 (4)	6 (<1)
Peripheral motor neuropathy	13* (2)	0
Muscular weakness	2 (<1)	1 (<1)
Hypoaesthesia	1 (<1)	0
Neuralgia	1* (<1)	0
Polyneuropathy	1 (<1)	1 (<1)

[a] MedDRA dictionary Version 22.0 was applied. Please note the number of patients with Grade ≥3 PN in the A+AVD arm is reported as 70 in the original Company submission, based on the 20 April 2017 data cut. The number was subsequently updated to 68 patients.

	A+AVD (n=662)	ABVD (n=659)
Autonomic neuropathy	0	1* (<1)

*Note: updating of results subsequent to the 20 April 2017 data cut means that patient numbers have changed for these preferred terms, and results may appear different to earlier data.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; PN, peripheral neuropathy; SMQ, standardised MedDRA query.

A8. Priority question. Please provide a results table with the number of patients experiencing Grade 3 or above treatment emergent adverse events (TEAE) in each arm of ECHELON-1 for each adverse event occurring in ≥5% of patients in either trial arm, and also the total number of patients experiencing a Grade 3 or above TEAE for each trial arm of the safety population for the 11 March 2023 data cut.

Response: In total, [redacted] patients ([redacted]%) in the A+AVD arm and [redacted] patients ([redacted]%) in the ABVD arm reported at least one Grade ≥3 TEAE. TEAEs by preferred term that occurred in ≥5% of patients in either treatment arm are shown in Table 8. Please note that peripheral neuropathy was a standardised MedDRA query, grouping multiple peripheral neuropathy preferred terms, and is not shown in Table 8 because no single preferred term relating to neuropathy was reported in ≥5% of patients at the March 2023 data cut-off (see Question B10). Patients who reported Grade ≥3 PN events by preferred term are presented in Table 7. The PN-related preferred term reported by the highest proportion of patients was peripheral sensory neuropathy (4.8% of patients).

Table 8: Patients reporting Grade ≥3 TEAEs that occurred in ≥5% of patients in either treatment arm | Safety population | March 2023 DCO

Preferred term, n (%)	A+AVD (n=662)	ABVD (n=659)
Patients with at least one Grade ≥3 TEAE	[redacted]	[redacted]
Neutropenia*	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Anaemia*	[redacted]	[redacted]

* Please note that the recorded rate of anaemia and neutropenia events was updated subsequent to the 20 April 2017 data cut, and the data above therefore differ from this earlier data cut (54 patients in the A+AVD arm reported anaemia; 260 patients in the ABVD arm reported neutropenia).
Note: rows present number and proportion of patients reporting TEAEs in total/by preferred term. Event severity

based on National Cancer Institute CTCAE Version 4.03. MedDRA Version 22.0 was applied. TEAEs are defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of frontline therapy.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; TEAE, treatment-emergent adverse event.

Baseline characteristics

A9. Please provide the PET status after Cycle 2 (PET2 status) for the subgroup of patients with Stage III and the subgroup with Stage IV HL at baseline in ECHELON-1, for each trial arm, including the relative risk and 95% confidence interval as reported for the overall study population in Section B.2.6.3 of the company submission.

Response: PET2 status by disease stage is presented in (Table 9). For patients with Stage III disease, the proportion achieving PET2 negativity was similar between arms. For patients with Stage IV disease, a numerical, but non-significant treatment benefit with A+AVD vs. ABVD was observed for the proportion achieving PET2 negativity, with a relative risk of 1.049 (95% CI 1.00, 1.10).

Table 9: PET2 status by Ann Arbor stage at initial diagnosis in ECHELON-1 | March 2023 DCO

n (%)	A+AVD	ABVD
ITT population	**N=664**	**N=670**
PET2 negative	588 (89)	577 (86)
PET2 positive	47 (7)	58 (9)
Missing PET at Cycle 2	29 (4)	35 (5)
PET2 negative status relative risk (95% CI)	1.028 (0.99, 1.07)	
Stage III	**n=237**	**n=246**
PET2 negative	209 (88)	219 (89)
PET2 positive	13 (5)	15 (6)
Missing PET at Cycle 2	15 (6)	12 (5)
PET2 negative status relative risk (95% CI)	0.991 (0.93, 1.06)	
Stage IV	**n=425**	**n=421**
PET2 negative	379 (89)	358 (85)
PET2 positive	34 (8)	42 (10)
Missing PET at Cycle 2	12 (3)	21 (5)
PET2 negative status relative risk (95% CI)	1.049 (1.00,1.10)	

Note: subgroup numbers do not sum to ITT data presented here and in the submission dossier, as some patients had missing staging data at baseline.

PET2 positive = Deauville score >3. PET2 negative = Deauville score ≤3.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; DCO, data cut-off; PET2, positron emission tomography at end of Cycle 2.

ECHELON-1 data

A10. Figure 16 and the economic model both include OS and PFS data from ECHELON-1 up to approximately 120 months, whereas the data reported in Figures 6 and 7 of the clinical effectiveness section of the company submission and the 9 April 2024 CSR addendum comprise of Kaplan-Meier (KM) plots to only 102 months. Please can the company:

a) explain the reason for this discrepancy in data for OS and PFS between the clinical effectiveness section of the company submission and the economic model;
b) provide separate OS and PFS KM plots including the data up to approximately 120 months reported in Figure 16 including the numbers at risk for each timepoint;
c) confirm the data provided in Tables 11 (Analysis of PFS) and 12 (Analysis of OS) of the CS relate to the data shown in Figure 16 and if not, provide the corresponding results based on the data in Figure 16;
d) provide the percentage OS and PFS and 95% confidence intervals for each trial arm at 108, 114 and 120 months.

Response (a): The Company would like to apologise for this oversight. Unfortunately, there was a formatting error which meant that the x-axis (time) of the PFS and OS Kaplan-Meier plots presented in the 9 April 2024 CSR addendum and Section B.2 of the CS were not updated for the March 2023 data-cut.

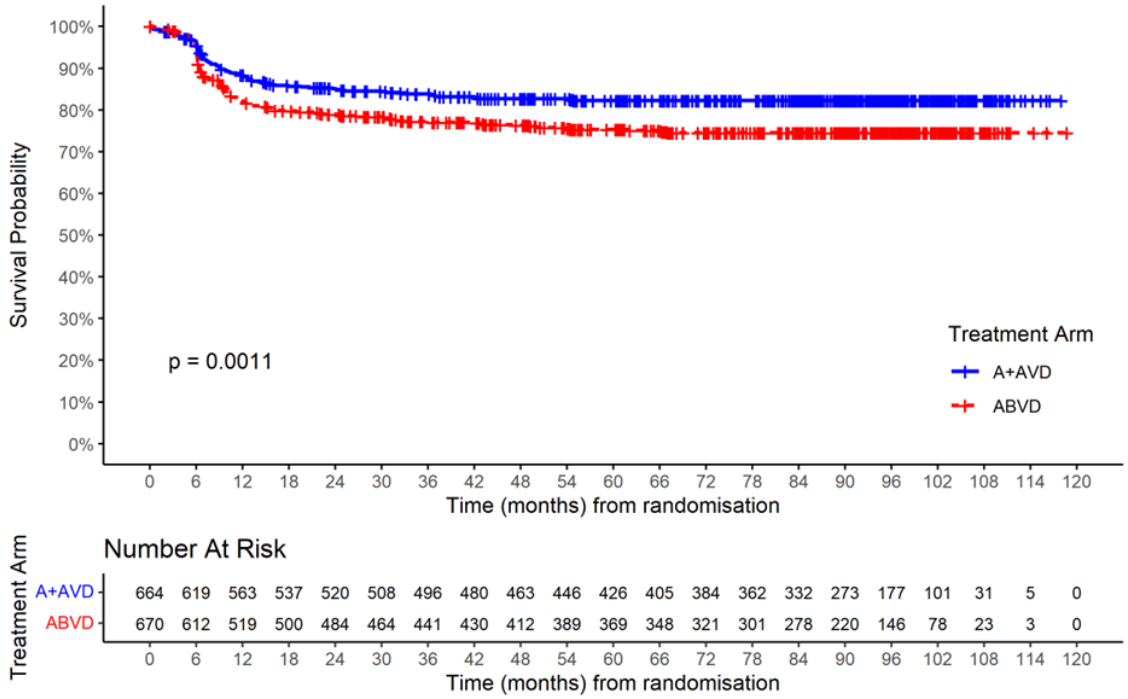
Importantly, this is a formatting error only, and the data presented in Section B.2 of the CS, including Figures 6 and 7, as well as the data presented in the 9 April 2024 CSR addendum are based on the final March 2023 data-cut from ECHELON-1. This has no impact on the PFS and OS analysis results (e.g. p-values, hazard ratios, medians, survival rates), which are all based on the March 2023 data-cut.

For clarity, the PFS and OS data used throughout the original Company submission, including the cost-effectiveness modelling, are based on the March 2023 data-cut

from ECHELON-1, and are unaffected by the formatting error which is isolated to Figures 6 and 7 in the CS and associated plots and tables in the CSR.

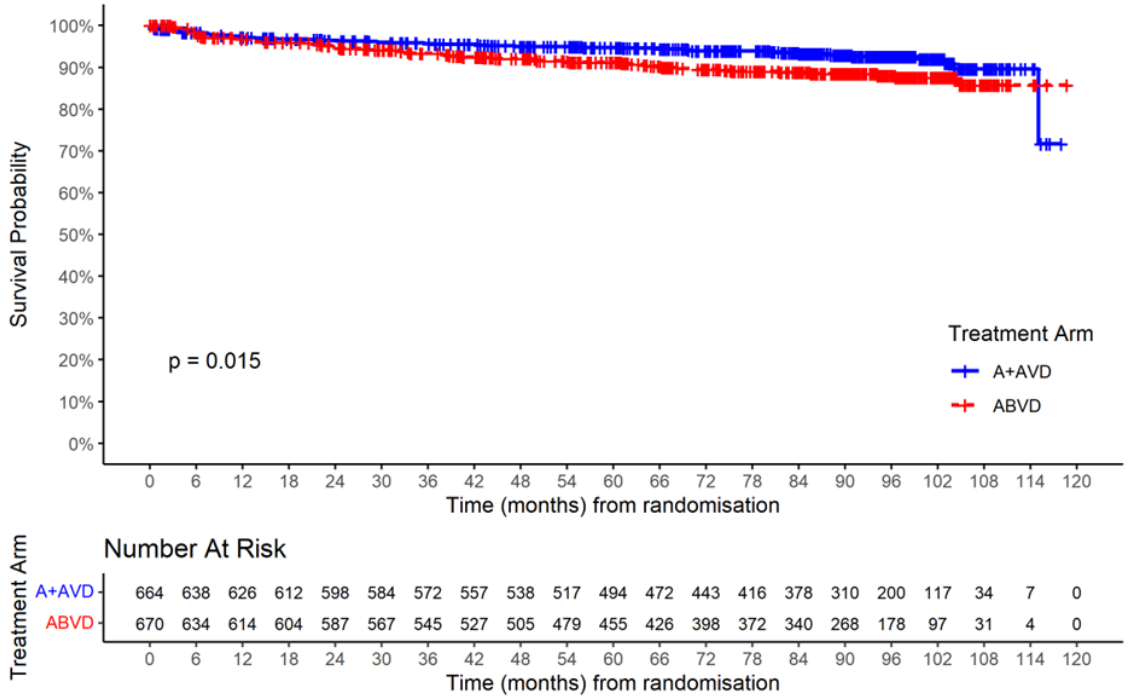
Response (b): Please see Figure 11 and Figure 12 for PFS and OS, respectively.

Figure 11: PFS (INV) Kaplan–Meier | ITT population | March 2023 DCO



Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; DCO, data cut-off; ITT, intent-to-treat; PFS, progression-free survival.

Figure 12: OS Kaplan–Meier | ITT population | March 2023 DCO



Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; DCO, data cut-off; ITT, intent-to-treat; OS, overall survival.

Response (c): The Company can confirm that the data in Tables 11 and 12 relate to the data shown in Figure 16. Importantly, as per the Company response to A10a, these data are based on the final March 2023 data-cut.

Response (d): Please see Table 10 for a summary of these data. No patients were followed to [redacted] months, as the maximum follow-up duration for OS and for PFS was [redacted] months in the A+AVD arm and [redacted] months in the ABVD arm.

Table 10: Summary of proportion surviving by timepoint in ECHELON-1 | ITT population | March 2023 DCO

% (95% CI), n	A+AVD (n=664)	ABVD (n=670)
PFS		
108 months	[redacted]; N=[redacted]	[redacted]; N=[redacted]
114 months	[redacted]; N=[redacted]	[redacted]; N=[redacted]
120 months	[redacted]	[redacted]

% (95% CI), n	A+AVD (n=664)	ABVD (n=670)
OS		
108 months	[redacted]; N=[redacted]	[redacted]; N=[redacted]
114 months	[redacted]; N=[redacted]	[redacted]; N=[redacted]
120 months	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; DCO, data cut-off; ITT, intent-to-treat; NA, not applicable.

A11. Please provide updated clinical effectiveness results for all outcomes reported in the company submission using the data-cut used to inform the economic model if a different data-cut has been used to the 11 Mar 2023 data-cut reported in the company submission.

Response: The Company can confirm that the relevant clinical effectiveness results for the outcomes reported in the submission are based on the 11 Mar 2023 data-cut, except for PET2 status (updated results from 11 Mar 2023 are provided in A9).

A12. Please clarify the reason for the absence of a reduction in PFS beyond 102 months despite a reduction in OS in the KM plots in Figure 16 of the CS.

Response: Beyond 102 months, there were [redacted] OS events observed in ECHELON-1 ([redacted] and [redacted] in the A+AVD and ABVD arms, respectively). For these [redacted] patients, their corresponding PFS event times ranged from [redacted] months to [redacted] months, and all patients were censored due to missing more than one visit (as per the statistical analysis plan). Therefore, when the [redacted] OS events were observed after 102 months, there is no corresponding drop in the PFS curve.

Section B: Clarification on cost-effectiveness data

Population

B1. Priority question. As stated in the company submission and supported by the company's and EAG's clinical experts, the late stage HL patient population can be seen as bimodal, with the highest rate of incidence occurring between the ages of 20-24 years and 75-79 years old. As such, the EAG is concerned that using a simplistic approach based on mean age may not appropriately capture the expected differences in these two different populations. Therefore, please provide a scenario which accounts for the bimodal population and <60 and ≥60 year old ECHELON-1 subgroup treatment effects. Please provide a weighted ICER based on the proportion of <60 and ≥60 year old patients in the ECHELON-1 trial.

Response: The company does not believe it is appropriate to consider the appraisal patient population as two separate populations based on age, and that doing so might have a negative impact on health equalities.

The EAG is correct that incidence is bimodal; however, feedback elicited from clinical experts at both the medical advisory board (November 2023) and market access advisory board (January 2024) confirmed that a patient considered suitable for ABVD-based treatment will receive it irrespective of age.[1] This is consistent with the BSH 2022 guidelines which state that it is reasonable to treat elderly patients (those aged >60 years) with ABVD-based treatment if they are not frail, provided that caution is taken over the use of bleomycin.[2]

For completeness, in response to the EAG's question, dependent and independent parametric curves (standard, MCMs, and one-knot splines) were fitted to the age <60 years and ≥60 years subgroup data from ECHELON-1. In addition, patient characteristics (age, proportion male, weight, BSA, baseline utility score, receipt of G-CSF, and IPS risk factor), dose intensity, time on treatment, concomitant medications, adverse events, and subsequent therapies have been updated in these subgroup analyses. Importantly, there are 1,148 and 186 patients informing the analyses for the <60 years and ≥60 years subgroup analyses, respectively.

Figure 13 and Figure 14 present the PFS and OS Kaplan–Meier curves in the age <60 years subgroup, respectively, and Figure 15 and Figure 16 present the Kaplan–Meier curves for PFS and OS in the age ≥60 years subgroup, respectively. For the age ≥60 years subgroup specifically, the number of patients and associated number of PFS and OS events were much lower than the ITT population (84 patients in the A+AVD arm vs 102 patients in the ABVD (six cycles) arm; PFS, [redacted] vs [redacted] events; OS, [redacted] vs [redacted] events, respectively).

Figure 13: PFS in ECHELON-1 | age <60 years population | March 2023 DCO

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cut off; PFS, progression-free survival

Figure 14: OS in ECHELON-1 | age <60 years population | March 2023 DCO

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cut off; OS, overall survival

Figure 15: PFS in ECHELON-1 | age ≥60 years population | March 2023 DCO

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cut off; PFS, progression-free survival

Figure 16: OS in ECHELON-1 | age ≥60 years population | March 2023 DCO

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cut off; OS, overall survival

Figure 17 presents a comparison of the selected base case parametric curves including adjusted background mortality, with the observed Kaplan-Meier data for the age <60 years subgroup. All analyses were performed in accordance with the NICE Decision Support Unit (DSU) TSDs 14 and 21 and supported by the recommendations from Palmer et al. (2023), aligning with the approach described Section B.3.3.2 of the Company submission.

- Aligned with the ITT population, independent MCM log-logistic curves were selected to extrapolate PFS in the age <60 years subgroup.
    - Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS are presented in the Appendix. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold. This is further supported by the different shapes shown in the observed hazard plots. Additionally, the log-cumulative hazard plots are not

straight lines, indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold. Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued.

- Except for the Gompertz, all standard independent parametric curves provided a poor visual fit to the data.
- The independent MCMs and one-knot spline parametric curves were shown to provide a good visual fit and provided very similar long-term extrapolations.
- The independent MCM log-logistic curves provided the lowest AIC and BIC goodness-of-fit scores across all MCM distributions.

- Aligned with the ITT population, the independent one-knot hazard curves were selected to extrapolate OS in the age <60 years subgroup.
  - Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for OS are presented in the Appendix. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold. Additionally, the log-cumulative hazard plots are not straight lines, indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold. Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued.
  - Except for the Gompertz, all standard independent parametric curves provided a poor visual fit to the data.

- The independent MCMs and one-knot spline parametric curves were shown to provide a good visual fit and were very similar based on long-term extrapolations.

- OS extrapolations using the independent MCMs predicted estimated cure rates and outcomes that were clinically implausible in the probabilistic analyses, aligning with the findings from the ITT analyses described in Section B.3.3.2 in the Company submission. Therefore, the complex hazard and survival functions observed for OS were extrapolated using one-knot splines, which capture a change in the hazards for patients who are cured, without assumptions about the number of heterogenous subgroups directly. The independent one-knot spline curves provided similar AIC and BIC goodness-of-fit scores; the one-knot hazard was selected in line with the ITT population.

Figure 17: Age <60 years PFS and OS extrapolations

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan-Meier; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival

Figure 18 presents a comparison of the selected base case parametric curves including adjusted background mortality, with the observed Kaplan-Meier data for the age ≥60 years subgroup.

- Aligned with the ITT population, the independent MCM log-logistic curves were selected to extrapolate PFS in the age ≥60 years subgroup.

- Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS are presented in the Appendix. The Schoenfeld residuals and the Grambsch-Therneau test indicate that the proportional hazards assumption may hold. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold. Additionally, the log-cumulative hazard plots are not straight lines, indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold. Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued

- Except for the Gompertz, all standard independent parametric curves provided a poor visual fit to the data.

- The independent MCMs and one-knot spline parametric curves were shown to provide a good visual fit and provided very similar long-term extrapolations.

- Although the independent MCM log-logistic curves do not reflect the lowest AIC and BIC goodness-of-fit scores, this curve selection provides the best fit when assuming that the selection of parametric curve should be the same in both treatment arms, as indicated by UK clinical experts and summarised in the original Company submission. The independent MCM logistic is the second-best fitting to the A+AVD data, with the same AIC score and +2 in the BIC score compared to the best fitting curve. The independent MCM logistic is the third best fitting to the ABVD data, with +14 in the AIC score and +11 in the BIC score compared to the best fitting curve.

- Aligned with the ITT population, the independent one-knot hazard curves were selected to extrapolate OS in the age <60 years subgroup.

    - Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for OS are presented in the Appendix. The

Schoenfeld residuals and the Grambsch-Therneau test indicate that the proportional hazards assumption may hold. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold. Additionally, the log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold. Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued.

- Except for the Gompertz, all standard independent parametric curves provided a poor visual fit to the data.
- The independent MCMs and one-knot spline parametric curves were shown to provide a good visual fit and were very similar based on long-term extrapolations.
- OS extrapolations using the independent MCMs predicted estimated cure rates and outcomes that were clinically implausible in the probabilistic analyses, which aligns with the findings from the ITT analyses described in Section B.3.3.2 in the Company submission. Therefore, the complex hazard and survival functions observed for OS were extrapolated using one-knot splines, which capture a change in the hazards for patients who are cured, without assumptions about the number of heterogenous subgroups directly. The independent one-knot spline curves provided similar AIC and BIC goodness-of-fit scores; the one-knot hazard was selected in line with the ITT population.

Of note, the mean age in the ≥60 years subgroup is [redacted]. Therefore, the adjusted background mortality drives the long-term extrapolations much earlier than observed in the age <60 years subgroup and the ITT population (of which the majority are <60 years). In addition, there is crossing observed across the different OS parametric curve selections for A+AVD and ABVD, the extent of which is reduced by the differential SMRs applied to the adjusted background mortality (1.05 and 1.10 for

A+AVD and ABVD, respectively); however, is still present after adjusting for background mortality. This does not reflect expectations of A+AVD vs. ABVD in this subgroup in UK clinical practice. This likely reflects the uncertainty in the observed OS data for the ≥60 years subgroup. In Figure 16, the Kaplan-Meier curves are shown to cross at ~90-months. However, at this point, only n=[redacted] and n=[redacted] patients inform outcomes in the A+AVD and ABVD arms, respectively. Therefore, the observed data are highly uncertain and should be interpreted with caution.

Figure 18: Age ≥60 years PFS and OS extrapolations

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan-Meier; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival

The Appendix details the survival analyses for all independent parametric curves, all of which are available within the CEM. In addition, dependent parametric curves are available within the CEM. Other subgroup specific data (patient characteristics, dose intensity, time on treatment, concomitant medications, adverse events, and subsequent therapies) are presented in the Appendix.

In ECHELON-1, N=1,148 (86.1%) patients were aged <60 years and N=186 (13.9%) patients were aged ≥60 years. Therefore, the cost-effectiveness results estimated by the CEM for the subgroup aged <60 years and aged ≥60 years were weighted by 86.1% and 13.9%, respectively, to provide an estimate of cost-effectiveness for the whole population. This scenario increases the ICER from £[redacted] to £[redacted] (Table 11).

Table 11: Results from Clarification Question B1 (weighted average from <60 years and ≥60 years subgroups)*

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year
*The concomitant medication inputs have been updated following the identification of an error in reporting after the submission of the first set of clarification questions.

Whilst these subgroup analyses have been conducted, the Company base case has not been updated as the Company maintains that the ITT population analyses are most relevant for decision making based on:

- Clinical expert opinion elicited by the Company indicated that the subgroup analyses based on the March 2023 data-cut would not impact the way they would treat previously untreated Stage III or IV HL due to the third and fourth bullet points raised below, and a patient considered suitable for ABVD-based treatment will receive it if they are deemed sufficiently fit to do so, irrespective of age

- There are considerably fewer patients informing the subgroup analyses versus the ITT analyses (1,334 patients; A+AVD, 664; ABVD, 670), and lower numbers of PFS and OS events. For the age ≥60 years subgroup in particular, data are only available for 84 and 102 patients in the A+AVD and ABVD arms, respectively)

- The subgroup analyses based on age breaks randomisation in ECHELON-1, as the study was not stratified by age and was only a pre-specified subgroup analysis for mPFS

- Considering the patient population as two separate populations on the basis of age might have a negative impact on health equalities.

B2. Priority question. As outlined in clarification question A3, the EAG considers that the population and treatment in the RATHL study more closely matches UK clinical practice than ECHELON-1. As such, please conduct the following analysis which the EAG considers to be the most robust approach for this comparison;

i) Perform the fully adjusted MAIC as requested in question A3.

ii) Perform appropriate survival analysis using the adjusted A+AVD PFS and OS curves produced by the MAIC compared to the (unadjusted) PET-adapted ABVD curves from RATHL.

iii) Use the adjusted baseline characteristics for A+AVD as the baseline value in the model.

Response (i): Please see response to Question A3.

Response (ii and iii): In response to the EAG's question, independent parametric curves (including standard parametric models, MCMs, and one-knot splines) were fitted to the MAIC-weighted A+AVD (ECHELON-1) data and digitised, unadjusted Stage III/IV subgroup PET-adapted ABVD Kaplan–Meier data from the RATHL study for PFS and OS. As described in response to A3, in the absence of individual patient level data, these survival analyses are reliant on digitised published data for PET-adapted ABVD from RATHL. In addition, patient characteristics used to inform the CEM and the HRQoL analyses (age, proportion male, weight, body surface area, baseline utility score, receipt of G-CSF, and IPS risk factor) have been updated in this scenario to reflect the MAIC-weighted A+AVD population (Appendix).

Figure 19 and Figure 20 present the PFS and OS Kaplan–Meier curves for the MAIC-weighted A+AVD (ECHELON-1) data and Stage III/IV subgroup PET-adapted ABVD data (RATHL) analyses, respectively.

Figure 19: PFS | MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD data (RATHL)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cut off; PFS, progression-free survival

Figure 20: OS | MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD data (RATHL)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cut off; OS, overall survival

Figure 21 presents a comparison of the selected base case parametric curves including adjusted background mortality, with the observed Kaplan–Meier data for the MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL) analyses. All parametric curve analyses were performed in accordance with the NICE Decision Support Unit (DSU) TSDs 14 and 21 and supported by the recommendations from Palmer et al. (2023), aligning with the approach described Section B.3.3.2 of the Company submission.

- Aligned with the base case presented in the Company submission, independent MCM log-logistic curves were selected to extrapolate PFS in the MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD data (RATHL) analyses.
    - Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS are presented in the response to A4b. As the proportional hazards assumption was shown to be violated, independent models were pursued.

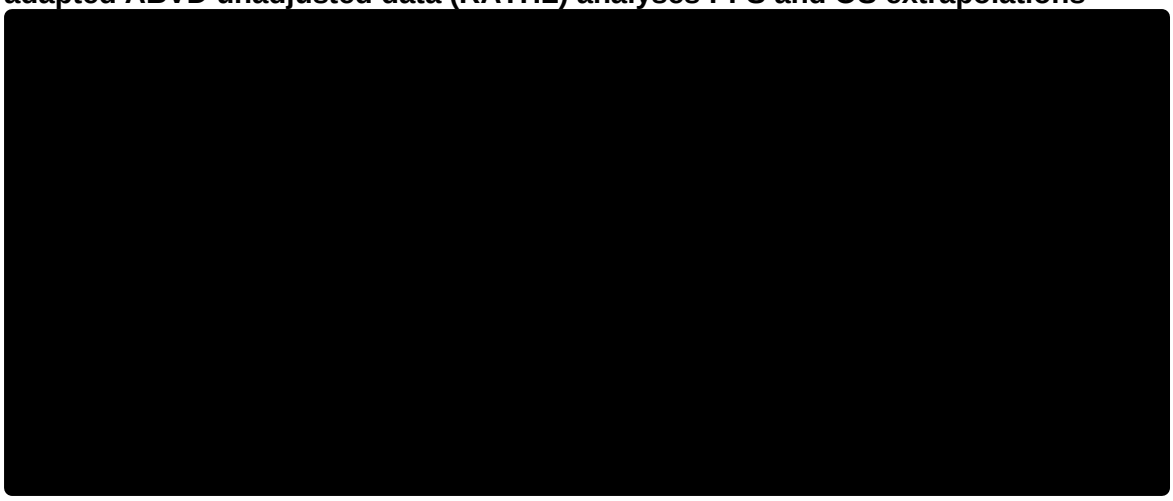
- Except for the Gompertz, all standard independent parametric curves provided a poor visual fit to the data. As the log-cumulative hazard plots indicated non-straight lines and because of the relevance of a cure in this setting, flexible parametric curves were considered more appropriate.
- The independent MCMs and one-knot spline parametric curves were shown to provide a good visual fit and provided very similar long-term extrapolations.
- The independent MCM log-logistic curves provided the lowest AIC and BIC goodness-of-fit scores for A+AVD and one of the lowest AIC and BIC goodness-of-fit scores for ABVD across all distributions.

- Aligned with the base case presented in the Company submission, the independent one-knot hazard curves were selected to extrapolate OS in the MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL) analyses.
  - Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for OS are presented in the response to A4b. As the proportional hazards assumption was shown to be violated, independent models were pursued.
  - Except for the Gompertz, all standard independent parametric curves provided a poor visual fit to the data. As the log-cumulative hazard plots indicated non-straight lines and because of the relevance of a cure in this setting, flexible parametric curves were considered more appropriate.
  - The independent MCMs and one-knot spline parametric curves were shown to provide a good visual fit and were very similar based on long-term extrapolations.
  - Per the base case, the complex hazard and survival functions observed for OS were extrapolated using one-knot splines, which

capture a change in the hazards for patients who are cured, without assumptions about the number of heterogenous subgroups directly. The independent one-knot spline curves provided similar AIC and BIC goodness-of-fit scores; the one-knot hazard was selected with the lowest AIC and BIC goodness-of-fit scores for A+AVD and a similar fit across all AIC and BIC scores for ABVD, in line with the ITT population.

As shown in Figure 21, the extrapolated A+AVD PFS curve crosses and remains above the extrapolated ABVD OS curve from approximately 15 years. Importantly, the weighted A+AVD Kaplan–Meier PFS data almost cross the PET-adapted ABVD Kaplan–Meier OS data. Therefore, the crossing of curves is driven by the observed data informing the extrapolations, and the independent modelling of treatments and endpoints.

Figure 21: MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL) analyses PFS and OS extrapolations



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan-Meier; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival

The Appendix details the survival analyses for all independent parametric curves, all of which are available within the CEM. Patient characteristics based on the weighted A+AVD data are presented in the Appendix. This scenario reduces the ICER from £[redacted] to £[redacted] (Table 12).

Table 12: Results from Clarification Question B2 (efficacy informed by MAIC-weighted A+AVD [ECHELON-1] and PET-adapted ABVD [RATHL])

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

While the Company appreciates the EAG's position that RATHL is the most appropriate source of data to inform the comparison of A+AVD vs PET-adapted ABVD, the Company maintains that use of ECHELON-1 to inform clinical outcomes for ABVD-based treatment is the most robust method, and that the MAIC comparing A+AVD to PET-adapted ABVD in RATHL should be used as evidence to support and reinforce the PFS and OS benefits observed with A+AVD. The rationale supporting this approach is provided in response to A3.

Model structure

B3. Please provide further justification for the use of a model structure in which all relapsed and refractory disease is characterised with a single progressed disease health state, particularly in light of the fact that all studies identified by the company in their SLR of published cost-effectiveness evaluations in this indication characterise progressed disease using multiple health states.

Response: As discussed in Section B.3.2.2. of the Company submission, the CEM comprised three mutually exclusive health states, including one "progressed disease/relapsed and/or refractory setting" health state.

The company would like to clarify that only six of the 11 published cost-effectiveness evaluations identified by the SLR characterised progressed disease into multiple health states based on transplant or response (detail was not presented in all studies). Notably, these six evaluations were informed by data with much shorter follow-up than used in the Company submission; all studies detailing the source used the primary data cut from ECHELON-1 (24.9 months vs the median follow-up of 89.2 months and 89.3 months used in the Company submission for PFS and OS, respectively). In addition, these six studies also utilised a Markov framework where

OS is estimated via surrogacy relationships between intermediate events (e.g., progression, transplant, subsequent therapies) and mortality, and relied on external data from several studies (further details of these studies can be found in the respective publications) to inform post-progression survival and associated assumptions.[3–6]

In the absence of mature OS data, this approach could be considered more appropriate and is commonly utilised in economic modelling in this situation.[7] However, the Company maintains that characterising relapsed and refractory disease into a single progressed disease health state is appropriate for decision-making based on the following:

- Feedback from UK clinical experts was that most PFS events are expected to occur within the first 24 months post-treatment and that the entire disease pathway and hence survival due to HL, including those with progressed disease, is expected to be captured within 7 years. Therefore, the ECHELON-1 follow-up is considered sufficient to capture all outcomes relating to the progressed disease health state.

- Given the maturity of the OS data presented in the Company submission (89.3 months median follow-up), it was possible to model OS directly.

- In ECHELON-1, [redacted]% (N=[redacted]) and [redacted]% (N=[redacted]) of patients experienced PFS events due to progressive disease in the A+AVD and ABVD arms, respectively, which translates into an incremental increase in events of [redacted]% for ABVD vs. A+AVD. Therefore, incorporation of additional post-progression health states and the associated modelling assumptions is unlikely to materially impact cost-effectiveness estimates for A+AVD and may introduce unnecessary uncertainty.

- The three selected health states align with the clinical pathway of care described in Section B.1.3 of the Company submission, clinical expert feedback on the clinical pathway of care, and the outcomes listed in the NICE final scope.[8]

Survival

B4. Priority question. Please provide additional evidence or justification for the use of the one-knot spline model over a MCM to extrapolate OS. The company states that the MCM provides clinically implausible probabilistic cure rates and outcomes due to the low number of events in the ECHELON-1 data resulting in large confidence intervals; however, the EAG notes that a low number of events would be present in each trial arm and therefore considers that both arms would be similarly affected.

Response: As described in Section B.3.2.2.1 and B.3.3.2.3 of the Company submission, independent MCMs and independent one-knot splines predicted highly congruent extrapolations when fitted to the OS data from ECHELON-1. Therefore, both one-knot splines and MCMs were considered plausible candidate models. This was also corroborated by UK clinicians at the January 2024 advisory board.

MCMs were initially considered appropriate to extrapolate OS to align with the goal of treatment in this setting, the high proportion of patients who are cured in this setting, and the base case approach to extrapolate PFS. Importantly, the clinical plausibility of predicted cure fractions was part of the curve selection process, and the deterministic predicted cure fractions for each of the MCMs are presented in Table 13. The exponential MCM and Gompertz MCM were the only distributions to predict clinically plausible cure fraction estimates which aligned with the literature and clinical expectations for both A+AVD and ABVD, whereby ~70–80% of patients with previously untreated Stage III or IV HL are currently cured by frontline treatment, and an expectation from UK clinical experts that the cure fraction for A+AVD is expected to be greater than for ABVD.[1, 9–11] This was corroborated by UK clinical experts at the January 2024 advisory board.

However, despite generating plausible deterministic cure fractions, the Gompertz MCM produced implausible probabilistic cure fractions due to the wide confidence intervals around the coefficients (Table 13). Whilst the exponential MCM confidence intervals are narrower than the Gompertz, modelling treatment arms independently yields clinically implausible relative cure fractions (i.e. A+AVD having a lower cure fraction than ABVD), which was considered a limitation of the MCM approach given this is not clinically plausible.

In addition, the Company disagrees with the statement in the question that “low number of events would be present in each trial arm and therefore considers that both arms would be similarly affected” based on the greater number of models which could not estimate a credible cure fraction for A+AVD vs. ABVD. This suggests both arms are not similarly affected and is likely due to fewer death events in the A+AVD arm (n=46; 6.9%) compared with the ABVD arm (n=69; 10.3%). More generally, the Company believe it is inappropriate to use a modelling approach that induces unnecessary uncertainty in the analysis, even if this is generally balanced across treatment arms.

Table 13: Predicted cure rates from independent MCMs

	A+AVD cure fraction (95% confidence intervals)	ABVD-based treatment cure fraction (95% confidence intervals)
MCM: Exponential	[redacted]	[redacted]
MCM: Weibull	[redacted]	[redacted]
MCM: Lognormal	[redacted]	[redacted]
MCM: Loglogistic	[redacted]	[redacted]
MCM: Gompertz	[redacted]	[redacted]
MCM: Generalised Gamma	[redacted]	[redacted]
MCM: Gamma	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; NE, not estimable; OS, overall survival

As discussed in Section B.3.3.2 of the Company submission, the one-knot splines provide a flexible approach to modelling complex hazards such as cure, without having to estimate the cure fraction. The one-knot splines provided a good visual fit to the OS data (Figure 22) and a better fit to the A+AVD arm than the exponential and Gompertz MCMs in the first 3 years. Additionally, the one-knot spline extrapolations aligned with expectations from UK clinicians, and critically, remained consistent with clinical expectations when modelled probabilistically. Therefore, the one-knot splines were considered more appropriate than the MCMs for OS.

Figure 22: Visual assessment of the fit of one-knot splines and MCMs to the observed OS data from ECHELON-1

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan-Meier; MCM, mixture cure model; OS, overall survival

B5. Priority question. The EAG's clinical experts have suggested that patients may not be considered cured until progression free for five years from the start of treatment, which the company has explored in a scenario analysis. Given that at the point of cure, PFS and OS rate of hazards will be equal as all patients who would have progressed have progressed, using the ECHELON-1 trial data please calculate conduct a scenario assuming a point of cure at the latest point in the trial when the rate of OS was equal to PFS.

Response: The Company would like to clarify that the CEM explores a cure timepoint between two and five years after treatment discontinuation, and not from the start of treatment as stated in the EAG's question.

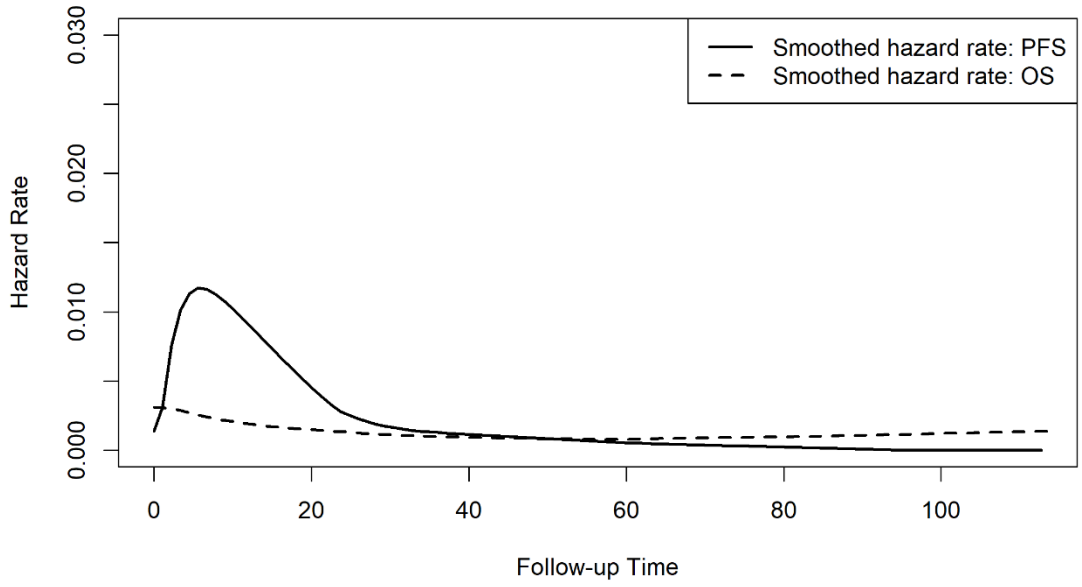
In addition, the Company disagrees with the statement in the question, that "…at the point of cure, PFS and OS rate of hazards will be equal as all patients who would have progressed have progressed". This is because the hazard of PFS is the competing risks of disease progression and death, whichever happens first, whereas the OS hazard is death at any time. Therefore, it is possible for the OS hazard to exceed the PFS hazard beyond the cure time point due to post-progression deaths, which is consistent with outcomes for this patient population. Therefore, the

Company does not believe the requested scenario is methodologically appropriate as a means of identifying the cure time point.

Following the EAG's question, smoothed hazard plots for PFS and OS have been created for the ITT population (Figure 23), the A+AVD arm (Figure 24), and the ABVD arm (Figure 25). These hazard plots indicate that the hazards for PFS and OS are similar from ~30 months (reflecting a two-year timepoint post-EOT) to 60 months, indicating that the cure timepoint is between two and five years after treatment discontinuation.

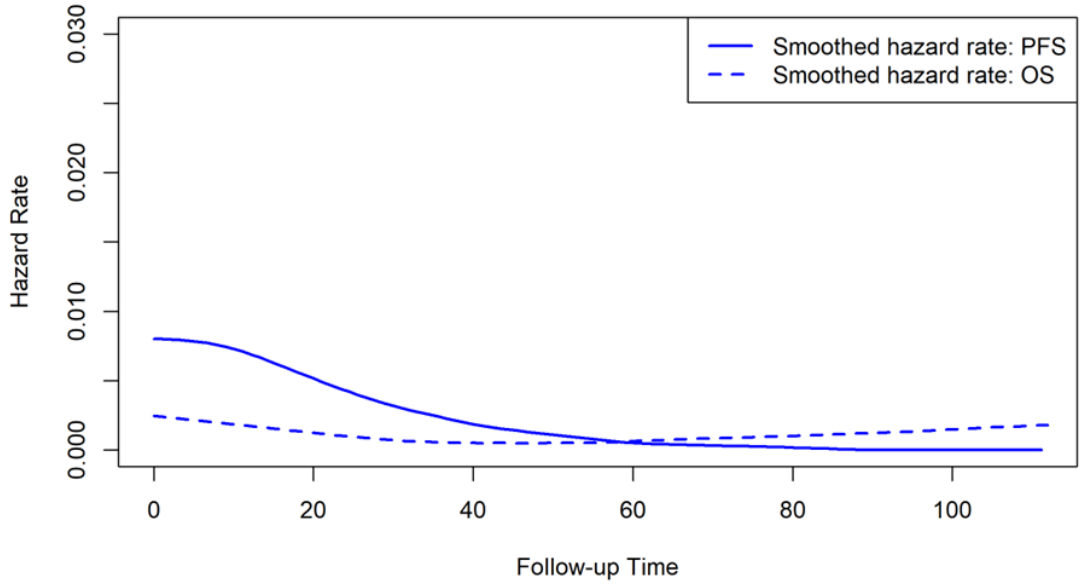
The corresponding scenario analyses using cure timepoints of 36 and 60 months are presented in Table 55 of the original Company submission; however, are presented in Table 14 and Table 15, respectively, for completeness. This has an immaterial impact on the ICER, which varies from the original base case of £[redacted] to £[redacted] and £[redacted], respectively.

Figure 23: Smoothed hazard plots – both treatments (ITT population)



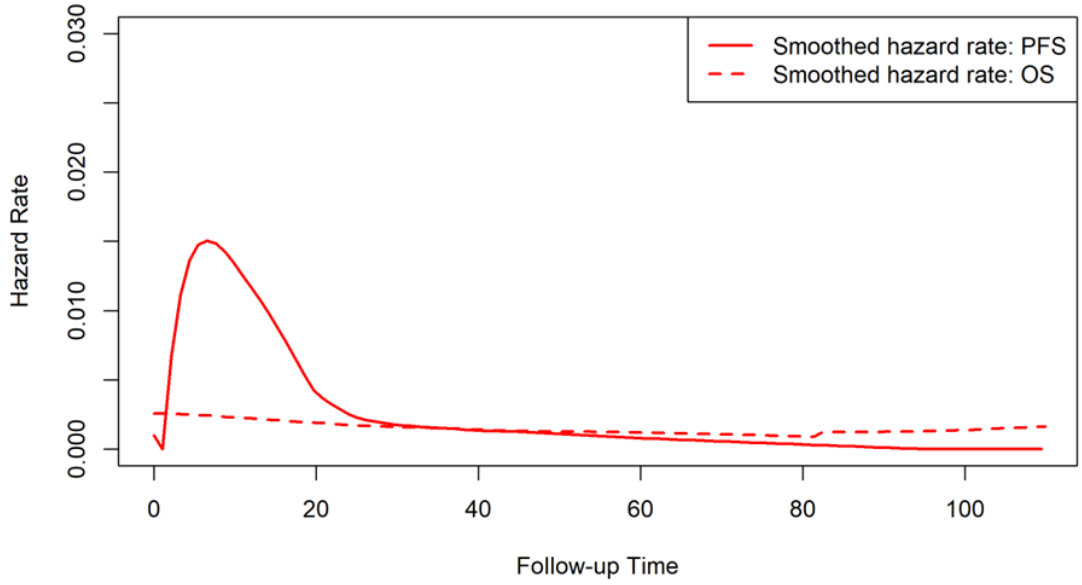
Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression-free survival

Figure 24: Smoothed hazard plots - A+AVD (ITT population)



Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression-free survival

Figure 25: Smoothed hazard plots - ABVD (ITT population)



Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression-free survival

Table 14: Results from Clarification Question B5 (cure timepoint of 36 months after frontline treatment)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

Table 15: Results from Clarification Question B5 (cure timepoint of 60 months after frontline treatment)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

B6. Priority question. The company has applied SMRs to background mortality in the model, to account for long-term excess mortality risk arising from secondary malignancies and other complications. A lower SMR has been applied for patients receiving A+AVD compared to patients receiving ABVD, although there is no evidence to support this. Furthermore, the values for the SMRs used are based on assumption and the proportion of secondary malignancies were found to be similar between treatment arms. As such, please could the company present scenarios in which the SMR applied to background mortality is equal in both treatment arms, and explore a range of alternative SMR values sourced from a review of the literature.

Response: The SMRs used in the Company submission were based on the observed ECHELON-1 data, supplemented with feedback from UK clinical experts experienced with treating patients with ABVD-based treatment in routine clinical practice. Given the timepoints at which the SMRs take effect (see response to B21), the extent of follow-up in ECHELON-1 (median follow-up of 89.2 months for PFS and 89.3 months for OS), and that the entire HL disease pathway is expected to be captured within 7 years, the Company believes it is appropriate to expect that only cured patients remain in the model at the time point the SMRs take effect. Therefore,

when making comparisons with the literature, these values should be compared with estimates in a *relapse-free* or *cured* population.

In response to the EAG's question, the Company has conducted a rapid targeted literature review to identify all relevant sources of SMR data in an appropriate patient population. The literature review was conducted using PubMed on 13 May 2024 using the search string *"Hodgkin" AND "lymphoma" AND ("excess mortality" OR "standardized mortality rate" OR "standardised mortality rate" OR "SMR")*. Treatment practice and outcomes have evolved over time, with several practice-defining trials published in the last decade.[12–16] Therefore, the year of publication was restricted to 2014–present i.e., the past 10 years, resulting in 101 hits for screening. Preliminary screening of these results was conducted by title to exclude citations relating to non-Hodgkin lymphoma, or nodular lymphocyte predominant-type Hodgkin lymphoma.

After title screening, 21 publications were subsequently assessed via abstract and/or full-text screening by a single reviewer, with the included and excluded studies confirmed by a second reviewer, to find results that included patients with classical/CD30+ HL, diagnosed and treated after the year 2000, and which presented all-cause mortality vs the general population. Publications in irrelevant interventions or the wrong line of therapy (e.g. those in which the whole patient population had received more than one line of therapy) were excluded. Seventeen publications were excluded based on: incorrect populations (four publications),[17–20] results only in patients treated with stem cell transplantation (two publications),[21, 22] incorrect outcomes (e.g. cardiovascular-disease-only SMRs; nine publications),[23–31] or patients diagnosed prior to the year 2000 (two publications).[32, 33]

In total, four publications were assessed further to explore their potential to provide SMRs relevant to the target population. These publications are summarised further below. Notably, no publication reported outcomes for patients who were: (1) relapse-free or cured, (2) diagnosed after 2000, and (3) for Stage III/IV only to align with the population for whom SMRs are applied within the CEM.

- **Glimelius *et al*. Long-term survival in young and middle-aged Hodgkin lymphoma patients in Sweden 1992-2009-trends in cure proportions by clinical characteristics. *Am J Hematol*. 2015;90(2):1128–34.**[34] **|** Glimelius

et al. (2015) estimated relative survival in a Swedish population-based cohort of 1,947 patients with HL diagnosed in 1992–2009 at ages 18–59 years. This paper presents the relative survival for those diagnosed between 2001–2009, for patients who do not relapse, and by stage of disease. However, relative survival is not presented by stage for the subgroup diagnosed between 2001–2009. Similarly, relative survival is not presented for those who do not relapse for the subgroup diagnosed between 2001–2009. Despite the limitations, the findings in the paper support the assumption of similar long-term mortality for patients who do not relapse vs the general population; the relative risk at 5 years for these patients is 0.99 and at 15 years is 0.95 i.e., patients with HL had 0.95 times the risk of survival compared to the general population. This equates to a 5% reduction in survival which supports an SMR applied to mortality rates of ~1.05 i.e., a 5% increase in the mortality rate compared to the general population.

- **Núñez-García *et al*. Long-term outcomes in Hodgkin lymphoma survivors. Temporary trends and comparison with general population. *Hematol Oncol*. 2023;41(3):407–414.**[35] **|** Núñez-García et al. (2023) was a single-institution retrospective study in a Spanish cohort. Survival outcomes in this cohort were considered implausible for the UK HL population, as the PFS Kaplan–Meier differed substantially from that observed in key HL studies, such as the RATHL study, with a high rate of disease progression in the first few years after treatment.[13–15] Likewise, this trend was unlike the PFS observed in ECHELON-1.[36] The Kaplan–Meier OS curve was likewise considered implausible as no plateau was evident as would be expected from other studies of HL, and considering the curative nature of HL treatment.[13, 37] Moreover, the SMRs presented increased over time (3.02 for patients diagnosed before 2000, vs 7.50 for patients diagnosed after 2000) which is inconsistent with both the literature and clinical expert opinion that mortality in HL vs the general population has improved over time.[1, 33] Therefore, this study was not considered appropriate to inform scenario analyses.

- **Dores *et al*. Cause-Specific Mortality Following Initial Chemotherapy in a Population-Based Cohort of Patients With Classical Hodgkin**

Lymphoma, 2000-2016. *J Clin Oncol*. 2020;38(35):4149–4162.[38] **|** Dores *et al*. (2020) was a study in US patients with HL, and may have limited relevance to the UK population and treatment pathway. The study did not provide an SMR for relapse-free or cured patients and was therefore not able to inform the SMRs for patients in whom treatment is successful. Although the authors provided an SMR (of 2.0) for all causes of death other than lymphoma in patients diagnosed 2001–2009, it was unclear to what extent this reflected relapse-free patients vs those on treatment, who would be expected to have a higher risk of adverse events (such as pulmonary toxicity). Moreover, reduced side effects in recent years have occurred from changing treatment practices due to studies such as the RATHL study, minimising exposure to toxic chemotherapy drugs where possible; as diagnoses up to 2009 will not reflect these changes to practice, this SMR will likewise not reflect current mortality in relapse-free patients.

- **Perez-Callejo *et al*. Long-term follow up of Hodgkin lymphoma. *Oncotarget*. 2018;9(14):11638–11645.**[39] **|** Perez-Callejo *et al*. (2018) did not examine outcomes in the subgroup of patients who are cured or relapse free and therefore does not provide a relevant SMR. Further limiting the relevance of this study were the small number of patients diagnosed after the year 2000 (n=96) and Stage I or II HL for the majority (64%) of the cohort. No subgroup analysis was provided by disease stage. Therefore, this study was not considered appropriate to inform scenario analyses.

In summary, Glimelius *et al*. (2015) supports the Company's base case, while the other three publications did not provide relevant data to inform the SMR. As a conservative assumption, a scenario analysis has been conducted where equal SMRs of 1.05 are assumed for A+AVD and ABVD (Table 16). This has further been explored with equal SMRs of 1.10 and 1.15 in Table 17 and Table 18, respectively. These SMRs align with those explored in published frontline lymphoma NICE appraisals (1.0 – 1.19 [note that the 1.19 assumed in TA641 equates to a 5% increase in mortality, and hence a 1.05 SMR]) and later line lymphoma NICE submissions (1.0 – 1.10) (Section B.3.2.2 of the Company submission). However, importantly, the Company believes that the SMR for frontline HL should at a

minimum be equal to, or less than the SMR for later line lymphomas to align with feedback received from UK clinical experts.

Table 16: Results assuming the same SMR (1.05) in both A+AVD and ABVD treatment arms

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

Table 17: Results assuming the same SMR (1.10) in both A+AVD and ABVD treatment arms

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

Table 18: Results assuming the same SMR (1.15) in both A+AVD and ABVD treatment arms

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

Whilst these scenarios are presented to explore the impact of equal SMRs, the base case reflects an SMR of 1.05 for A+AVD and 1.10 for ABVD. As stated earlier in this response, the SMRs used in the base case are based on the observed ECHELON-1 data, supplemented with feedback from UK clinical experts experienced with treating patients with ABVD-based treatment in routine clinical practice. This aligns with the four studies identified by the cost-effectiveness SLR (Section B.3.1 of the Company

submission) that included excess mortality in addition to background mortality (Delea *et al* [2019], pCODR Expert Review Committee [2020], Vijenthira *et al* [2018], and Vijenthira *et al* [2020]); all four used differential rates for A+AVD and ABVD, acknowledging differing mortality due to treatment-related toxicities and second malignancies.[3, 40–42]

HRQoL

B7. Please can the company justify their approach for including a covariate for PD off-treatment and not PD on-treatment given the duration of subsequent treatments and the impact to HRQoL. As a scenario please include a PD on-treatment covariate in the utility regression. If insufficient data was directly captured from the trial to inform a robust covariate, please use alternative sources/methods to inform the PD on-treatment utility.

Response: Progression status (progression-free [PF] versus progressive disease [PD]) and treatment status (on treatment versus off treatment) were explored as independent explanatory variables in the mixed-effects repeated-measures linear regression models. A patient's progression status was determined by the occurrence of PD at the time of the EQ-5D-3L assessment, and importantly, treatment status was defined as 'on' versus 'off' frontline treatment and not subsequent treatment. For clarity, utility for PD was not estimated separately for patients who were on or off treatment. Therefore, in summary, utility values were predicted using the linear mixed-effects regression model for three CEM health states: 1) PF, on treatment, 2) PF, off treatment, and 3) PD. The Company acknowledges that the footnote of Table 35 of the original submission is misleading in this regard.

Consequently, and given the small proportion of patients experiencing PD and the similarity of subsequent therapy use in each treatment, the Company do not believe it is necessary to estimate PD utility by subsequent treatment status. Moreover, due to expected challenges in running regression analysis due to data availability (missing values and inconsistency across reporting) post-progression, the requested scenario analysis has not been conducted.

In relation, the uncertainty associated with the saturated utility regression was explored in the one-way sensitivity analysis presented in Section B.3.11.2 of the

Company submission, which demonstrated that varying all parameters between their lower and upper bounds varies the ICER between £[redacted] and £[redacted]. Therefore, the uncertainty in the saturated utility regression used in the base case approach has an immaterial impact on the results.

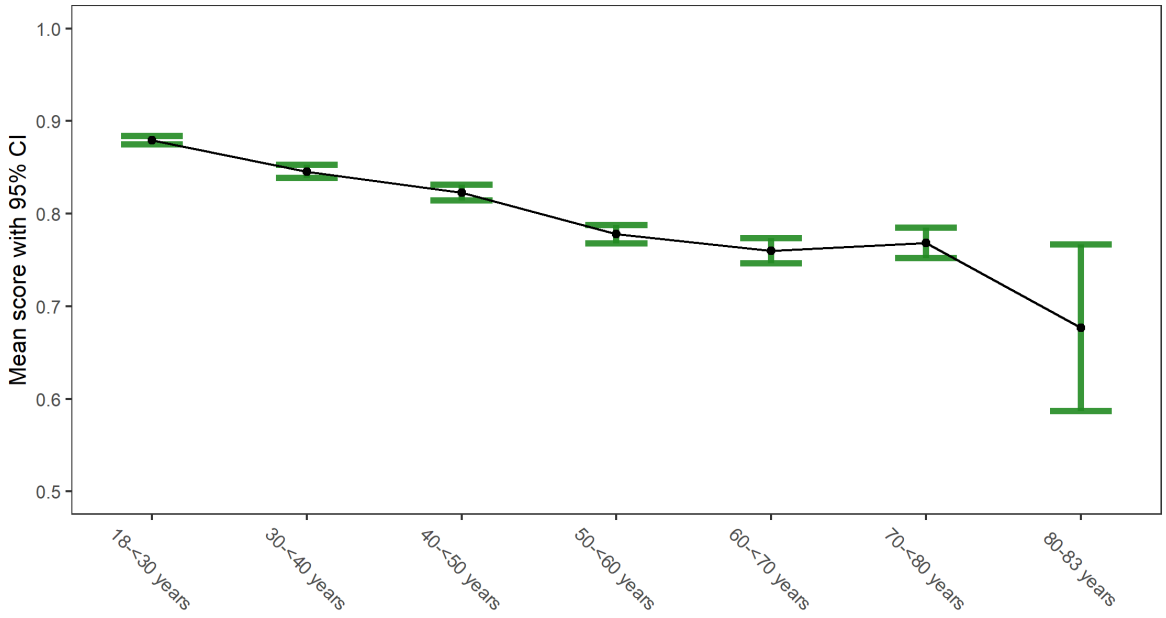
B8. Please can the company provide justification for including age as a linear variable in the regression models used to derive the health state utility values used in the model, given that HRQoL is not expected to change linearly with age.

Response: Age was included in the regression model as a linear variable as a simplification, as this was supported by the plot of mean utility scores by age categories (Figure 26), which indicates a decrease in HRQoL is associated with an increase in baseline age and appears to follow a broadly linear trend (noting that the two highest age categories included the least number of patients, with n=60 and n=4 patients, respectively).

Inclusion of age as a linear variable in the utility regression also allows the CEM to reflect the impact of aging as the utility decrement for age is multiplied by the associated mean age in each model cycle. In contrast, modelling age as a categorical variable would lose this granularity.

Additionally, inclusion of age as a linear variable is consistent with TA641 (sALCL; one of the two published frontline lymphoma NICE TAs). It should be noted that TA874 (DLBCL; the second of the two published frontline lymphoma NICE TAs) did not fit a regression model to the utility data presented in the submission.

Figure 26: Mean EQ-5D scores (and 95% confidence interval) by age category



Abbreviations: CI, confidence interval; EQ-5D, EuroQol 5-dimensions

B9. Please can the company provide goodness of fit statistics and residual plots for both the 'saturated' and 'reduced' regression models used to derive health state utility values.

Response: Goodness-of-fit statistics and residual plots are presented in Table 19, and Figure 27, respectively. The comparative goodness-of-fit statistics indicate that the 'reduced' model is associated with lower AIC and BIC values; however, the differences between the models are marginal.

Table 19: Comparative utility regression goodness-of-fit statistics

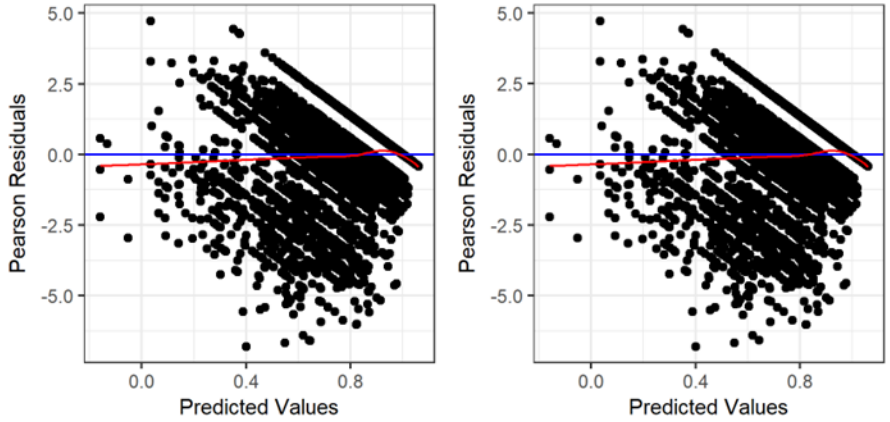
Model	AIC	BIC	logLik	deviance	Chi-sq	Df	Pr(>Chi-sq)
Reduced	-13576	-13514	6796.1	-13592	-	-	-
Saturated	-13570	-13439	6802.3	-13604	12.317	9	0.196

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; Chi-sq, Chi-squared; Df, degrees of freedom

The residuals in both models appear approximately normally distributed. However, the plots indicate that the residual variance decreases as the fitted values increase, which may suggest that the assumption of constant error variance may not hold. This means that the variability in EQ-5D-3L scores changes as the predicted values

increase, and some observations may have more influence than others on the fitted model.

Figure 27: Residual plots (L: Saturated model; R: Reduced model)



Despite the points noted above, the approach adopted for the analysis of EQ-5D is consistent with previously published analyses of HRQoL, and importantly, whether the 'saturated' or 'reduced' model is used has an immaterial impact on the ICER.

Adverse events

B10. Priority question. Peripheral neuropathy (PN) as defined by the Standardized MedDRA Query (SMQ) is considered an adverse event of special interest for patients who are treated with brentuximab. In the ECHELON-1 trial CSR (Table 12. aa) [redacted] of patients reported grade ≥3 peripheral neuropathy or above; however, the adverse event was not included in the economic model. As such,

a) **Please justify why PN was not included in the model given its status as an adverse event of special interest and high rate of incidence in the trial.**

b) **Please conduct a scenario analysis including all grade ≥3 forms of peripheral neuropathy captured in the safety study, using the mean (SD) of time to resolution for patients with resolved events and the**

proportion of patients with unresolved PN events as requested for in question A6.

Response (a): The Company would like to clarify that the CEM includes Grade ≥3 drug-related treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients from ECHELON-1, which corresponds to Table 12.k in the CSR. In addition, as per the Company response to Question A8, peripheral neuropathy was a standardised MedDRA query, grouping multiple peripheral neuropathy preferred terms, and is not shown in Table 12.k or captured in the CEM because no single preferred term relating to neuropathy was reported in ≥5% of patients at the March 2023 data cut-off.

In the standardised MedDRA query, peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, muscular weakness, hypoesthaesia, neuralgia, polyneuropathy, and autonomic neuropathy. The number of patients experiencing a Grade ≥3 TEAE for each of these components of peripheral neuropathy is presented in Table 7 in response to Question A7.

Response (b): In responding to the EAG's questions and to ensure consistency throughout the CEM, the CEM has been updated to inform drug-related TEAEs occurring in ≥5% of patients and concomitant medications from the March 2023 data cut-off from ECHELON-1. The original Company submission leveraged data from the primary data cut, which corresponded to the CSR. Table 20 compares the drug-related TEAEs occurring in ≥5% of patients from the primary data cut with the final data cut from ECHELON-1. Table 21 compares the concomitant medications from the primary data cut with the final data cut from ECHELON-1.

Table 20: Grade ≥3 drug-related TEAEs | ≥5% of patients | ECHELON-1 primary vs final data cut

	ECHELON-1 (April 2017 DCO)		ECHELON-1 (March 2023 DCO)	
	A+AVD	ABVD	A+AVD	ABVD
N	662	659	662	659
Anaemia, n (%)	46 (6.95%)	18 (2.73%)	[redacted]	[redacted]
Febrile neutropenia, n (%)	120 (18.13%)	46 (6.98%)	[redacted]	[redacted]

	ECHELON-1 (April 2017 DCO)		ECHELON-1 (March 2023 DCO)	
	A+AVD	ABVD	A+AVD	ABVD
Neutropenia, n (%)	344 (51.96%)	242 (36.72%)	[redacted]	[redacted]
Neutrophil count decreased, n (%)	81 (12.24%)	64 (9.71%)	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DCO, data cutoff; N, number; TEAE, treatment-emergent adverse events.

Table 21: Concomitant medication use | ECHELON-1 primary vs final data cut*

	ECHELON-1 (April 2017 DCO)		ECHELON-1 (March 2023 DCO)	
Treatment	**A+AVD**	**ABVD**	**A+AVD**	**ABVD**
Anti-infectives				
Acyclovir	148 (22.36%)	101 (15.33%)	[redacted]	[redacted]
Levofloxacin	131 (19.79%)	106 (16.08%)	[redacted]	[redacted]
Pain management				
Oxycodone	95 (14.35%)	64 (9.71%)	[redacted]	[redacted]
Tramadol	95 (14.35%)	61 (9.26%)	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine
*The concomitant medication inputs have been updated following the identification of an error in reporting after the submission of the first set of clarification questions.

Table 22 presents the impact of this update which has an immaterial impact on results (the ICER increases from £[redacted] to £[redacted]). The drug-related TEAEs occurring in ≥5% of patients and concomitant medications from the March 2023 data cut-off are included in the updated base case.

Table 22: Results from aligning the CEM with the drug-related TEAEs occurring in ≥5% of patients and concomitant medications from the March 2023 data cut-off*

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year
*The concomitant medication inputs have been updating following the identification of an error after the submission of the first set of clarification questions.

Following the EAG's request, peripheral neuropathy has now been included as an option within the CEM based on the Grade ≥3 under the SMQ of Peripheral Neuropathy. As per Question A7, 68 patients ([redacted]%) in the A+AVD arm and 11 patients ([redacted]%) in the ABVD arm reported one or more Grade ≥3 peripheral neuropathy events. In line with the approach taken in the Company submission, the RATHL study informed Grade ≥3 peripheral neuropathy for patients treated with ABVD (cycles 1–2; 1.66%), AVD (cycles 3–6; 3.06%), and escBEACOPP (cycles 3−6; 3.85%) via the PET-adapted approach.[12] These inputs were weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3–6), and 16.3% escBEACOPP (cycles 3–6) as per the approach and reporting in the Company submission. Johnson et al. (2016) reported Grade ≥3 data for any neurologic event, which was assumed to correspond to the grouped peripheral neuropathy term.

Peripheral neuropathy is assumed to incur zero cost, which aligns with the assumptions agreed by the Committee in TA641, where page 3 of the FAD states that *"excluding costs for grades 3 and 4 peripheral neuropathy is appropriate"*.[43] Based on clinical expert opinion in TA641, no costs were included for Grade 3–4 peripheral neuropathy on the basis that management of this TEAE is to modify the dose or schedule of brentuximab vedotin or discontinue treatment in line with the SmPC. To support the response to this question, the Company elicited feedback from a UK clinical expert who confirmed that peripheral neuropathy in previously untreated HL would be managed in the same way via dose modifications or discontinuation. Dose modifications observed in ECHELON-1 are already reflected in the base case CEM through the application of relative dose intensity and mean treatment duration for A+AVD and ABVD.

In addition, in line with TA641, the HRQoL impact related to peripheral neuropathy is assumed to be reflected by the utility regression fit to the EQ-5D-3L data collected in ECHELON-1. Mean time to resolution of resolved peripheral neuropathy events is [redacted] and [redacted] weeks for A+AVD and ABVD (Table 7), respectively, and given EQ-5D-3L data were collected in ECHELON-1 during post-treatment follow-up every 3 months until 3 years after the last dose of frontline therapy or development of confirmed progressive disease, the impact of peripheral neuropathy events is expected to be captured by the AE coefficient included in the utility regression

model. Therefore, when including peripheral neuropathy in the scenario, the utility decrement estimated in the utility regression model for AEs (-0.03) is applied to the proportion of patients experiencing peripheral neuropathy. The duration of peripheral neuropathy is calculated based on the average of the mean time to resolution of resolved peripheral neuropathy events from ECHELON-1 ([redacted] and [redacted] weeks for A+AVD and ABVD, respectively; see Company response to Question A8), which equates to [redacted] days. Aligning with the approach described in Section B.3.4.4 of the Company submission, the utility decrement was multiplied by the proportion of patients experiencing peripheral neuropathy and the mean duration of peripheral neuropathy, equating to a QALY loss specific to peripheral neuropathy of −0.0018 and −0.0003 for A+AVD and ABVD, respectively, applied in the first treatment cycle.

Updating the drug-related TEAEs occurring in ≥5% of patients from the March 2023 data cut-off for ECHELON-1 (Table 8) and including peripheral neuropathy events increases the ICER from £[redacted] to £[redacted] (Table 23). Inclusion of peripheral neuropathy, in addition to updating TEAEs and concomitant medications based on the March 2023 data cut, are included in the updated base case. Of note, the ICER estimate may be conservative given the Company has not included the cost and HRQoL impact of pulmonary toxicity which is an AESI for ABVD.

Table 23: Results from Clarification Question B10b (drug-related TEAEs occurring in ≥5% of patients and concomitant medications from the March 2023 data cut-off and inclusion of peripheral neuropathy events)*

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.
*The concomitant medication inputs have been updating following the identification of an error after the submission of the first set of clarification questions.

In line with the scenario presented in the Company submission exploring the use of the literature to inform AE-related HRQoL decrements, as well as the EAG's Question B11, a scenario is presented which informs utility decrements for TEAEs based on the literature. This uses the inputs from the original submission for anaemia, neutropenia, febrile neutropenia, and neutrophil count decreased and a

decrement of −0.33 for peripheral neuropathy. This utility decrement is sourced from Swinburn et al. (2015), a utility study which reports utility values for relapsed/refractory HL based on vignettes evaluated by members of the general public using the time trade-off method, which informed scenarios analyses in TA641 and TA478.[44] Updating the drug-related TEAEs occurring in ≥5% of patients from the March 2023 data cut-off for ECHELON-1, including peripheral neuropathy events, and sourcing the utility decrements for AEs from the literature increases the ICER from £[redacted] to £[redacted] (Table 24).

Table 24: Results from Clarification Question B10b (drug-related TEAEs occurring in ≥5% of patients from the March 2023 data cut-off, inclusion of peripheral neuropathy events, and utility decrements informed by the literature)*

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.
*The concomitant medication inputs have been updating following the identification of an error after the submission of the first set of clarification questions.

B11. Please can the company discuss the face validity of the adverse event disutility calculated using the HRQoL regression model given the calculated disutility using the literature based approach.

Response: Table 25 compares the utility decrement associated with Grade ≥3 adverse events that was estimated from the saturated regression model presented in the Company submission with those reported in the literature (TA641 and TA874).[43, 45] A scenario analysis was presented in the Company submission which used utility decrements from the two previously published frontline lymphoma appraisals, which demonstrated a negligible impact on results (increased the ICER by only [redacted]%) (Table 55 of the Company submission).

In addition, both TA641 and TA874 referenced older NICE appraisals as the sources of these utility data (TA478 and TA306), which provided the original sources: Swinburn et al. (2010) or Nafees et al. (2008) for anaemia, Lloyd et al. (2006) or

Nafees et al. (2008) for febrile neutropenia, Nafees et al. (2008) for neutropenia, and assumptions based on equivalence with neutropenia or no utility impact for neutrophil count decreased.[46–48] Although these studies have been used to inform utility in other frontline, and later line, lymphoma NICE appraisals, they do not provide utilities specifically for patients with Hodgkin's lymphoma.[49–51] Specifically, Swinburn et al. (2010) estimated utility values for patients with metastatic renal cell carcinoma, Lloyd et al. (2006) estimated utility values for patients with metastatic breast cancer, and Nafees et al. (2008) estimated utility values for patients with non-small-cell lung cancer. Additionally, these studies are all societal valuation studies eliciting utilities from the general population, which does not align with the preference stated in the NICE manual for patient-reported utilities.[52]

The Company acknowledges that the utility decrements derived from the saturated utility regression model are lower than those reported in TA641 and TA874. However, the Company base case estimates are based on EQ-5D-3L data reported by patients in a pivotal, Phase III trial, ECHELON-1, for the population and interventions of interest, thereby aligning with the NICE manual and DSU guidance (TSD 6) and the source of efficacy inputs in the CEM.[53] Therefore, the Company maintains that the utility decrements estimated from ECHELON-1 are valid despite being lower than the literature values, and are therefore appropriate for the base case.

To support the response to this question, the Company sought feedback from a UK clinical expert who indicated that febrile neutropenia is likely to have the greatest impact on HRQoL. To explore this, a scenario was conducted which derives disutility for febrile neutropenia based on the ratio of neutropenia to febrile neutropenia observed in TA874; this equates to a utility decrement of −0.04 for febrile neutropenia (−0.03 from the utility regression x (−0.15/−0.09 from TA874) = −0.04). This scenario increases the ICER from £[redacted] to £[redacted] (Table 26).

Table 25: Utility decrements for adverse events in the CEM

Event	ECHELON-1 – Saturated utility regression (base case)	NICE TA641	NICE TA874
Anaemia	-0.03	-0.09	-0.25
Febrile neutropenia	-0.03	-0.09	-0.15
Neutropenia	-0.03	NA	-0.09
Neutrophil count decreased	-0.03	0.00	-0.09

Abbreviations: CEM, cost-effectiveness model; NA, not available

Table 26: Results from Clarification Question B11 (scenario exploring AE decrement for febrile neutropenia based on the ratio of neutropenia to febrile neutropenia observed in TA874)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

Costs and health care resource use

B12. Priority question. Please provide details of how the proportions of patients expected to receive each subsequent treatment reported in Table 47 of the Company Submission were elicited or derived.

Response: As described in Section B.3.5.4.1 of the Company submission, the distribution of subsequent therapies observed in ECHELON-1 was applied in the Company base case and a scenario analysis was conducted to explore using distributions informed by UK clinical experts.

The pathway of care and proportion of patients expected to receive each subsequent treatment based on clinical opinion was elicited via feedback received at two advisory board engagements conducted by the Company (discussed in Section B.1.3.4. of the Company submission) and additional one-to-one interviews.

Importantly, the treatment pathway diagram presented in Figure 129 in the Appendix was developed during the medical advisory board in November 2023, and the

eight clinical experts in attendance aligned on the structure of the pathway and the proportions expected to receive each subsequent treatment in UK clinical practice. Additional validation of this diagram was elicited at the market access advisory board in January 2024, where all clinical experts in attendance agreed with the pathway and proportions presented. Of note, that the proportion of patients who relapse following ASCT (50%) vs the proportion cured (50%) was informed by the literature, as supported by clinical expert opinion.[54, 55] The proportion receiving an allogenic SCT at any stage during the pathway was assumed to be 10% to align with the low number of patients expected to receive allogeneic SCT in relapsed/refractory HL.[56]

Clinical experts at the market access advisory board in January 2024 were asked how they would expect the pathway to differ for post-ABVD vs post-A+AVD, and feedback informed the development of Figure 54 in the Appendix. Key differences raised were regarding the use of brentuximab vedotin at later lines, with clinical advisors stating that they would expect to use less brentuximab vedotin following frontline A+AVD compared to after frontline ABVD. For example, it was stated that ~40% of patients would receive brentuximab vedotin-based therapy in the transplant eligible (bridge to transplant) setting following ABVD, whereas this was expected to be approximately 0–10% after A+AVD. The pathway was adjusted to reflect the reduced use of subsequent brentuximab vedotin post-A+AVD based on clinical opinion at the advisory board and additional follow up interactions.

The proportions of patients receiving each treatment throughout the pathway were combined to derive the estimated proportions of patients receiving each subsequent treatment which are presented in Table 47 of the Company Submission.

Of note, in responding to this question, the Company identified an error in the proportion of patients who receive subsequent brentuximab vedotin following A+AVD and would like to apologise for this. In Table 47 of the Company submission, 23.53% of patients were assumed to receive brentuximab vedotin after A+AVD. An error was identified in how this proportion was derived; the correct proportion of patients who progress on A+AVD and are expected to receive subsequent brentuximab vedotin is 13.1%, derived by combining the proportion of patients receiving brentuximab vedotin throughout the pathway presented in Figure 129. The Company has rectified this error, and an updated scenario analysis is presented in Table 27. This does not

affect the original or updated Company base case as subsequent therapy distributions are informed by ECHELON-1.

Table 27: Results from clarification question B12 (updated subsequent brentuximab vedotin use following A+AVD)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

B13. Priority question. Can the company provide an explanation to why the company's clinical experts considered 0% of patients would receive radiation given its use by patients in the ECHELON-1 trial.

Response: In responding to this question, the Company has identified an error in the reporting of the number and proportion of patients receiving radiation in ECHELON-1 and would like to apologise for this. In ECHELON-1, [redacted]% of patients in the A+AVD arm and [redacted]% of patients in the ABVD arm ([redacted] and [redacted] patients in the A+AVD and ABVD arms, respectively) received radiation as a subsequent anti-cancer therapy based on the March 2023 data-cut. This equates to 41.91% and 38.36% of patients who go on to receive subsequent anti-cancer therapy in the A+AVD and ABVD arms, respectively.

Once this is corrected, the ICER decreases from £[redacted] to £[redacted] (Table 28). Correcting the radiotherapy use from ECHELON-1 is included in the updated base case. The Company has also run an additional scenario where the proportion of patients receiving radiation is 0%, and all other subsequent therapies are informed by ECHELON-1. This has an immaterial impact on the ICER, increasing from £[redacted] to £[redacted] (Table 29).

Table 28: Results from Clarification Question B13 (updated radiotherapy use as observed in ECHELON-1)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/ QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

Table 29: Results from Clarification Question B13 (proportion of patients receiving radiation 0% and all other subsequent therapies informed by ECHELON-1)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

The Company acknowledges the EAG's point that the proportions of patients who receive radiation in ECHELON-1 differ to the feedback elicited from UK clinical experts. In summary, clinical expert view elicited by the Company during advisory board engagements was that radiation is rarely used in the relapsed/refractory HL setting in the UK. To support the response to this question, the Company reached out to a further UK clinical expert who confirmed that radiation is used "*highly infrequently*". They indicated that they may use radiation as a supportive bridge to ASCT if their multi-agent chemotherapy response is verging on satisfactory; however, this is rare and may only be relevant for 5–10% of patients. In addition, they also indicated that the UK is a lower user of radiation compared to other markets, which may explain the differential between the two sources given ECHELON-1 is a global trial.

Subsequent treatment costs

B14. Priority: The company submission (CS) states that the duration of pembrolizumab treatment as a subsequent therapy is aligned with the duration of nivolumab treatment (13 cycles). Please can the company provide further

justification for the appropriateness of this assumption. Please also provide a scenario in which the duration of subsequent pembrolizumab treatment is 14.8 months, in line with the median time on therapy observed in the KEYNOTE-087 trial (see Supplemental Table 3, Armand et al. 2023).(1)

Response: The assumption of equivalent subsequent therapy durations for nivolumab and pembrolizumab was a simplifying assumption based on their similar mechanism of action. Additionally, this is further supported by the similarity in the median durations of treatment reported in KEYNOTE-087 for pembrolizumab (14.8 months) vs. CheckMate205 for nivolumab (14.3 months).[57, 58] Finally, clinical expert feedback elicited by the Company indicated that the treatment durations are expected to be similar in UK clinical practice.

Following the EAG's question, the CEM now includes a scenario in which patients receive 200mg every 3 weeks for 14.8 months as per KEYNOTE-087.[57] This is converted into the 3-week treatment cycle length specific to pembrolizumab treatment in the relapsed or refractory Hodgkin's lymphoma setting, which equates to 21.45 3-week cycles. Using the duration of subsequent pembrolizumab from the KEYNOTE-087 trial reduces the base case ICER from £[redacted] to £[redacted] (Table 30). Using the duration of subsequent pembrolizumab from the KEYNOTE-087 trial is included in the updated base case.

Table 30: Results from Clarification Question B14 (pembrolizumab subsequent therapy duration 14.8 months)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

B15. The CS states that the duration of brentuximab vedotin monotherapy as a subsequent treatment is 9.24 cycles, based on TA446. However, the duration of brentuximab vedotin treatment in TA446 is 9.7 cycles (see page 173 of the company

submission for TA446). Please can the company provide an explanation for this discrepancy.

Response: The Company would like to apologise for any confusion caused here. The 9.24 treatment cycles was calculated based on the total acquisition costs of £69,355 reported in TA446 divided by the cost per cycle estimated in the Company model.[59] Of note, the £69,355 estimate also reflects total discounted acquisition costs for brentuximab vedotin monotherapy as a subsequent treatment. Following the EAG's question, the CEM now includes an option to model subsequent brentuximab vedotin monotherapy assuming 9.7 treatment cycles via a bottom-up approach which aligns with the approach conducted for other subsequent therapies. For the purposes of the response to this question, the Company has maintained the original base case dose; however, a scenario analysis has also been conducted to explore the combined impact of the revised treatment duration and the updated dose in response to Question B18. Using the duration of subsequent brentuximab vedotin from TA446 reduces the base case ICER from £[redacted] to £[redacted] (Table 31). Using the duration of subsequent brentuximab vedotin from TA446 is included in the updated base case.

Table 31: Results from Clarification Question B15 (brentuximab vedotin subsequent therapy duration 9.7 cycles)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year.

B16. The CS states that the duration of nivolumab monotherapy as a subsequent treatment is 13 cycles, based on TA462. However, the EAG have been unable to identify this value in the documentation for TA462. Please can the company explain how the duration of treatment for nivolumab has been derived.

Response: The Company identified the 13-cycle assumption for nivolumab based on Table 33 in the second set of Committee papers in TA462, which indicates that a

median of 13 doses of nivolumab were received when combining CheckMate 039 and CheckMate 205.[60] In line with the EAG's request, the CEM now includes a scenario where the duration of subsequent nivolumab treatment is 14.3 months, to align with the median duration of treatment observed in CheckMate 205.[61] In the Company CEM, this is converted into the 2-week treatment cycle length specific to nivolumab treatment in the relapsed or refractory Hodgkin's lymphoma setting, which equates to 31.09 2-week cycles. Of note, the previously assumed 13 cycles referred to in the EAG's question corresponds to 13 4-week model cycles, and therefore, there is minimal difference between the original Company base case and the scenario presented in response to this question. For the purposes of the response to this question, the Company has maintained the original base case dose of 3 mg/kg; however, a scenario analysis has also been conducted to explore the combined impact of the extended treatment duration and the updated dose in response to Question B17. Using the duration of subsequent nivolumab from TA462 reduces the base case ICER from £[redacted] to £[redacted] (Table 32). Using the duration of subsequent nivolumab from TA462 is included in the updated base case.

Table 32: Results from Clarification Question B16 (nivolumab subsequent therapy duration 16.9 months)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

B17. The EAG notes that a dosage of 3 mg/kg for each administration is used for nivolumab in the economic model. However, the SmPC for nivolumab states that the appropriate dosage for classical Hodgkin lymphoma is 240 mg. Please can the company provide an explanation for this discrepancy.

Response: The dose of 3mg/kg for each administration of nivolumab was selected as this aligns with the dose used in TA462, and specifically the dose referenced in Section 2 in the Final Appraisal Determination document.[61] Following the EAG's

question, the CEM now includes an option to model the dose of nivolumab as 240 mg every two weeks in line with the SmPC.[62] Of note, this does not impact the results as the previous assumed dose (3 mg/kg) equated to 225.19 mg every two weeks, which was subsequently rounded to the nearest whole vial (240 mg) (Table 33). The 240 mg dose will form part of the Company's updated base case.

Table 33: Results from Clarification Question B17 (nivolumab dose of 240mg every two weeks)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

B18. The EAG notes that a dosage of 1.2 mg/kg is used for brentuximab vedotin monotherapy as a subsequent treatment in the economic model. However, the SmPC for brentuximab vedotin states that a dosage of 1.8 mg/kg should be used in the relapsed/refractory setting. Please can the company provide an explanation for this discrepancy.

Response: The EAG is correct that 1.8 mg/kg every 3 weeks is the relevant dose for brentuximab vedotin monotherapy in the relapsed or refractory Hodgkin's lymphoma setting.

However, the Company CEM used a 1.2 mg/kg dose instead of 1.8 mg/kg to ensure the correct subsequent brentuximab vedotin cost was applied in the CEM, given the CEM cycle length is 4 weeks rather than 3 weeks. Specifically, the 1.2 mg/kg dose was applied twice every 4 weeks in the CEM (i.e. 1.2 x 2 = 2.4), which equates to 1.8 mg/kg every 3 weeks (i.e. 1.8 x (4/3) = 2.4).

Following the EAG's question, and to align with the approach conducted for other subsequent therapies in B14 – B17, the CEM now includes an option to model the dose of brentuximab vedotin as 1.8 mg/kg once per 3-week treatment cycle. Importantly, this does not impact the results as, in the base case, the CEM

calculates the number of cycles required to ensure the cost of subsequent brentuximab vedotin equals £[redacted] to predict total acquisition costs from TA446.[59]

In response to B15, a scenario is presented fixing the number of cycles for subsequent brentuximab vedotin at 9.7 cycles. Based on 1.8 mg/kg every 3 weeks, the cost per 3-week cycle is £[redacted], and £[redacted] multiplied by 9.7 cycles results in a total cost of £[redacted]. This results in a lower cost for brentuximab vedotin monotherapy in the relapsed/refractory setting than estimated in TA446; the estimate in TA446 is likely to be more accurate as it accounts for the distribution of weight, required in the calculations, using method of moments. Whereas, in this submission, the costs of subsequent therapies are simplified and based on the average weight or BSA – this may underestimate the true cost of subsequent brentuximab vedotin. Using the dose of 1.8 mg/kg (B18) and 9.7 treatment cycles (B15) for subsequent brentuximab vedotin from TA446 increases the base case ICER from £[redacted] to £[redacted] (Table 34).

As a conservative assumption and to align with calculations for other subsequent therapies, the dose of 1.8mg/kg (B18) and 9.7 treatment cycles (B15) for subsequent brentuximab vedotin are adopted in the updated base case.

Table 34: Results from Clarification Question B15 and B18 (1.8 mg/kg (Question 18) and 9.7 treatment cycles (Question 15) for subsequent brentuximab vedotin)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

B19. The CS states that the cost for ASCT includes a cost for bone marrow harvest, while the cost for alloSCT includes a cost for peripheral blood stem cell harvest. The EAG considers that applying a single harvesting cost, comprising of a weighted average of the costs for the two harvesting procedures, to both ASCT and alloSCT

would be more appropriate. Please can the company provide a scenario using this methodology.

Response: In the original Company submission, the costs of harvesting were informed by the individual codes: NHS Reference Costs 2021/22 SA18Z bone marrow harvest (elective) for ASCT and SSA34Z peripheral blood stem cell harvest (elective) for alloSCT. Table 35 presents the number of finished consultant episodes (FCEs) and the national average unit costs reported in the NHS Reference Costs 2021/22. The individual codes were weighted by the proportion of patients receiving an ASCT or alloSCT as a subsequent therapy based on the ECHELON-1 trial data i.e., SA18Z was weighted by [redacted]% and [redacted]% in the A+AVD and ABVD treatment arms for the costs of ASCT, respectively and SA34Z was weighted by [redacted]% and [redacted]% for the costs of alloSCT, respectively.

Table 35: Costs of harvesting for ASCT and alloSCT

NHS currency code	Number of FCEs	National average unit cost
SA18Z	55	£5,808.35
SA34Z	302	£5,374.62

Abbreviations: alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; FCE, finished consultant episode; NHS, National Health Service

In response to the EAG's question, a scenario has been conducted where, instead of applying separate harvesting costs for ASCT and alloSCT based on the individual NHS currency codes in the CEM, a single weighted cost of harvesting (£5,441) that accounts for both bone marrow and peripheral blood stem cell harvesting, is applied for both ASCT and alloSCT. This weighted cost was calculated by weighting the national average unit costs by the number of FCEs. The weight cost of harvesting was then further weighted by the proportion of patients receiving an ASCT or alloSCT as a subsequent therapy based on the ECHELON-1 trial data i.e., £5,441 was weighted by [redacted]% and [redacted]% in the A+AVD and ABVD treatment arms for the costs of ASCT, respectively and £5,441 was weighted by [redacted]% and [redacted]% for the costs of alloSCT, respectively. Using the weighted cost of harvesting for both ASCT and alloSCT has minimal impact on the ICER, which increases from £[redacted] to £[redacted] (Table 36). Using the weighted cost of harvesting for both ASCT and alloSCT is included in the updated base case.

Table 37 shows the breakdown of total costs for ASCT and alloSCT in each treatment arm, weighted by the proportion of patients receiving these subsequent therapies, using the Company's original approach. Table 38 shows the breakdown of harvesting, ASCT, and alloSCT in each treatment arm, weighted by the proportion of patients receiving these subsequent therapies, following the EAG's request.

Table 36: Results from Clarification Question B19 (separating weighted harvesting costs from total SCT costs)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

Table 37: Breakdown of weighted costs comprising SCTs (original Company approach)

	ASCT	alloSCT	Total*
A+AVD	£10,246	£7,598	£17,844
ABVD-based treatment	£11,135	£14,236	£25,371

*Total costs are from the CEM. There may be slight differences due to rounding when summing the harvest, ASCT, and alloSCT costs directly from the table.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; SCT, stem cell transplant

Table 38: Breakdown of weighted costs comprising SCTs (EAG approach)

	Harvest	ASCT	alloSCT	Total*
A+AVD	£2,121	£8,431	£7,183	£17,734
ABVD-based treatment	£2,635	£9,162	£13,458	£25,256

*Total costs are from the CEM. There may be slight differences due to rounding when summing the harvest, ASCT, and alloSCT costs directly from the table.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; SCT, stem cell transplant

B20. The costs for long-term follow-up for ASCT and alloSCT have been obtained from TA874, and inflated using the NHSCII prices index from 2019/20 to 2020/21. In order to align with other costs used in the model, the EAG believe it would be more appropriate to inflate the costs to 2021/22, using the provisional figures for 2021/22

available from the PSSRU. Please provide a scenario using the long-term follow-up costs for ASCT and alloSCT inflated to 2021/22 values.

Response: Following the EAG's request, the CEM now includes an option to use the provisional inflation indices from PSSRU 2022 to inflate the costs for long-term follow-up for ASCT and alloSCT to 2021/22 values and align with the cost year for other costs in the CEM.[63] This reduces the base case ICER from £[redacted] to £[redacted] (Table 39). Using the provisional inflation indices from PSSRU 2022 to inflate the costs for long-term follow-up for ASCT and alloSCT to 2021/22 values is included in the updated base case.

Table 39: Results from Clarification Question B20 (inflation indices from 2021/22)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

Mortality

B21. The CS states that "long-term outcomes are driven by the adjusted background mortality, which takes effect at [redacted] and [redacted] years for PFS and [redacted] and [redacted] years for OS, for A+AVD and ABVD-based treatment, respectively" can the company confirm these time points are those at which the adjusted background mortality rate exceeds the mortality rate from ECHELON-1. If not, please explain the significance of these values in the model.

Response: The EAG is correct that these time points are those at which the adjusted background mortality rate exceeds the mortality rate from the extrapolated ECHELON-1 data. These correspond to the points at which the MAX() function takes over in columns K and M in the "PFS" sheet of the CEM, and K and L in the "OS" sheet, for A+AVD and ABVD, respectively.

Adverse event costs

B22. The EAG notes that neutropenia, neutrophil count decreased and febrile neutropenia have been costed by assuming a non-elective short stay context for treatment, based on input from clinical experts, only patients with febrile neutropenia would be likely to be admitted. Furthermore, the cost used for febrile neutropenia in the model (£646.71) is lower than the cost for neutropenia and neutrophil count decreased (£655.34), which potentially lacks face validity. Please provide further justification for the costs used.

Response: The CEM includes the costs of drug-related treatment emergent Grade ≥3 adverse events and, as Grade ≥3 adverse events are defined as those which are severe or medically significant, where hospitalisation or prolongation of hospitalisation is indicated, the Company believed it was reasonable to assume non-elective short stay costs were appropriate.[64]

The specific unit costs were based on the NHS Reference Costs 2021/22 agranulocytosis with complications score 5–8 for neutropenia and neutrophil count decreased and agranulocytosis with complications score 9–12 for febrile neutropenia, which of note, are based on 492 and 231 finished consultant episode (FCE) observations, respectively.[65] Febrile neutropenia was assumed to have a greater complications score based on feedback from UK clinical experts. As the EAG highlights, the unit cost for complications score 5–8 (£655.34) is slightly higher than the cost for complications score 9–12 (£646.71). The Company is unclear why this may be the case, particularly considering the number of FCE observations these are based on.

To support the response to this question, the Company also reached out to a UK clinical expert who confirmed that only patients with febrile neutropenia would be admitted for hospitalisation, and that anaemia, neutropenia and neutrophil count decreased would be managed in an outpatient or day case setting. Therefore, a scenario analysis has been conducted which explores the impact of assuming the non-elective short stay agranulocytosis with complications score 9–12 for febrile neutropenia, and the same HRG codes for neutropenia and neutrophil count decreased within a day case setting as costs for an outpatient setting are unavailable. Of note, the cost of anaemia already reflected an outpatient setting in

the original Company base case. The cost of agranulocytosis with CC Score 5–8 in a day case setting corresponds to a cost of £387.69, based on 125 FCEs. In this scenario, the costs of febrile neutropenia (£646.71) are greater than those assumed for neutropenia and neutrophil count decreased (£387.69), aligning with the expectation that febrile neutropenia is more costly to treat. This scenario has minimal impact on the ICER, which reduces from £[redacted] to £[redacted] (Table 40). Using the HRG codes for neutropenia and neutrophil count decreased within a day case setting is included in the updated base case.

Table 40: Results from Clarification Question B22 (HRG codes for neutropenia and neutrophil count decreased within a day case setting)

	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALY, quality adjusted life year

General questions

B23. The EAG notes that prednisolone and prednisone have been used interchangeably as components in the escBEACOPDac treatment regimen throughout the company submission. Please can the company confirm that prednisolone should be used rather than prednisone in this context.

Response: The Company would like to apologise for any confusion caused with respect to prednisolone vs. prednisone use throughout the submission. For clarity, as part of the escBEACOPDac regimen, prednisolone is used in UK clinical practice, as per the British Society for Haematology (BSH) guidelines, whereas prednisone is used in the US, as per the National Comprehensive Cancer Network (NCCN) guidelines, and therefore, the CEM should reference prednisolone as the EAG suggests.[2, 66] The CEM has hence been updated throughout. Importantly, all inputs in the CEM and information presented in Section B3 of the original Company submission appropriately correspond to prednisolone, so a simple text update was conducted throughout the CEM for clarity.

Clarification of CQ B2

B24. Given the maturity of the data, cure being the aim of treatment and a significant proportion of patients achieving cure post treatment, the EAG considers that a MCM is the most robust method to extrapolate both the PFS and OS trial data. However, as the company has identified, under probabilistic conditions the cure fractions for A+AVD OS are improbably high, reaching 100% in many instances when using the log-logistic model. As such, when conducting the MAIC requested between A+AVD from ECHELON-1 mapped to the PET-adjusted approach from RATHL (clarification question B2) please make sure to extrapolate both PFS and OS using a MCM and a spline model (if still preferred in the company base case), providing summary statistics of the cure fractions under probabilistic conditions.

Response: The Company would like to clarify that under probabilistic conditions, the cure fractions for OS estimated using the ECHELON-1 population, were found to be improbably low and high – as shown in Figure 28. The MAIC-weighted A+AVD (ECHELON-1) and Stage III/IV subgroup PET-adapted ABVD unadjusted (RATHL) PFS and OS data have been extrapolated using both MCMs and splines, and all results are available in Table 57.

In line with the response to B2, independent parametric curves (including standard parametric curves, MCMs, and one-knot splines) were fitted to the MAIC-weighted A+AVD (ECHELON-1) data and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL) for PFS and OS. This is presented as an alternative, updated base case within the response. In this “alternative, updated base case”, where these sources are used, alongside patient characteristics reflecting the MAIC-weighted A+AVD data, the independent log-logistic MCMs were used to extrapolate PFS, and the independent one-knot hazard splines were used to extrapolate OS (rationale presented in response to B2).

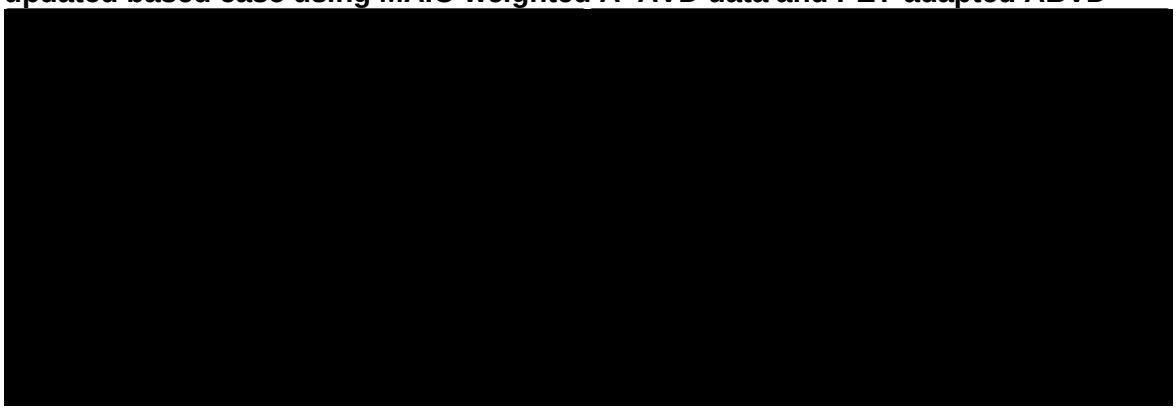
The deterministic ICER using the MAIC-weighted A+AVD (ECHELON-1) data and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL) is £[redacted] (Table 12). The probabilistic ICER is £[redacted]. In response to the EAG’s question, the probabilistic cure rates are recorded in the CEM when MCMs are used and a PSA is conducted, in the “PSA” sheet.

PFS cure fractions

In the alternative base case using the MAIC-weighted A+AVD data and PET-adapted ABVD data from the Stage III/IV subgroup from RATHL, the cure rates predicted by the independent log-logistic MCMs across 1,000 simulations ranged from [redacted]% for A+AVD and from [redacted]% for ABVD-based treatment. The histograms for predicted cure rates across the 1,000 simulations are presented in Figure 28 for A+AVD and ABVD. These ranges align with the cure rates presented in Table 25 of the Company submission based on the log-logistic MCMs fitted to the ECHELON-1 data i.e., [redacted]% and [redacted]% for A+AVD and ABVD, respectively.

The independent log-logistic MCMs predict PFS cure rates which align with the literature and clinical expectations across both data sources i.e., ECHELON-1, and MAIC-weighted A+AVD data and PET-adapted ABVD data from the Stage III/IV subgroup from RATHL. As presented in the Company submission, the literature indicates that approximately 70–80% of patients with previously untreated CD30+ Stage III or IV HL are cured with current first-line treatments, which was validated by UK clinical experts at the Company's advisory boards in November 2023 and January 2024. The cure rates predicted by the independent log-logistic MCMs across 1,000 simulations align with this range.

Figure 28: Histogram of predicted cure rates across 1,000 probabilistic iterations | updated based case using MAIC-weighted A+AVD data and PET-adapted ABVD



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched adjusted indirect comparison; PET, positron emission tomography

OS cure fractions

Table 41 compares the cure fractions and confidence intervals (CIs) estimated for OS when using the ECHELON-1 data, and when using the MAIC-weighted A+AVD (ECHELON-1) data and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL). In line with the findings in the Company submission using the ECHELON-1 data (Section B.3.3.2.3), only the independent exponential and Gompertz MCMs predict clinically plausible deterministic cure fractions for A+AVD and ABVD. However, the predicted 95% CIs associated with each cure fraction estimated by the exponential or Gompertz MCM still appear implausibly low and/or high. For example, for ABVD-based treatment, the lower bound of the MCM exponential ([redacted]%) does not correspond to the literature nor clinical expectations. Similarly, for A+AVD, the lower bound of the MCM Gompertz ([redacted]%) does not align with these expectations and is lower than the lower bound of the Gompertz MCM for ABVD-based treatment ([redacted]%), which does not align with the data from ECHELON-1. Finally, for A+AVD, the upper bound of the Gompertz MCM ([redacted]%) is implausibly high. Whilst Table 41 provides a reference for comparison across the two data sources (ECHELON-1 compared with MAIC-weighted A+AVD (ECHELON-1) data and Stage III/IV subgroup PET-adapted ABVD unadjusted data (RATHL)), inferences regarding the differences are challenging as different data sources were used in the extrapolation.

In response to the EAG's question, probabilistic scenarios have been conducted using the independent exponential MCMs (1) and independent Gompertz MCMs (2) for OS:

1. In the scenario using the MAIC-weighted A+AVD data and PET-adapted ABVD data from the Stage III/IV subgroup from RATHL and assuming the independent exponential MCMs for OS, the deterministic and probabilistic ICERs are £[redacted] and £[redacted] (Table 58), respectively. The predicted cure rates across 1,000 simulations ranged from [redacted]% for A+AVD and from [redacted]% for ABVD-based treatment. The histograms for predicted cure rates across the 1,000 simulations are presented in Figure 30 for A+AVD and ABVD.

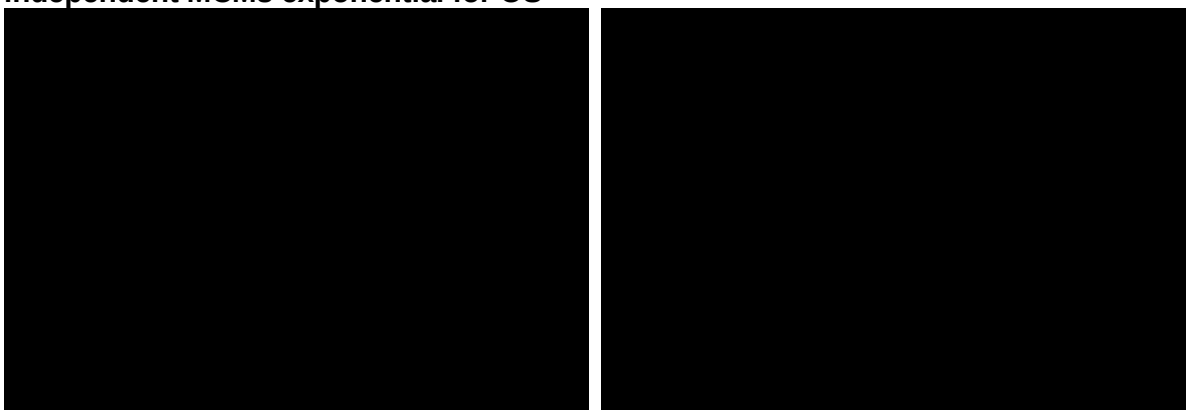
2. In the scenario using the MAIC-weighted A+AVD data and PET-adapted ABVD data from the Stage III/IV subgroup from RATHL and assuming the independent Gompertz MCMs for OS, the deterministic and probabilistic ICERs are £[redacted] and £[redacted] (Table 58), respectively. The predicted cure rates across 1,000 simulations ranged from [redacted]% for A+AVD and from [redacted]% for ABVD-based treatment. The histograms for predicted cure rates across the 1,000 simulations are presented in Figure 30 for A+AVD and ABVD.

Table 41: A comparison of predicted cure rates from OS extrapolations when using the ECHELON-1 data and when using the MAIC-weighted A+AVD data and PET-adapted ABVD data from the Stage III/IV subgroup from RATHL

	Base case using ECHELON-1		Base case using MAIC-weighted A+AVD and PET-adapted ABVD	
	A+AVD (95% CI)	ABVD-based treatment (95% CI)	A+AVD (95% CI)	ABVD-based treatment (95% CI)
MCM: Exponential	[redacted]	[redacted]	[redacted]	[redacted]
MCM: Weibull	[redacted]	[redacted]	[redacted]	[redacted]
MCM: Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
MCM; log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
MCM: Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
MCM: Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
MCM: Gamma	[redacted]	[redacted]	[redacted]	[redacted]

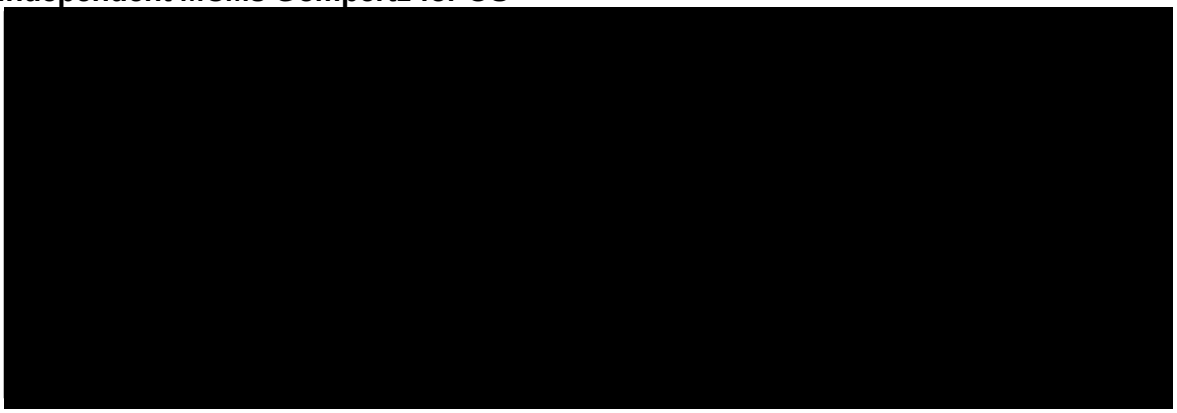
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; MAIC, matched adjusted indirect comparison; MCM, mixture cure model; OS, overall survival; PET, positron emission tomography.

Figure 29: Histogram of predicted cure rates across 1,000 probabilistic iterations | scenario analysis using MAIC-weighted A+AVD data and PET-adapted ABVD and independent MCMs exponential for OS



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched adjusted indirect comparison; MCM, mixture cure model; OS, overall survival; PET, positron emission tomography

Figure 30: Histogram of predicted cure rates across 1,000 probabilistic iterations | scenario analysis using MAIC-weighted A+AVD data and PET-adapted ABVD and independent MCMs Gompertz for OS



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matched adjusted indirect comparison; MCM, mixture cure model; OS, overall survival; PET, positron emission tomography

Updated cost-effectiveness results

The base case ICER presented in the Company submission was £[redacted], including the existing PAS for brentuximab vedotin available in the NHS in the form of a simple discount of [redacted]%. The "updated base case" increases the ICER from £[redacted] to £[redacted] (+0.98%) when using the ECHELON-1 data. An "alternative updated base case" is also provided using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL, in response to B2, which reduces the ICER from £[redacted] to £[redacted] (-44.60%). Table 42 presents the step change from the original base case ICER to the updated base case ICER. The updated base case includes the following updates:

- Drug-related Grade ≥3 TEAEs occurring in ≥5% of patients and concomitant medications sourced from the March 2023 data cut (see response to B10)
- The inclusion of the peripheral neuropathy based on Grade ≥3 SMQ of Peripheral Neuropathy (see response to B10)
- Correction to the number and proportion of patients receiving radiotherapy observed in ECHELON-1 (see response to B13)
- Using the duration of subsequent pembrolizumab from KEYNOTE-087 (see response to B14)
- Using the duration of subsequent brentuximab vedotin from TA446 (see response to B15) and the dose of 1.8mg/kg (see response to B18)
- The duration of subsequent nivolumab from TA462 (see response to B16)
- The dose of 240mg for subsequent nivolumab (see response to B17)
- The weighted cost of harvesting for both ASCT and alloSCT (see response to B19)
- The provisional inflation indices from PSSRU 2022 to inflate the costs for long-term follow-up for ASCT and alloSCT to 2021/22 values (see response to B20)
- The HRG codes for neutropenia and neutrophil count decreased within a day case setting (see response to B22)

Table 42: Step change in base case ICER from original to updated

	ECHELON-1 trial data		MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL	
	ICER step change	**% change each step**	**ICER step change**	**% change each step**
Original base case	[redacted]	NA	[redacted]	
Drug-related Grade ≥3 TEAEs occurring in ≥5% of patients and concomitant medications sourced from the March 2023 data cut (B10)	[redacted]	0.01%	[redacted]	0.01%
Inclusion of the peripheral neuropathy based on the Grade ≥3 under the SMQ of Peripheral Neuropathy (B10)	[redacted]	0.15%	[redacted]	0.08%
Correction to the number and proportion of patients receiving radiotherapy observed in ECHELON-1 (B13)	[redacted]	-0.02%	[redacted]	-0.01%
Duration of subsequent pembrolizumab from the KEYNOTE-087 trial (B14)	[redacted]	-0.78%	[redacted]	-0.58%
Duration of subsequent brentuximab vedotin from TA446 (B15) and the dose of 1.8mg/kg (B18)	[redacted]	3.66%	[redacted]	2.75%
Duration of subsequent nivolumab from TA462 (see response to B16)	[redacted]	-1.86%	[redacted]	-1.25%

	ECHELON-1 trial data		MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL	
Dose of 240mg for subsequent nivolumab (B17)	[redacted]	0.00%	[redacted]	0.00%
Weighted cost of harvesting for both ASCT and alloSCT (B19)	[redacted]	0.03%	[redacted]	0.02%
Provisional inflation indices from PSSRU 2022 (B20)	[redacted]	-0.07%	[redacted]	-0.05%
HRG codes for neutropenia and neutrophil count decreased within a day case setting (B22)	[redacted]	-0.06%	[redacted]	-0.05%
Combined impact; updated Company base case	[redacted]	[redacted]		

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; HRG, health-related group; ICER, incremental cost-effectiveness ratio; PET, positron emission tomography; PSSRU, personal social services research unit; QALY, quality adjusted life year; SMQ, Standardised MedDRA Queries; TEAE, treatment-emergent adverse event

Base case incremental cost-effectiveness analysis results

In the updated base case analysis using the ECHELON-1 data and the PAS price for brentuximab vedotin, A+AVD accrues [redacted] additional QALYs at an additional cost of [redacted], resulting in an ICER of [redacted] (Table 43). The net health benefit (NHB) is [redacted] and [redacted] and the net monetary benefit (NMB) is [redacted] and [redacted], based on WTP thresholds of £20,000 and £30,000, respectively (Table 43). All costs and results presented include the PAS.

In the alternative updated base case analysis using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data and the PAS price for brentuximab vedotin, A+AVD accrues [redacted] additional QALYs at an additional cost of [redacted], resulting in an ICER of [redacted] (Table 44). The NHB is [redacted] and [redacted] and the NMB is [redacted] and [redacted], based on WTP thresholds of £20,000 and £30,000, respectively (Table 44). All costs and results presented include the PAS.

Table 43: Updated base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALY, quality adjusted life year.

Table 44: Alternative updated base case results (MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD-based treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALY, quality adjusted life year.

The clinical outcomes estimated from the CEM have not changed in the updated base case when using the ECHELON-1 data; these are presented in Appendix J.1.1 in the Company submission.

Table 45 and Table 46 present the observed vs. predicted PFS and OS outcomes when using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL. Figure 31 and Figure 32 present the base case PFS and OS extrapolations for A+AVD and ABVD, respectively, over a lifetime (60-year) horizon using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL.

Table 45: Observed vs. predicted PFS outcomes | Log-logistic MCMs including adjusted background mortality for A+AVD and ABVD | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

	Observed		Predicted	
	MAIC-weighted A+AVD	PET-adapted ABVD from RATHL	MAIC-weighted A+AVD	PET-adapted ABVD from RATHL
Median	NR	NR	[redacted]	[redacted]
Mean	NA	NA	[redacted]	[redacted]
% progression-free at				
6 months	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	NR	NR	[redacted]	[redacted]
20 years	NR	NR	[redacted]	[redacted]
30 years	NR	NR	[redacted]	[redacted]
40 years	NR	NR	[redacted]	[redacted]
50 years	NR	NR	[redacted]	[redacted]
60 years	NR	NR	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival; vs., versus.

Table 46: Observed vs. predicted OS outcomes | one-knot splines (hazards) including adjusted background mortality for A+AVD and ABVD | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

	Observed		Predicted	
	MAIC-weighted A+AVD	PET-adapted ABVD from RATHL	MAIC-weighted A+AVD	PET-adapted ABVD from RATHL
Medians	NR	NR	[redacted]	[redacted]
Means	NA	NA	[redacted]	[redacted]
% surviving at				
1 year	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]

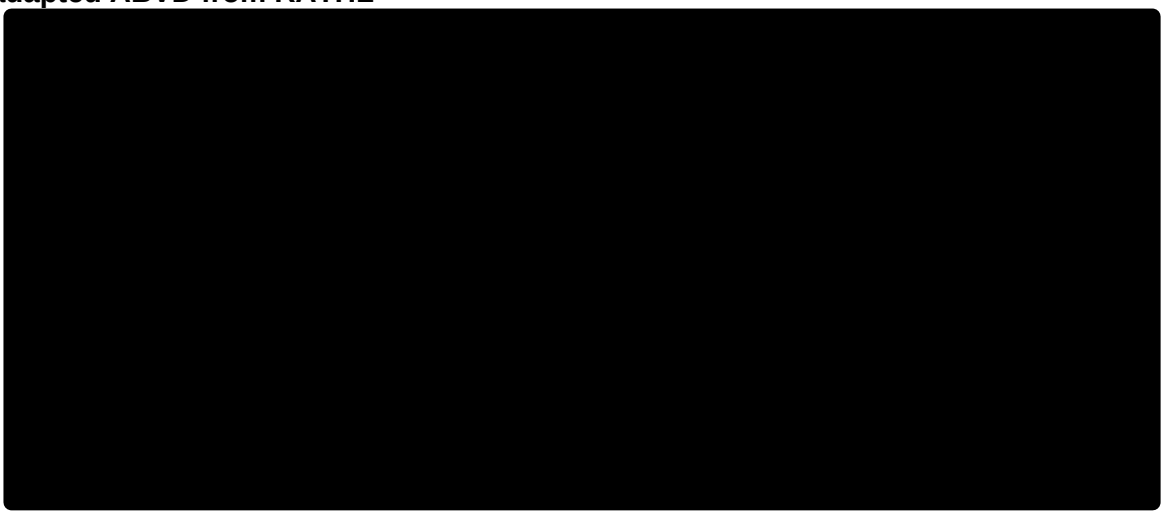
	Observed		Predicted	
	MAIC-weighted A+AVD	**PET-adapted ABVD from RATHL**	**MAIC-weighted A+AVD**	**PET-adapted ABVD from RATHL**
8 years	[redacted]	[redacted]	[redacted]	[redacted]
9 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	NR	NR	[redacted]	[redacted]
20 years	NR	NR	[redacted]	[redacted]
30 years	NR	NR	[redacted]	[redacted]
40 years	NR	NR	[redacted]	[redacted]
50 years	NR	NR	[redacted]	[redacted]
60 years	NR	NR	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; NR, not reported; OS, overall survival; vs., versus.

Figure 31: Alternative updated base case PFS and OS extrapolations (A+AVD) | MAIC-weighted A+AVD data

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival

Figure 32: Alternative updated base case PFS and OS extrapolations (ABVD) | PET-adapted ABVD from RATHL



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival

Table 47 and Table 48 present the disaggregated QALYs and costs by health state using the ECHELON-1 data. Table 49 presents the resource use predicted by the CEM in the base case incremental cost-effectiveness analysis by category of cost using the ECHELON-1 data. These results correspond to the updated base case presented in Table 43.

Table 50 and Table 51 present the disaggregated QALYs and costs by health state using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data. Table 52 presents the resource use predicted by the CEM in the base case incremental cost-effectiveness analysis by category of cost using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data. These results correspond to the updated base case presented in Table 44.

Table 47: Summary of QALY gain by health state | ECHELON-1 data | Updated base case

Health state	Total QALYs A+AVD	Total QALYs ABVD	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	143.84%
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	43.67%
AEs	[redacted]	[redacted]	[redacted]	[redacted]	0.17%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event; QALY, quality-adjusted life year

Table 48: Summary of costs by health state | ECHELON-1 data | Updated base case

Health state	Total costs A+AVD	Total costs ABVD	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	134.92%
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	34.92%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Table 49: Summary of predicted resource use by category of cost | ECHELON-1 data | Updated base case

Item	Total costs A+AVD	Total costs ABVD	Increment	Absolute increment	% absolute increment
Acquisition	[redacted]	[redacted]	[redacted]	[redacted]	125.54%
Administration	[redacted]	[redacted]	[redacted]	[redacted]	1.00%
Concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	9.76%
Monitoring and follow-up care (pre-progression)	[redacted]	[redacted]	[redacted]	[redacted]	0.14%
Monitoring and follow-up care (post-progression)	[redacted]	[redacted]	[redacted]	[redacted]	5.59%
Subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	29.33%
AEs	[redacted]	[redacted]	[redacted]	[redacted]	0.48%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event

Table 50: Summary of QALY gain by health state | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Health state	Total QALYs A+AVD	Total QALYs ABVD	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	105.40%
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	5.32%
AEs	[redacted]	[redacted]	[redacted]	[redacted]	0.08%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event; QALY, quality-adjusted life year

Table 51: Summary of costs by health state | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Health state	Total costs A+AVD	Total costs ABVD	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	121.93%

Health state	Total costs A+AVD	Total costs ABVD	Increment	Absolute increment	% absolute increment
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	21.93%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Table 52: Summary of predicted resource use by category of cost | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Item	Total costs A+AVD	Total costs ABVD	Increment	Absolute increment	% absolute increment
Acquisition	[redacted]	[redacted]	[redacted]	[redacted]	113.62%
Administration	[redacted]	[redacted]	[redacted]	[redacted]	0.92%
Concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	8.76%
Monitoring and follow-up care (pre-progression)	[redacted]	[redacted]	[redacted]	[redacted]	0.02%
Monitoring and follow-up care (post-progression)	[redacted]	[redacted]	[redacted]	[redacted]	0.64%
Subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	21.29%
AEs	[redacted]	[redacted]	[redacted]	[redacted]	0.44%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event

Exploring uncertainty

Probabilistic sensitivity analysis

The PSA, described in Section B.3.11.1 in the Company submission, has been updated to reflect the updated base case using the ECHELON-1 data (Figure 33 and Figure 34 presenting the cost-effectiveness plane and CEAC, respectively) and to reflect the alternative updated base case using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL (Figure 35 and Figure 36 presenting the cost-effectiveness plane and CEAC, respectively).

The probabilistic ICER for the updated base case is £[redacted]; this is congruent with the deterministic ICER of £[redacted], as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 33). The proportions of simulations considered cost-effective at a threshold of £20,000 and £30,000 per QALY are [redacted]% and [redacted]% when using the ECHELON-1 data, respectively.

The probabilistic ICER for the alternative updated base case, using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data, is £[redacted]; this is congruent with the deterministic ICER of £[redacted], as demonstrated by the overlap in markers showing the deterministic and probabilistic base case in the cost-effectiveness plane (Figure 35). The proportions of simulations considered cost-effective at a threshold of £20,000 and £30,000 per QALY are [redacted]% and [redacted]% when using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data, respectively.

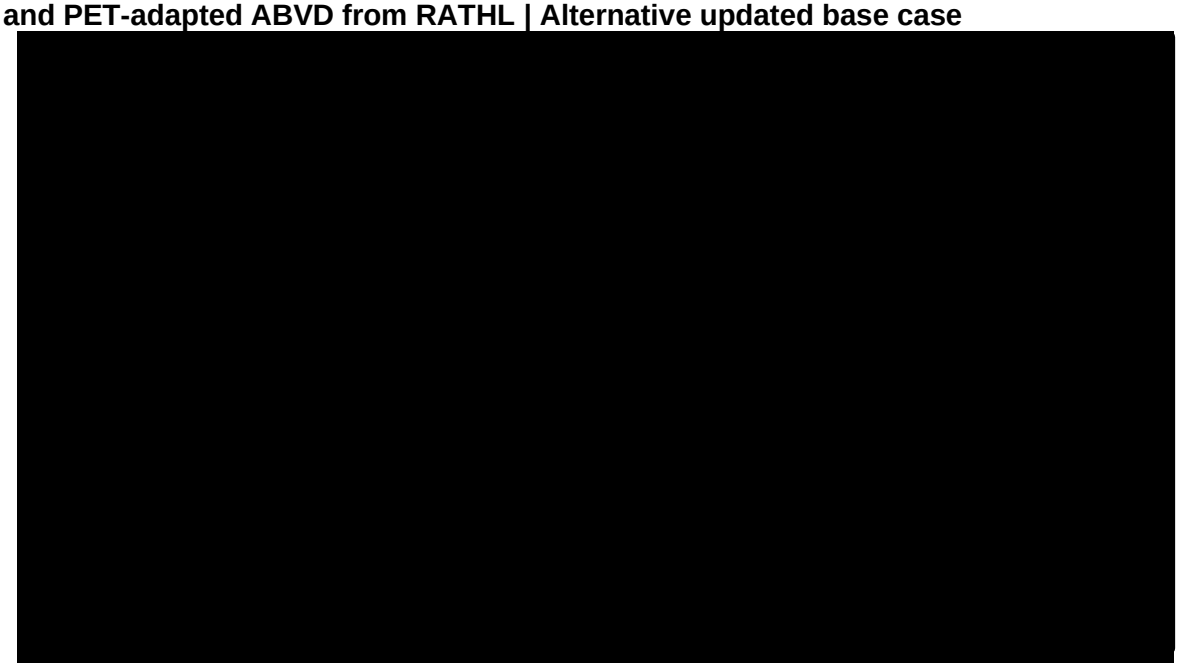
Figure 33: Cost-effectiveness plane | 1,000 iterations | ECHELON-1 data | Updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Figure 34: Cost-effectiveness acceptability curve | ECHELON-1 data | Updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CEAC, cost-effectiveness acceptability curve

Figure 35: Cost-effectiveness plane | 1,000 iterations | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Figure 36: Cost-effectiveness acceptability curve | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CEAC, cost-effectiveness acceptability curve

Deterministic sensitivity analysis

The one-way sensitivity analysis (OWSA), described in Section B.3.11.2 in the Company submission, has been updated to reflect the updated base case using the updated base case (using ECHELON-1) and alternative updated base case (using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL).

In the updated base case, using the ECHELON-1 data, results for the ten most influential parameters are shown in Table 53 and depicted in a tornado diagram in Figure 37, Figure 38, and Figure 39, based on the ICER, NMB at a WTP of £20,000 and NMB at a WTP of £30,000, respectively.

In the alternative updated base case, using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data, results for the ten most influential parameters are shown in Table 54 and depicted in a tornado diagram in Figure 40, Figure 41, and Figure 42, based on the ICER, NMB at a WTP of £20,000 and NMB at a WTP of £30,000, respectively.

Results are consistent with the original OWSA; the SMR has the biggest impact on results, with ICERs varying from £[redacted] (upper bound of SMR for ABVD) to £[redacted] (upper bound of SMR for A+AVD) in the updated base case, and varying

from £[redacted] (upper bound of SMR for ABVD) to £[redacted] (upper bound of SMR for A+AVD) in the alternative updated base case based on the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data. As detailed in Section B.3.11.2 in the Company submission, the results of this scenario should be interpreted carefully as varying these parameters independently, as per the objective of the OWSA, leads to results which are misaligned with clinical opinion. Specifically, the lower bounds for the SMRs for A+AVD and ABVD are 1.0 and 1.0, respectively, whereas the upper bounds for the SMRs for A+AVD and ABVD are 1.27 and 1.33, respectively, based on 10% uncertainty and a gamma distribution. When varying the upper bound for the SMR for A+AVD, the analysis assumes that the excess mortality is 27% greater than the general population in the A+AVD arm, compared to only 10% greater than the general population in the ABVD arm i.e. the base case. This is not considered clinically plausible (see Section B.3.2.2.1 in the Company submission). Additionally, as explained in Section B.3.2.2.1 of the Company submission, UK clinical experts highlighted that excess mortality in frontline HL is expected to be lower than in the frontline lymphomas considered in TA641 and TA874 (sALCL and DLBCL, respectively), and the maximum SMR explored in these appraisals was 1.1 i.e. 10% greater than the general population. To explore the uncertainty associated with the SMRs, clinically plausible SMR alternatives are explored in scenario analyses (Table 55 to Table 58).

In line with the original base case OWSA, the costs associated with subsequent brentuximab vedotin monotherapy also influence the cost-effectiveness results. As there is a higher proportion of patients receiving subsequent brentuximab vedotin monotherapy in the ABVD treatment arm ([redacted]%) compared to the A+AVD treatment arm ([redacted]%) based on ECHELON-1, varying this parameter has a larger impact on the costs accrued in the ABVD arm compared to the A+AVD arm. A probabilistic scenario analysis explores the subsequent therapy distribution as informed by UK clinical experts with a smaller difference i.e. 13.01% brentuximab vedotin monotherapy use in the A+AVD arm and 47.9% in the ABVD arm (results for the updated base case results and alternative updated base case results are presented in Table 56 and Table 58, respectively).

Remaining parameters are shown to have a limited impact on results.

Table 53: One-way sensitivity analysis | ECHELON-1 data | Updated base case

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
SMR: A+AVD	[redacted]	[redacted]
SMR: ABVD	[redacted]	[redacted]
Parametric curves | PFS	[redacted]	[redacted]
Concomitant medication costs | Filgrastim	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 | ABVD: alloSCT or donor lymphocyte infusion	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 | ABVD: PD-1 monotherapy (nivolumab)	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 | ABVD: BV monotherapy	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 | ABVD: PD-1 monotherapy (pembrolizumab)	[redacted]	[redacted]
Proportion of subsequent therapy use - ECHELON-1 | A+AVD: PD-1 monotherapy (nivolumab)	[redacted]	[redacted]
Time on Treatment | AAVD: Brentuximab (IV)	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogenic stem cell transplant; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate.

Figure 37: Tornado diagram | ICER | ECHELON-1 data | Updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio

Figure 38: Tornado diagram | NMB at a WTP of £20,000 | ECHELON-1 data | Updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; NMB, net monetary benefit; WTP, willingness to pay

Figure 39: Tornado diagram | NMB at a WTP of £30,000 | ECHELON-1 data | Updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; NMB, net monetary benefit; WTP, willingness to pay

Table 54: One-way sensitivity analysis | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Parametric curves | OS	[redacted]	[redacted]
SMR: A+AVD	[redacted]	[redacted]
Parametric curves | PFS	[redacted]	[redacted]
SMR: ABVD	[redacted]	[redacted]
Concomitant Medication Costs | Filgrastim	[redacted]	[redacted]
Proportion of subsequent therapy - ECHELON-1 | ABVD: alloSCT or donor lymphocyte infusion	[redacted]	[redacted]

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Proportion of subsequent therapy - ECHELON-1 | ABVD: PD-1 monotherapy (nivolumab)	[redacted]	[redacted]
Proportion of subsequent therapy - ECHELON-1 | ABVD: BV monotherapy	[redacted]	[redacted]
Age (years): ECHELON-1	[redacted]	[redacted]
Time on Treatment | AAVD: Brentuximab (IV)	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogenic stem cell transplant; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate.

Figure 40: Tornado diagram | ICER | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio

Figure 41: Tornado diagram | NMB at a WTP of £20,000 | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; NMB, net monetary benefit; WTP, willingness to pay

Figure 42: Tornado diagram | NMB at a WTP of £30,000 | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL | Alternative updated base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; NMB, net monetary benefit; WTP, willingness to pay

Scenario analysis

The scenario analyses, described in Section B.3.11.3 in the Company submission, have been updated to reflect the updated base case using the ECHELON-1 data (Table 55 and Table 56 for deterministic and probabilistic scenarios, respectively) and to reflect the alternative updated base case using the MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL (Table 57 and Table 58 for deterministic and probabilistic scenarios, respectively). In line with the Company submission and due to the number of scenario analyses explored, the ten scenarios that demonstrated the biggest impact on the cost-effectiveness results in the deterministic analyses were conducted probabilistically.

Probabilistic scenario analyses included discount rates of 0% for costs and health outcomes, discount rates of 1.5% for costs and health outcomes, independent exponential MCMs to extrapolate OS for A+AVD and ABVD, primary prophylaxis with G-CSF as per ECHELON-1, independent standard Gompertz curves to extrapolate OS for A+AVD and ABVD, OS KM with adjusted background mortality for A+AVD and ABVD, baseline characteristics from the RATHL study, independent Gompertz MCMs to extrapolate OS for A+AVD and ABVD, excluding RDI, and a subsequent therapy distribution informed by UK clinical experts.

As discussed in the Company submission (Section B.3.11.3) and in the response to B24, when explored probabilistically, the independent Gompertz MCM fit to the

ECHELON-1 data for OS yielded implausible predicted outcomes. Specifically, the predicted cure rates range from [redacted]% to [redacted]% and [redacted]% to [redacted]% based on the 95% confidence intervals for the MCM Gompertz curves fitted to A+AVD for ABVD, respectively. These ranges are considered clinically implausible and do not fit the ECHELON-1 data, nor the literature, and hence lead to implausibly wide variations in the probabilistic ICER. Therefore, the probabilistic ICER for the parametric MCMs for OS when using the ECHELON-1 trial data should be interpreted with caution. This phenomenon was not observed when using the MAIC-weighted A+AVD data and PET-adapted ABVD data from RATHL.

The remaining results are congruent to the deterministic scenarios and vary the ICER from −56.60% to +13.81% compared to the base case probabilistic ICER when using the updated base case assumptions and from -57.19% to +27.94% when using the alternative updated base case assumptions (MAIC-weighted A+AVD data and PET-adapted ABVD data from RATHL).

Table 55: Deterministic scenario analyses results | ECHELON-1 data | Updated base case

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
Updated base case	[redacted]	-	-
Time horizon: 50-years	[redacted]	[redacted]	1.68%
Time horizon: 70-years	[redacted]	[redacted]	-0.06%
Exclude half-cycle correction	[redacted]	[redacted]	0.04%
Discount rates: 0%	[redacted]	[redacted]	-56.31%
Discount rates: 1.5%	[redacted]	[redacted]	-35.60%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	-7.68%
PFS: KM and adjusted background mortality	[redacted]	[redacted]	2.95%

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
PFS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	3.23%
PFS: independent MCMs Weibull for A+AVD and ABVD	[redacted]	[redacted]	3.07%
PFS: independent MCMs log-normal for A+AVD and ABVD	[redacted]	[redacted]	0.49%
PFS: independent MCMs log-logistic for A+AVD and ABVD	[redacted]	[redacted]	0.00%
PFS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	4.08%
PFS: independent MCMs generalised gamma for A+AVD and ABVD	[redacted]	[redacted]	2.61%
PFS: independent MCMs gamma for A+AVD and ABVD	[redacted]	[redacted]	2.28%
PFS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	3.36%
PFS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	-2.07%
PFS: independent one-knot splines (hazard) for A+AVD and ABVD	[redacted]	[redacted]	-0.17%
PFS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	-0.43%

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
OS: KM and adjusted background mortality	[redacted]	[redacted]	9.10%
OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	9.78%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	6.28%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	9.18%
OS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	0.54%
OS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	0.49%
PET-adapted ABVD: 100% of ABVD-based comparator	[redacted]	[redacted]	-0.13%
PET-adapted ABVD: 95% of ABVD-based comparator	[redacted]	[redacted]	-0.07%
SMR 1.10 for A+AVD and 1.15 for ABVD	[redacted]	[redacted]	0.99%
Cure timepoint: 36-months	[redacted]	[redacted]	-0.38%
Cure timepoint: 60-months	[redacted]	[redacted]	0.07%
AE disutilities: literature	[redacted]	[redacted]	1.79%
AE disutilities: excluded	[redacted]	[redacted]	-0.17%
Second malignancies: included	[redacted]	[redacted]	0.24%

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	0.89%
RDI: excluded	[redacted]	[redacted]	5.57%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	-9.11%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

Table 56: Probabilistic scenario analyses results | ECHELON-1 data | Updated base case

	Deterministic ICER	Probabilistic ICER	Change from probabilistic base case	% change from probabilistic base case
Updated base case with ECHELON-1 data	[redacted]	[redacted]	NA	NA
Discount rates: 0%	[redacted]	[redacted]	[redacted]	-56.60%
Discount rates: 1.5%	[redacted]	[redacted]	[redacted]	-34.71%
OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	7.78%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	[redacted]	-12.64%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	13.81%
OS: KM and adjusted background mortality	[redacted]	[redacted]	[redacted]	7.75%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	[redacted]	-8.95%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	64.60%
RDI: excluded	[redacted]	[redacted]	[redacted]	4.15%
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	[redacted]	1.20%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA,

Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

Table 57: Deterministic scenario analyses results | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data | Alternative updated base case

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
Alternative updated base case	[redacted]	-	-
Time horizon: 50-years	[redacted]	[redacted]	2.82%
Time horizon: 70-years	[redacted]	[redacted]	-0.23%
Exclude half-cycle correction	[redacted]	[redacted]	0.04%
Discount rates: 0%	[redacted]	[redacted]	-56.97%
Discount rates: 1.5%	[redacted]	[redacted]	-37.02%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	1.89%
PFS: KM and adjusted background mortality	[redacted]	[redacted]	4.43%
PFS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	2.29%
PFS: independent MCMs Weibull for A+AVD and ABVD	[redacted]	[redacted]	3.78%
PFS: independent MCMs log-normal for A+AVD and ABVD	[redacted]	[redacted]	0.17%
PFS: independent MCMs log-logistic for A+AVD and ABVD	[redacted]	[redacted]	0.00%
PFS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	1.22%

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
PFS: independent MCMs generalised gamma for A+AVD and ABVD	[redacted]	[redacted]	-1.46%
PFS: independent MCMs gamma for A+AVD and ABVD	[redacted]	[redacted]	3.74%
PFS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	1.23%
PFS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	-5.95%
PFS: independent one-knot splines (hazard) for A+AVD and ABVD	[redacted]	[redacted]	-5.13%
PFS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	-7.16%
OS: KM and adjusted background mortality	[redacted]	[redacted]	41.13%
OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	11.38%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	26.79%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	10.17%
OS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	2.05%

Scenario	Deterministic ICER	Change from deterministic base case	% change from deterministic base case
OS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	4.34%
PET-adapted ABVD: 100% of ABVD-based comparator	[redacted]	[redacted]	-0.12%
PET-adapted ABVD: 95% of ABVD-based comparator	[redacted]	[redacted]	-0.06%
SMR 1.10 for A+AVD and 1.15 for ABVD	[redacted]	[redacted]	1.10%
Cure timepoint: 36-months	[redacted]	[redacted]	-4.43%
Cure timepoint: 60-months	[redacted]	[redacted]	-8.12%
AE disutilities: literature	[redacted]	[redacted]	0.90%
AE disutilities: excluded	[redacted]	[redacted]	-0.08%
Second malignancies: included	[redacted]	[redacted]	0.18%
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	2.80%
RDI: excluded	[redacted]	[redacted]	4.93%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	-8.18%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

Table 58: Probabilistic scenario analyses results | MAIC-weighted A+AVD data and PET-adapted ABVD from RATHL data | Alternative updated base case

	Deterministic ICER	Probabilistic ICER	Change from probabilistic base case	% change from probabilistic base case
Alternative updated base case	[redacted]	[redacted]	NA	NA
Discount rates: 0%	[redacted]	[redacted]	[redacted]	-57.19%
Discount rates: 1.5%	[redacted]	[redacted]	[redacted]	-37.12%
OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	17.58%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	[redacted]	-9.08%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	5.76%
OS: KM and adjusted background mortality	[redacted]	[redacted]	[redacted]	29.43%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	[redacted]	2.78%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	[redacted]	27.94%
RDI: excluded	[redacted]	[redacted]	[redacted]	3.95%
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	[redacted]	4.00%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

References

1. Takeda. Data on file: Virtual advisory board. 2024.
2. Follows GA, Barrington SF, Bhuller KS, *et al.* Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. *British Journal of Haematology*. 2022;197(5):558–572. https://doi.org/10.1111/bjh.18083.
3. Delea TE, Sharma A, Grossman A, *et al.* Cost-effectiveness of brentuximab vedotin plus chemotherapy as frontline treatment of stage III or IV classical Hodgkin lymphoma. *Journal of Medical Economics*. 2019;22(2):117–130.
4. Huntington SF, Von Keudell GR, Davidoff AJ, Gross CP, Prasad SA. Cost-effectiveness analysis of brentuximab vedotin with chemotherapy in newly diagnosed stage III/IV Hodgkin lymphoma. *Journal of Clinical Oncology Conference*. 2018;36(15):Supplement 1.
5. Moskowitz CH, Nademanee A, Masszi T, *et al.* Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 2015;385(9980):1853–1862. https://doi.org/10.1016/S0140-6736(15)60165-9.
6. Chen R, Gopal AK, Smith SE, *et al.* Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016;128(12):1562–1566. https://doi.org/10.1182/blood-2016-02-699850.
7. Woods B, Sideris E, Palmer S, Latimer N, Abrams M. NICE DSU Technical Support Document 19: partitioned survival analysis for decision modelling in health care: a critical review. (Technical Support Documents). 2017.
8. NICE. Health Technology Evaluation | Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including Review of TA594) | Final scope. 2024.
9. Mina A, Vakkalagadda C, Pro B. Novel Therapies and Approaches to Relapsed/Refractory HL Beyond Chemotherapy. *Cancers*. 2019;11(3):421. https://doi.org/10.3390/cancers11030421.
10. Potre O, Pescaru M, Sima A, *et al.* Evaluation of the Relapse Risk and Survival Rate in Patients with Hodgkin Lymphoma: A Monocentric Experience. *Medicina*. 2021;57(10):1026. https://doi.org/10.3390/medicina57101026.
11. Vassilakopoulos TP, Asimakopoulos JV, Konstantopoulos K, Angelopoulou MK. Optimizing outcomes in relapsed/refractory Hodgkin lymphoma: a review of current and forthcoming therapeutic strategies. *Therapeutic Advances in Hematology*. 2020;11:204062072090291. https://doi.org/10.1177/2040620720902911.
12. Johnson P, Federico M, Kirkwood A, *et al.* Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *New England Journal of Medicine*. 2016;374(25):2419–2429. https://doi.org/10.1056/NEJMoa1510093.
13. Luminari S, Fosså A, Trotman J, *et al.* Long Follow-up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma (RATHL) Trial (CRUK/07/033) Confirms the Safety of Both De-Escalation and Intensification of Chemotherapy. *Blood*. 2022;140(Supplement 1):766–767. https://doi.org/10.1182/blood-2022-162780.
14. Stephens DM, Li H, Schöder H, *et al.* Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. *Blood*. 2019;134(15):1238–1246. https://doi.org/10.1182/blood.2019000719.
15. Borchmann P, Goergen H, Kobe C, *et al.* PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label,

international, randomised phase 3 trial by the German Hodgkin Study Group. *The Lancet*. 2017;390(10114):2790–2802.
16. Casasnovas R-O, Bouabdallah R, Brice P, *et al.* Positron Emission Tomography–Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study. *Journal of Clinical Oncology*. 2022;40(10):1091–1101. https://doi.org/10.1200/JCO.21.01777.
17. Xavier AC, Epperla N, Taub JW, Costa LJ. Excess mortality among 10-year survivors of classical Hodgkin lymphoma in adolescents and young adults. *Am J Hematol*. 2018;93(2):238–245. https://doi.org/10.1002/ajh.24964.
18. Lia K, R. K. Jørgensen R, Wold BL, *et al.* Overall survival and causes of death in elderly patients with Hodgkin lymphoma: a Norwegian population-based case-control study. *ENEngelskEnglishOverall survival and causes of death in elderly patients with Hodgkin lymphoma: a Norwegian population-based case-control study*. 2023. https://doi.org/10.3324/haematol.2023.283721.
19. Lagerlöf I, Holte H, Glimelius I, *et al.* No excess long-term mortality in stage I-IIA Hodgkin lymphoma patients treated with ABVD and limited field radiotherapy. *Br J Haematol*. 2020;188(5):685–691. https://doi.org/10.1111/bjh.16232.
20. Bhuller KS, Zhang Y, Li D, *et al.* Late mortality, secondary malignancy and hospitalisation in teenage and young adult survivors of Hodgkin lymphoma: report of the Childhood/Adolescent/Young Adult Cancer Survivors Research Program and the BC Cancer Agency Centre for Lymphoid Cancer. *Br J Haematol*. 2016;172(5):757–768. https://doi.org/10.1111/bjh.13903.
21. Smeland KB, Kiserud CE, Lauritzsen GF, *et al.* A national study on conditional survival, excess mortality and second cancer after high dose therapy with autologous stem cell transplantation for non-Hodgkin lymphoma. *Br J Haematol*. 2016;173(3):432–443. https://doi.org/10.1111/bjh.13965.
22. Smeland KB, Kiserud CE, Lauritzsen GF, *et al.* Conditional survival and excess mortality after high-dose therapy with autologous stem cell transplantation for adult refractory or relapsed Hodgkin lymphoma in Norway. *Haematologica*. 2015;100(6):e240-243. https://doi.org/10.3324/haematol.2014.119214.
23. GBD 2019 Asia and All Cancers Collaborators. Temporal patterns of cancer burden in Asia, 1990-2019: a systematic examination for the Global Burden of Disease 2019 study. *Lancet Reg Health Southeast Asia*. 2024;21:100333. https://doi.org/10.1016/j.lansea.2023.100333.
24. Driessen J, Visser O, Zijlstra JM, *et al.* Primary therapy and relative survival in classical Hodgkin lymphoma: a nationwide population-based study in the Netherlands, 1989-2017. *Leukemia*. 2021;35(2):494–505. https://doi.org/10.1038/s41375-020-0875-0.
25. de Vries S, Schaapveld M, Kardaun JW, *et al.* Comparing causes of death of Hodgkin lymphoma and breast cancer patients between medical records and cause-of-death statistics. *Clin Epidemiol*. 2018;10:1523–1531. https://doi.org/10.2147/CLEP.S161359.
26. Boyne DJ, Mickle AT, Brenner DR, *et al.* Long-term risk of cardiovascular mortality in lymphoma survivors: A systematic review and meta-analysis. *Cancer Med*. 2018;7(9):4801–4813. https://doi.org/10.1002/cam4.1572.
27. Zhang H, He M, Zhang P, *et al.* Long-term risks of cardiovascular death among older patients with major hematological malignancies: a population-based cohort study from SEER database. *Cancer Epidemiol Biomarkers Prev*. 2024. https://doi.org/10.1158/1055-9965.EPI-23-1635.
28. Mignozzi S, Santucci C, Medina HN, Negri E, La Vecchia C, Pinheiro PS. Cancer mortality in Germany-born Americans and Germans. *Cancer Epidemiol*. 2024;88:102519. https://doi.org/10.1016/j.canep.2023.102519.

29. Liu W, Qi J, Liu J, *et al.* Mortality Rate of Lymphoma in China, 2013-2020. *Front Oncol*. 2022;12:902643. https://doi.org/10.3389/fonc.2022.902643.
30. Radkiewicz C, Bruchfeld JB, Weibull CE, *et al.* Sex differences in lymphoma incidence and mortality by subtype: A population-based study. *Am J Hematol*. 2023;98(1):23–30. https://doi.org/10.1002/ajh.26744.
31. Lamb M, Painter D, Howell D, *et al.* Lymphoid blood cancers, incidence and survival 2005-2023: A report from the UK's Haematological Malignancy Research Network. *Cancer Epidemiol*. 2024;88:102513. https://doi.org/10.1016/j.canep.2023.102513.
32. de Vries S, Schaapveld M, Janus CPM, *et al.* Long-Term Cause-Specific Mortality in Hodgkin Lymphoma Patients. *JNCI: Journal of the National Cancer Institute*. 2021;113(6):760–769. https://doi.org/10.1093/jnci/djaa194.
33. Bouliotis G, Bessell EM. Hodgkin disease (1973–2002): long-term survival and cure fractions. *Leukemia & Lymphoma*. 2015;56(5):1278–1285. https://doi.org/10.3109/10428194.2014.949259.
34. Glimelius I, Ekberg S, Jerkeman M, *et al.* Long-term survival in young and middle-aged Hodgkin lymphoma patients in Sweden 1992-2009-trends in cure proportions by clinical characteristics. *Am J Hematol*. 2015;90(12):1128–1134. https://doi.org/10.1002/ajh.24184.
35. Núñez-García B, Clemente MB, Sánchez JC, *et al.* Long-term outcomes in Hodgkin lymphoma survivors. Temporary trends and comparison with general population. *Hematol Oncol*. 2023;41(3):407–414. https://doi.org/10.1002/hon.3131.
36. Straus DJ, Długosz-Danecka M, Connors JM, *et al.* Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2021;8(6):e410–e421. https://doi.org/10.1016/S2352-3026(21)00102-2.
37. Ansell SM, Radford J, Connors JM, *et al.* Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. *N Engl J Med*. 2022;387(4):310–320. https://doi.org/10.1056/NEJMoa2206125.
38. Dores GM, Curtis RE, Dalal NH, Linet MS, Morton LM. Cause-Specific Mortality Following Initial Chemotherapy in a Population-Based Cohort of Patients With Classical Hodgkin Lymphoma, 2000-2016. *J Clin Oncol*. 2020;38(35):4149–4162. https://doi.org/10.1200/JCO.20.00264.
39. Perez-Callejo D, Zurutuza L, Royuela A, *et al.* Long-term follow up of Hodgkin lymphoma. *Oncotarget*. 2018;9(14):11638–11645. https://doi.org/10.18632/oncotarget.24392.
40. pCODR EXPERT REVIEW COMMITTEE. Seattle Genetics Inc submission. For the treatment of previously untreated patients with stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine. FINAL RECOMMENDATION. 2020.
41. Vijenthira A, Chan K, Cheung M, Prica A. Cost-Effectiveness and Cost-Utility Analysis of ABVD Versus Beacopp in the treatment of advanced-stage hodgkin lymphoma. *Blood*. 2018;132:2248.
42. Vijenthira A, Chan K, Cheung MC, Prica A. Cost-effectiveness of first-line treatment options for patients with advanced-stage Hodgkin lymphoma: a modelling study. *The Lancet Haematology*. 2020;7(2):e146–e156.
43. NICE. TA641: Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma. 08/12/2020. Last accessed: 04/10/2024. https://www.nice.org.uk/guidance/ta641.

44. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leukemia & Lymphoma*. 2015.
45. NICE. TA874: Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta874/ [last accessed: 09/01/2024]. 2023.
46. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6:84. https://doi.org/10.1186/1477-7525-6-84.
47. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. *Curr Med Res Opin*. 2010;26(5):1091–1096. https://doi.org/10.1185/03007991003712258.
48. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer*. 2006;95(6):683–690. https://doi.org/10.1038/sj.bjc.6603326.
49. NICE. TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta872/ [last accessed: 09/01/2024]. 2023.
50. NICE. TA677: Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta677/ [last accessed: 09/01/2024]. 2021.
51. NICE. TA567: Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta567/ [last accessed: 09/01/2024]. 2019.
52. NICE. NICE health technology evaluations: the manual. 01/31/2022. Last accessed: 04/01/2024. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.
53. Dias S, Sutton AJ, Welton NJ, Ades A. NICE DSU Technical Support Document 6: embedding evidence synthesis in probabilistic cost-effectiveness analysis: software choices. (Technical Support Documents). 2011.
54. Mei M, Chen R. How to Approach a Hodgkin Lymphoma Patient With Relapse After Autologous SCT: Allogeneic SCT. *Clinical Lymphoma, Myeloma and Leukemia*. 2018;18(1):26–33. https://doi.org/10.1016/j.clml.2017.11.003.
55. Samara Y, Mei M. Autologous Stem Cell Transplantation in Hodgkin Lymphoma—Latest Advances in the Era of Novel Therapies. *Cancers (Basel)*. 2022;14(7):1738. https://doi.org/10.3390/cancers14071738.
56. BSBMTCT. 2022 UK & ROI Transplant Activity Table by Disease. *British Society of Blood and Marrow Transplantation*. 2022. Last accessed: 05/22/2024. https://bsbmtct.org/activity/2022/.
57. Armand P, Zinzani PL, Lee HJ, *et al.* Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. *Blood*. 2023;142(10):878–886. https://doi.org/10.1182/blood.2022019386.
58. Ansell SM, Bröckelmann PJ, von Keudell G, *et al.* Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study. *Blood Advances*. 2023;7(20):6266–6274. https://doi.org/10.1182/bloodadvances.2023010334.
59. NICE. TA446: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 06/28/2017. Last accessed: 04/11/2024. https://www.nice.org.uk/guidance/ta446.

60. NICE. TA462: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. Committee papers. 2017. Last accessed: 05/22/2024. https://www.nice.org.uk/guidance/ta462/documents/committee-papers-2.
61. NICE. TA462: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. 2017. Last accessed: 10/19/2023. https://www.nice.org.uk/guidance/ta462.
62. EMC. Opdivo (nivolumab) 10 mg/ml concentrate for solution for infusion. SmPC. 2024. Last accessed: 05/22/2024. https://www.medicines.org.uk/emc/product/6888/smpc.
63. PSSRU. Unit Costs of Health and Social Care. 2022. Last accessed: 03/20/2024. https://kar.kent.ac.uk/100519/1/Unit%20Costs%20of%20health%20and%20Social%20Care%202022%20%28amended%2013%20July%202023%29.pdf.
64. US Department of Health and Human Services, National Intitutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Quick reference. 2017.
65. NHS England. 2021/22 National Cost Collection Data Publication (2023). Accessed at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. Last accessed on: 09/01/2024. 2023. .
66. Hoppe RT, Advani RH, Ai WZ, *et al.* NCCN Guidelines® Insights: Hodgkin Lymphoma, Version 2.2022. *J Natl Compr Canc Netw*. 2022;20(4):322–334. https://doi.org/10.6004/jnccn.2022.0021.

Appendix

Additional survival analyses

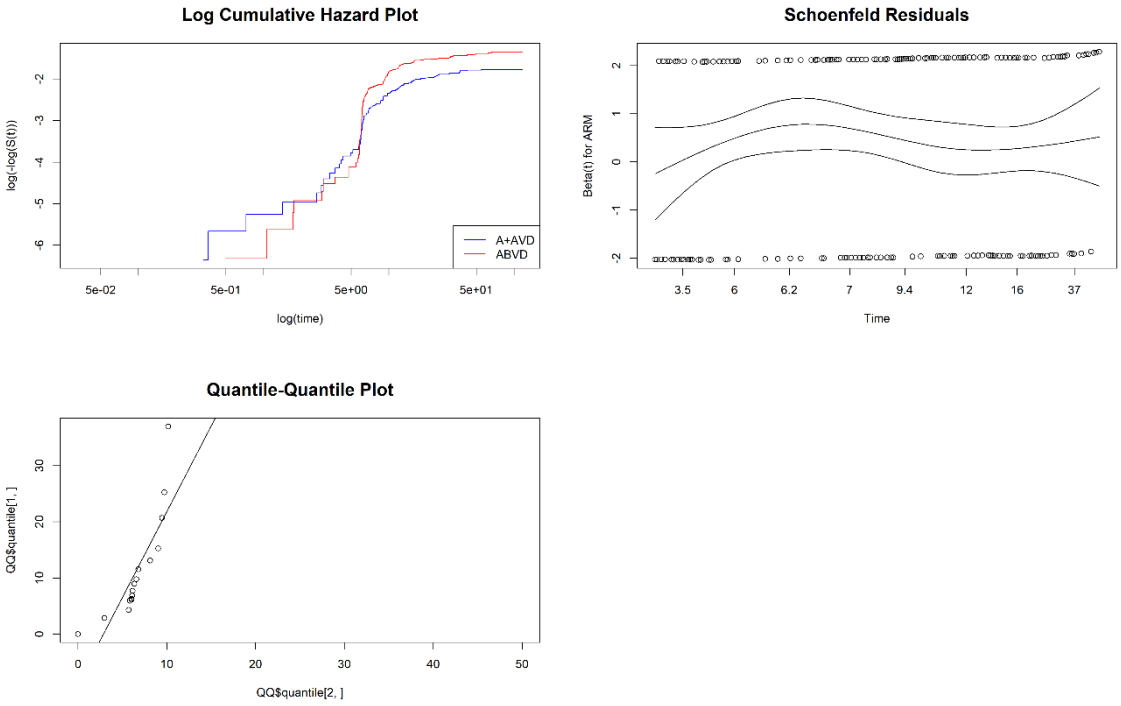
Age subgroup <60 years

PFS

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS are presented in Figure 43. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.9564. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold.

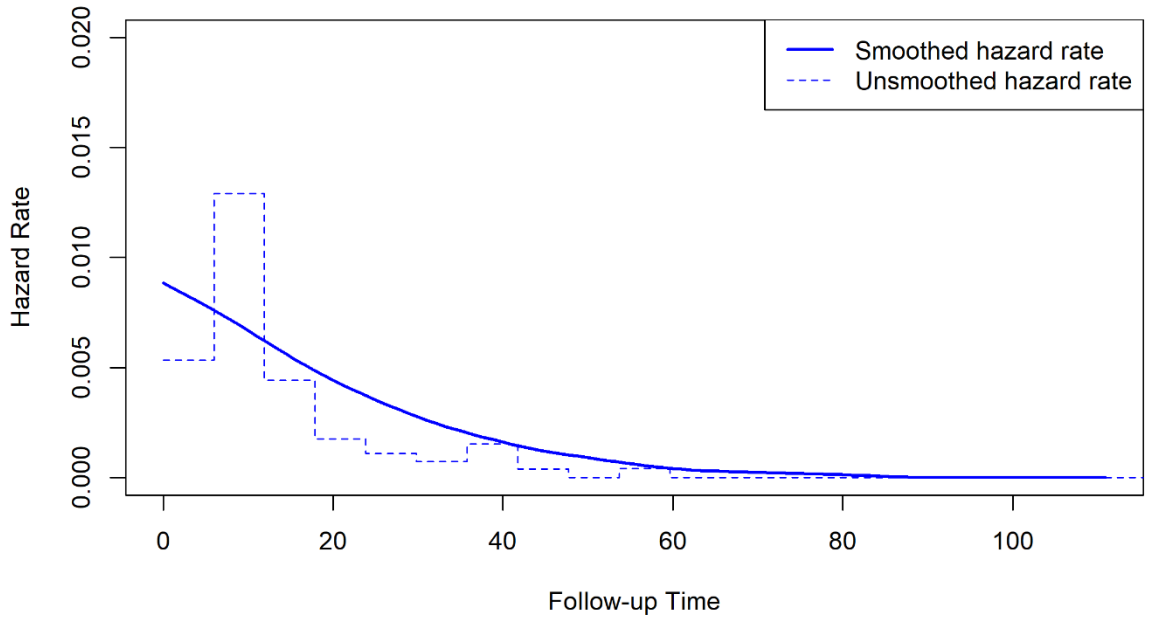
This is further supported by the different shapes shown in the observed hazard plots; the hazard of progression or death is shown to gradually decrease in the A+AVD arm (Figure 44), whereas the hazard of progression or death is shown to first increase before gradually decreasing in the ABVD arm (Figure 45). Additionally, the log-cumulative hazard plots are not straight lines, indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold (Figure 43). Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case.

Figure 43: PFS proportional hazards and accelerated failure time tests (<60-years)



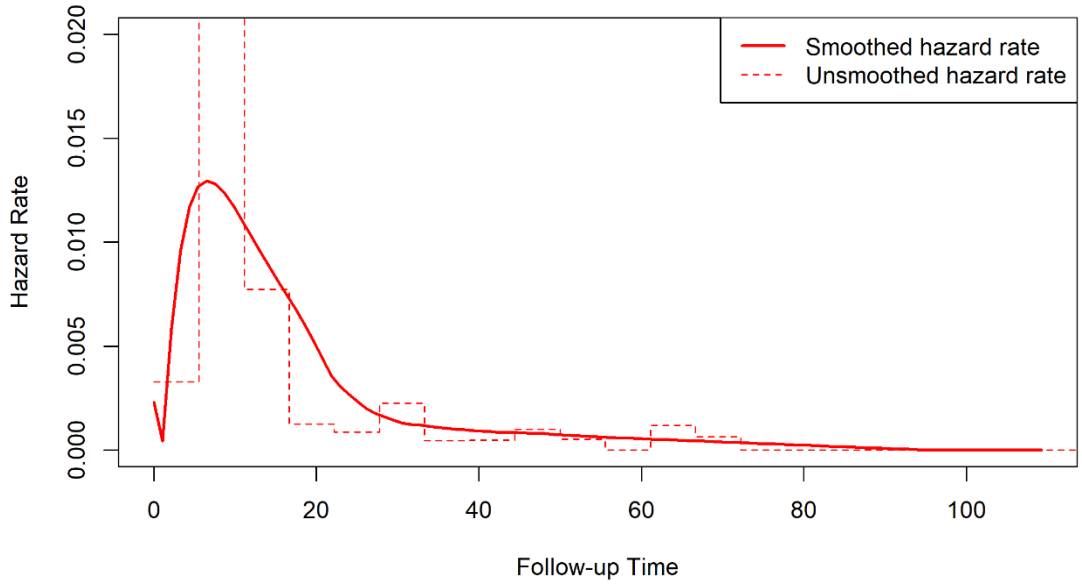
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 44: Observed hazards | A+AVD | PFS per INV (<60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

Figure 45: Observed hazards | ABVD | PFS per INV (<60 years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 46 presents the extrapolated independent standard parametric curves for A+AVD, excluding adjusted background mortality across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 59 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 47.

Figure 46: PFS independent standard parametric models | A+AVD (<60 years)

[redacted]

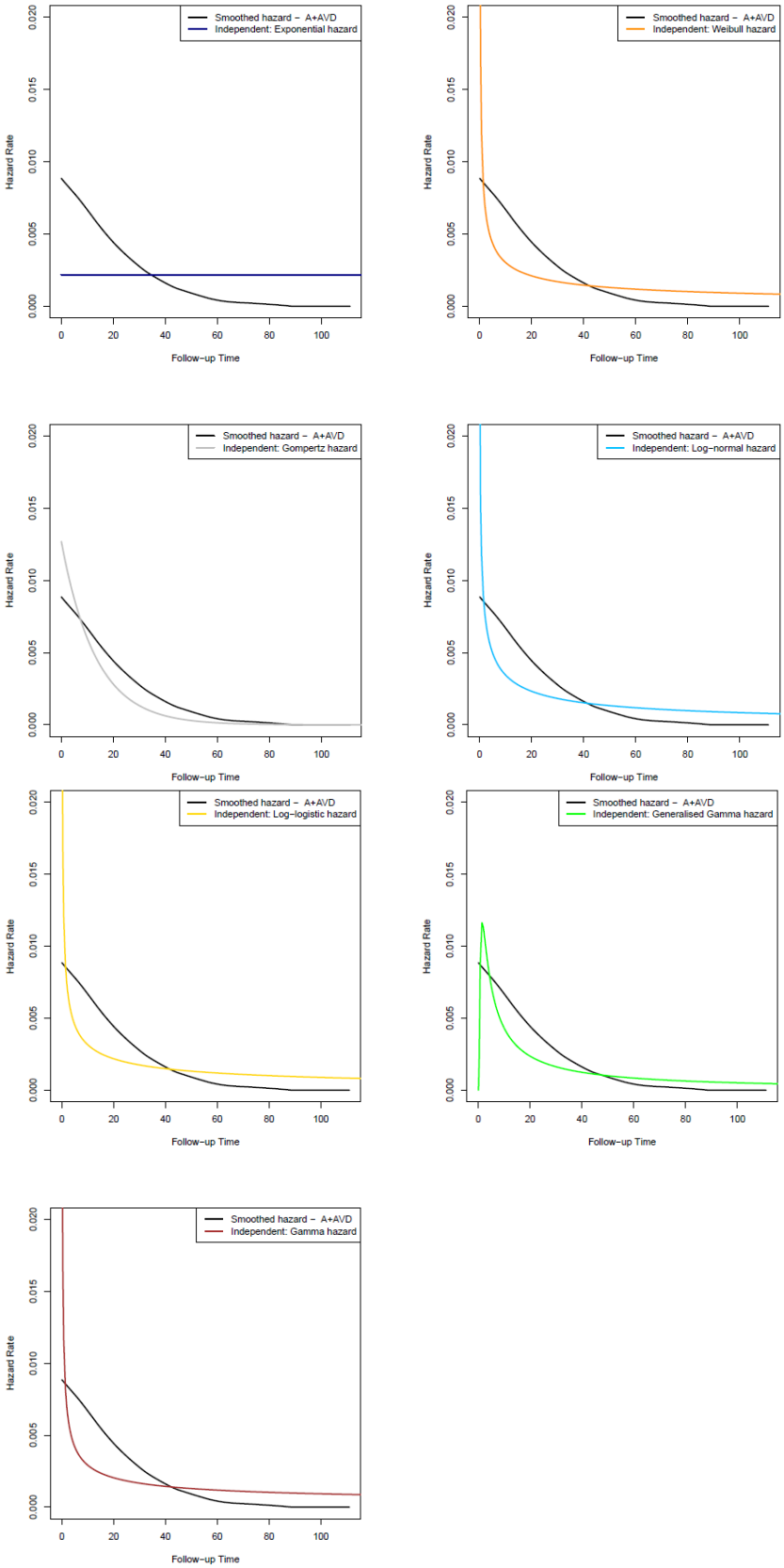
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 59: PFS independent standard parametric models AIC and BIC values | A+AVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	1242	7	1247	7
Weibull	1175	5	1183	5
Lognormal	1159	3	1168	3
Loglogistic	1171	4	1180	4
Gompertz	1095	1	1104	1
Generalised Gamma	1131	2	1144	2
Gamma	1178	6	1186	6

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 47: Comparison of predicted independent standard parametric models and observed hazards for PFS | A+AVD (<60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 48 presents the extrapolated independent standard parametric curves for ABVD, excluding adjusted background mortality across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 60 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 49.

Figure 48: PFS independent standard parametric models | ABVD (<60 years)

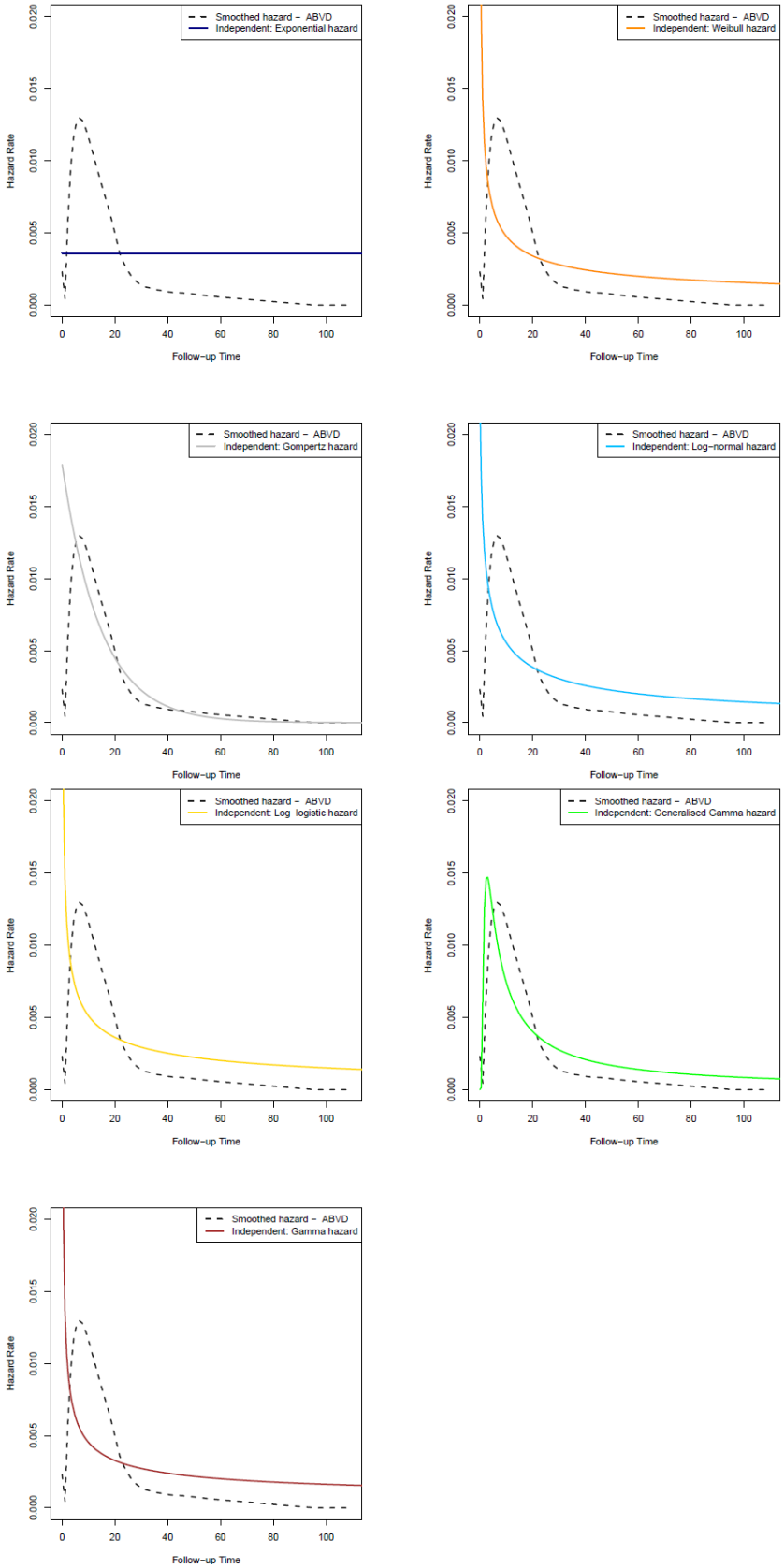
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 60: PFS independent standard parametric models AIC and BIC values | ABVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	1620	7	1625	7
Weibull	1542	5	1551	5
Lognormal	1516	3	1524	3
Loglogistic	1534	4	1543	4
Gompertz	1440	1	1449	1
Generalised Gamma	1459	2	1472	2
Gamma	1548	6	1557	6

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 49: Comparison of predicted independent standard parametric models and observed hazards for PFS | ABVD (<60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 50 presents the extrapolated independent MCM parametric curves for A+AVD – excluding adjusted background mortality – across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 61 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 51.

Figure 50: PFS independent MCM parametric models | A+AVD (<60 years)

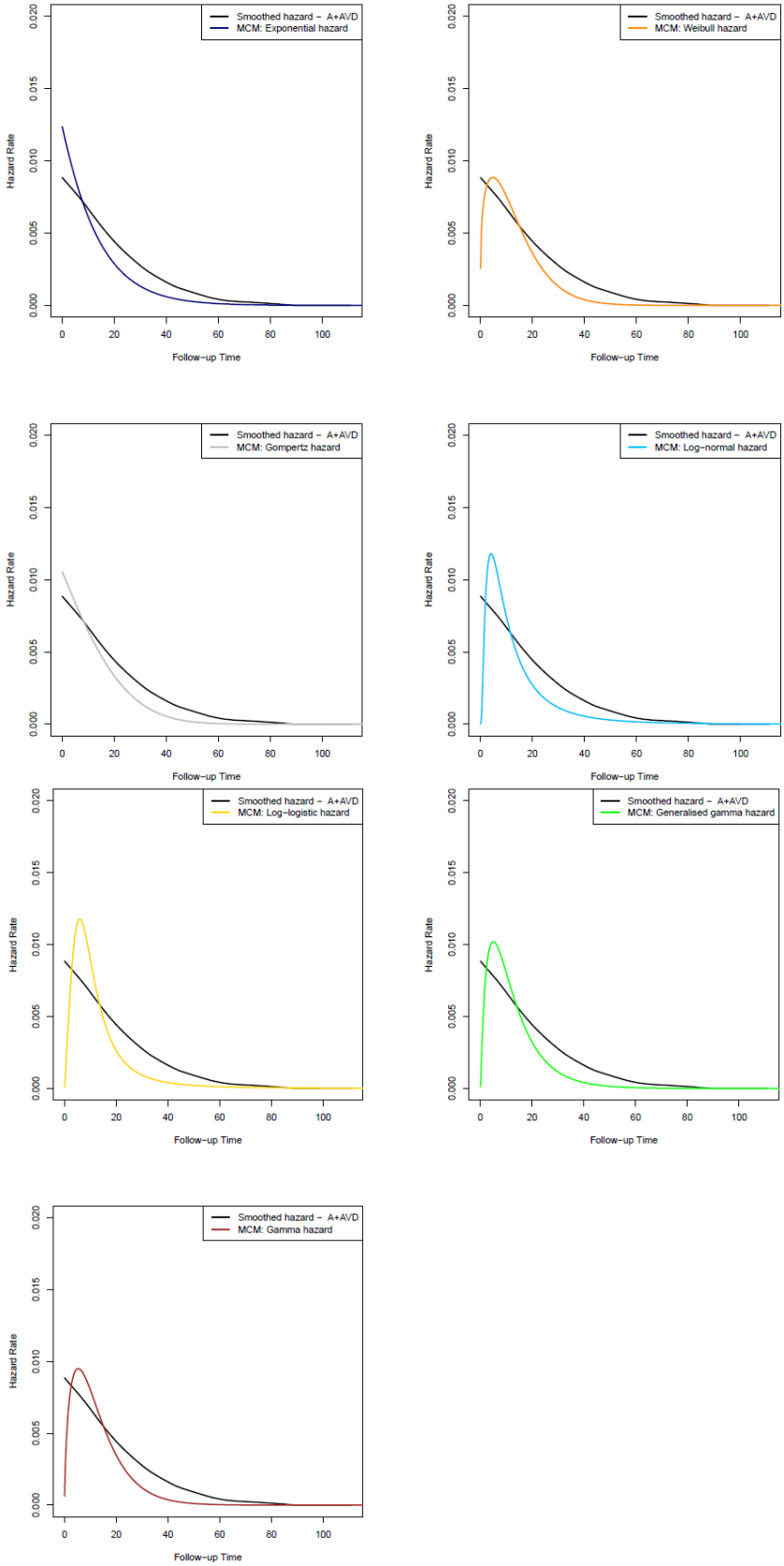
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 61: PFS independent MCM parametric models AIC and BIC values | A+AVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1094	7	1103	4
MCM: Weibull	1087	4	1101	3
MCM: Lognormal	1091	5	1104	6
MCM: Loglogistic	1080	1	1093	1
MCM: Gompertz	1094	6	1107	7
MCM: Generalised Gamma	1086	3	1103	5
MCM: Gamma	1085	2	1098	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 51: Comparison of predicted independent MCM parametric models and observed hazards for PFS | A+AVD (<60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 52 presents the extrapolated independent MCM parametric curves for ABVD, excluding adjusted background mortality across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 62 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 53.

Figure 52: PFS independent MCM parametric models | ABVD (<60 years)

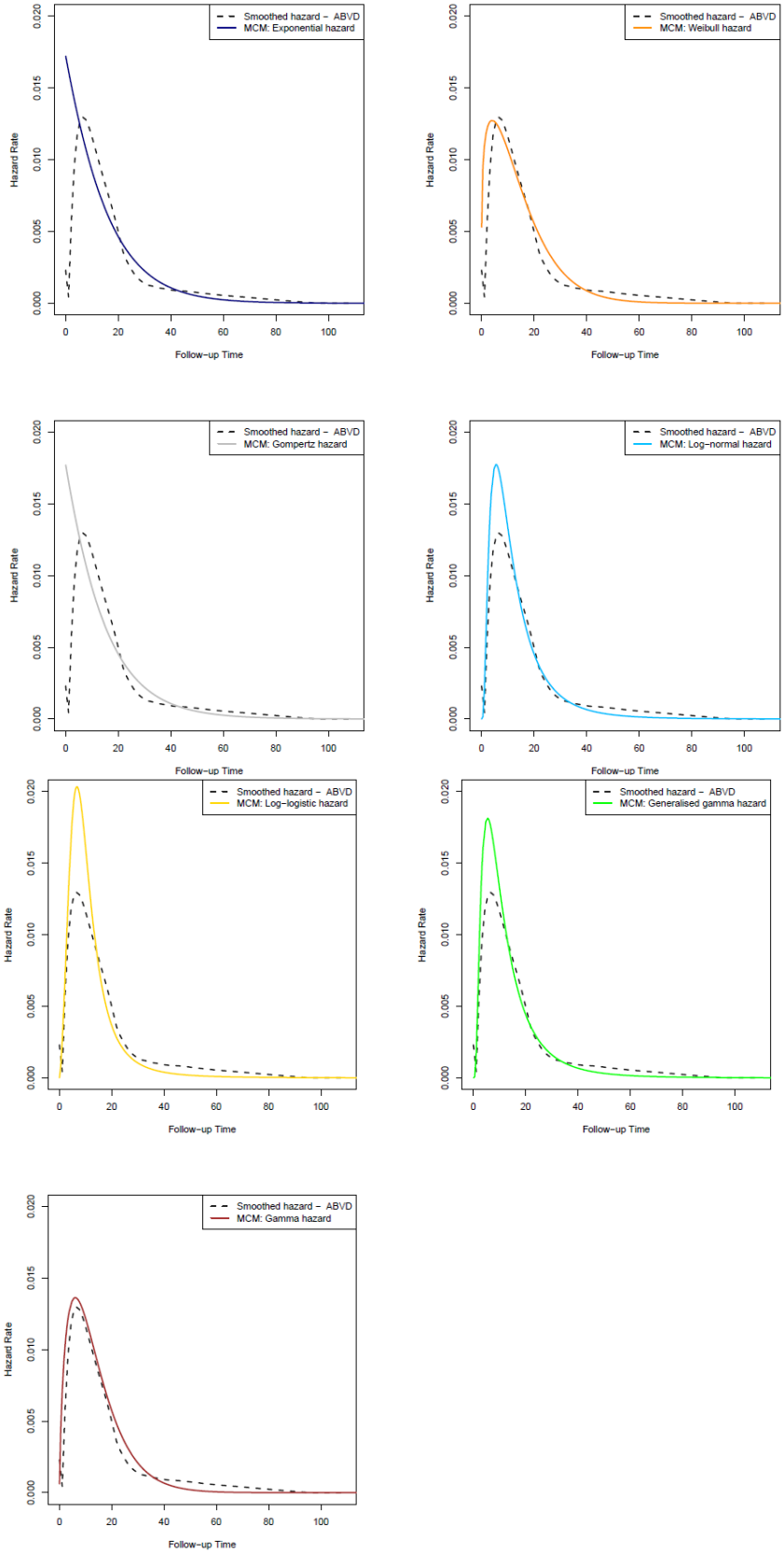
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 62: PFS independent MCM parametric models AIC and BIC values | ABVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1439	6	1448	6
MCM: Weibull	1433	5	1446	5
MCM: Lognormal	1399	2	1412	2
MCM: Loglogistic	1386	1	1399	1
MCM: Gompertz	1441	7	1454	7
MCM: Generalised Gamma	1401	3	1418	3
MCM: Gamma	1422	4	1435	4

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 53: Comparison of predicted independent MCM parametric models and observed hazards for PFS | ABVD (<60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 54 presents the extrapolated independent one-knot spline parametric curves for A+AVD, excluding adjusted background mortality across a 20-year time horizon. Note: the one-knot normal was unable to converge. Therefore, this is not presented. The corresponding AIC and BIC values are presented in Table 63 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 55.

Figure 54: PFS independent one-knot splines parametric models | A+AVD (<60 years)

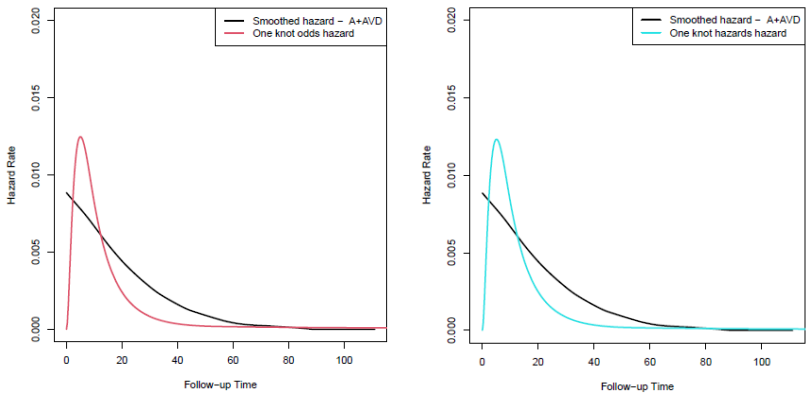
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 63: PFS independent one-knot splines parametric models AIC and BIC values | A+AVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	1087	2	1100	2
One-knot hazard	1087	1	1100	1
One-knot normal	NA	NA	NA	NA

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 55: Comparison of predicted independent one-knot splines parametric models and observed hazards for PFS | A+AVD (<60-years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival.

Figure 56 presents the extrapolated independent one-knot splines parametric curves for ABVD – excluding adjusted background mortality – across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 64 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 57.

Figure 56: PFS independent one-knot splines parametric models | ABVD (<60-years)

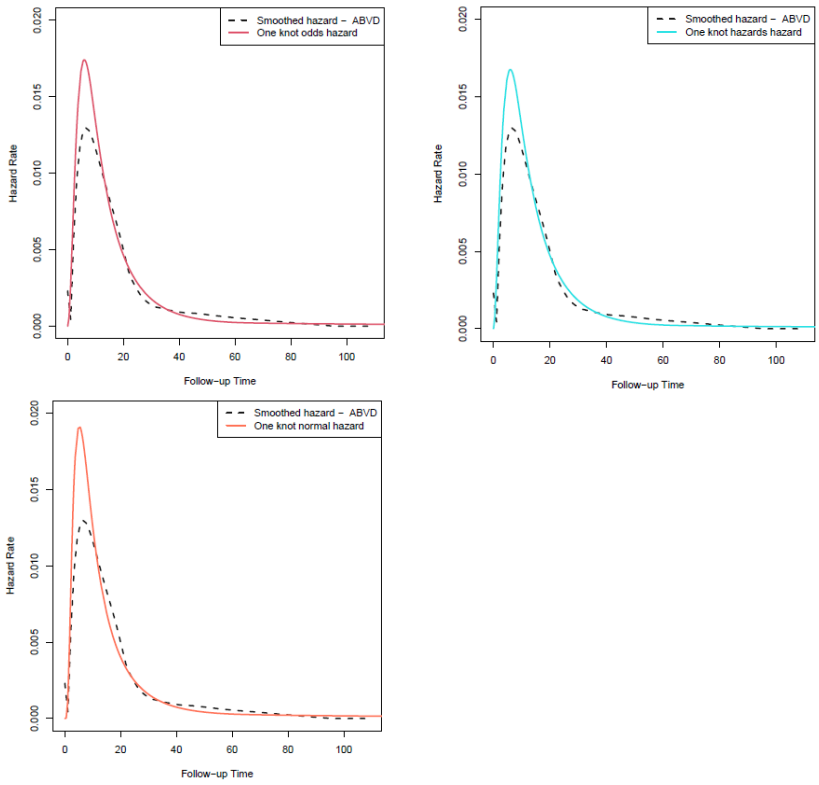
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 64: PFS independent one-knot splines parametric models AIC and BIC values | ABVD (<60-years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	1393	1	1406	1
One-knot hazard	1395	2	1408	2
One-knot normal	1397	3	1410	3

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 57: Comparison of predicted independent one-knot splines parametric models and observed hazards for PFS | ABVD (<60-years)



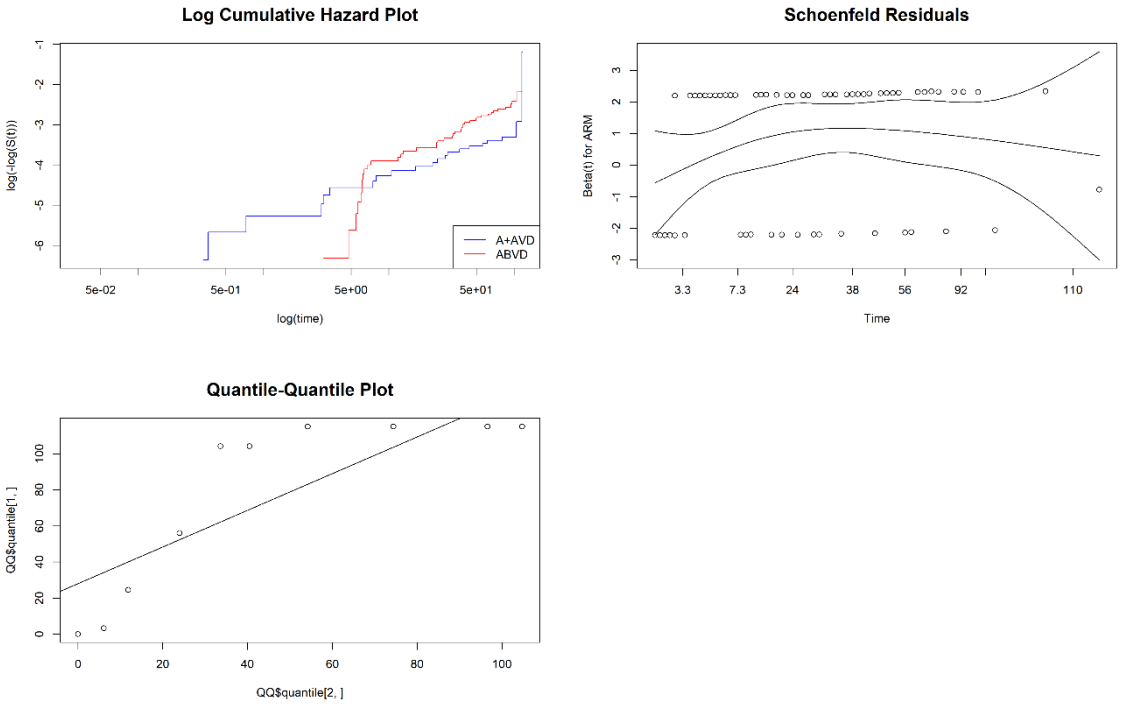
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

OS

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for OS are presented in. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.2509. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold.

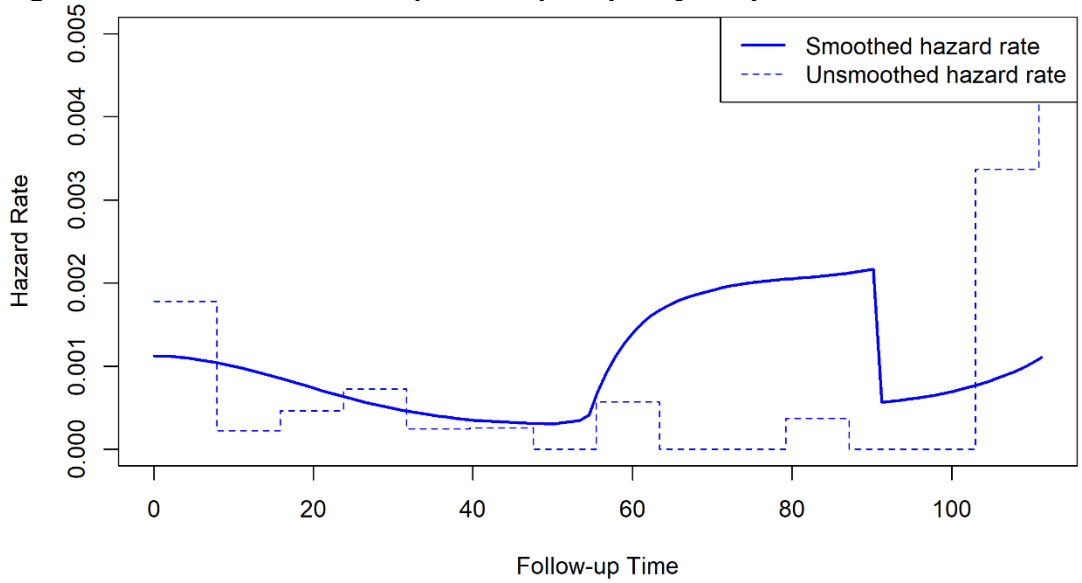
Additionally, the log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold (Figure 58). Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case. The shape of the observed hazards shown in the hazard plots are similar for A+AVD and ABVD; Figure 59 and Figure 60 for A+AVD and ABVD, respectively.

Figure 58: OS proportional hazards and accelerated failure time tests (<60-years)



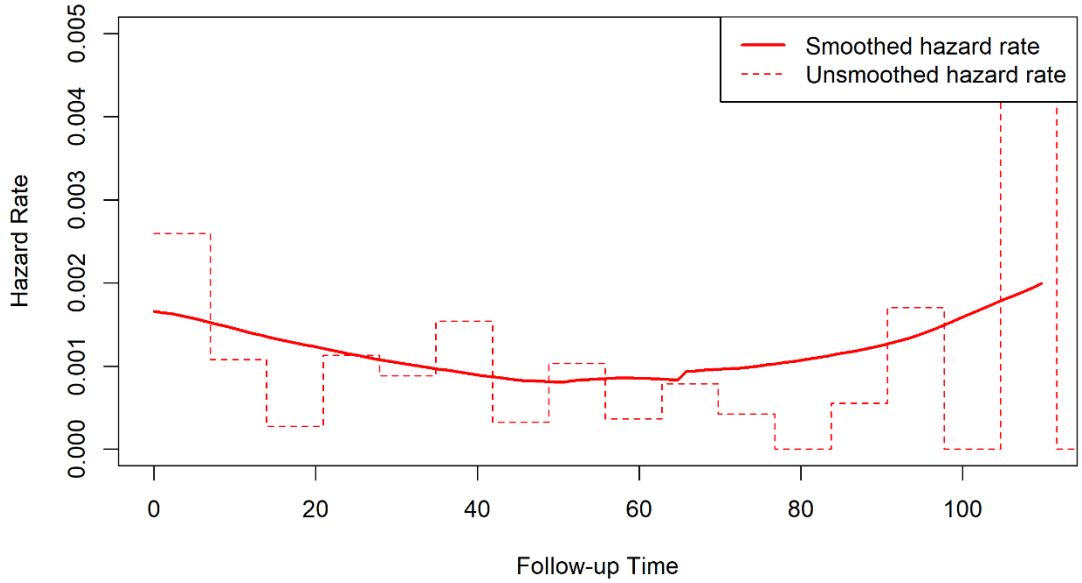
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival.

Figure 59: Observed hazards | A+AVD | OS (<60-years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 60: Observed hazards | ABVD | OS (<60-years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival.

Figure 61 presents the extrapolated independent standard parametric curves for A+AVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 65 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 62.

Figure 61: OS independent standard parametric models | A+AVD (<60-years)

[redacted]

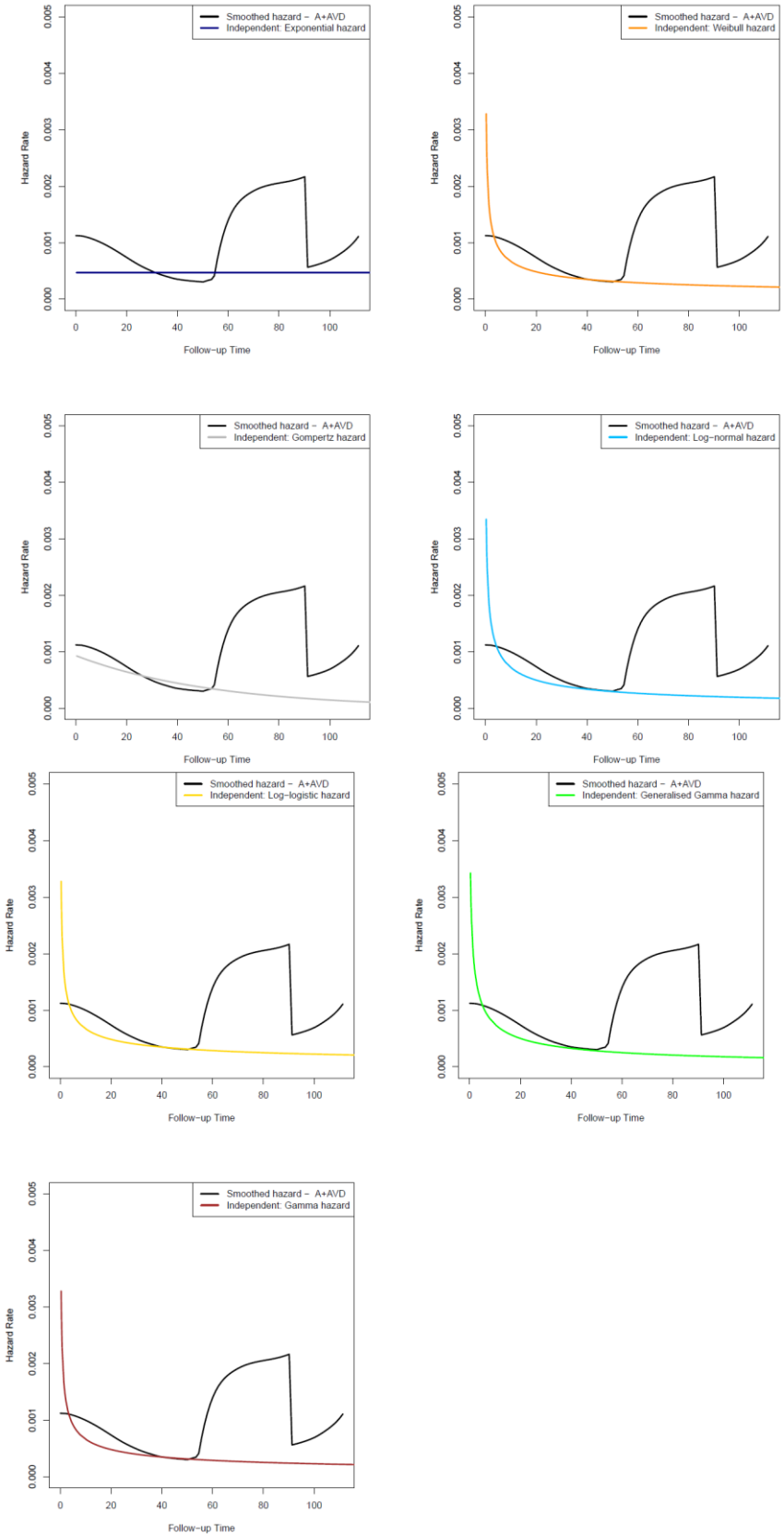
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 65: OS independent standard parametric models AIC and BIC values | A+AVD (<60-years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	366	7	370	5
Weibull	357	3	366	3
Lognormal	357	1	365	1
Loglogistic	357	4	366	4
Gompertz	363	6	372	7
Generalised Gamma	359	5	372	6
Gamma	357	2	366	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 62: Comparison of predicted independent standard parametric models and observed hazards for OS | A+AVD (<60-years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, progression-free survival

Figure 63 presents the extrapolated independent standard parametric curves for ABVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 66 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 64.

Figure 63: OS independent standard parametric models | ABVD (<60-years)

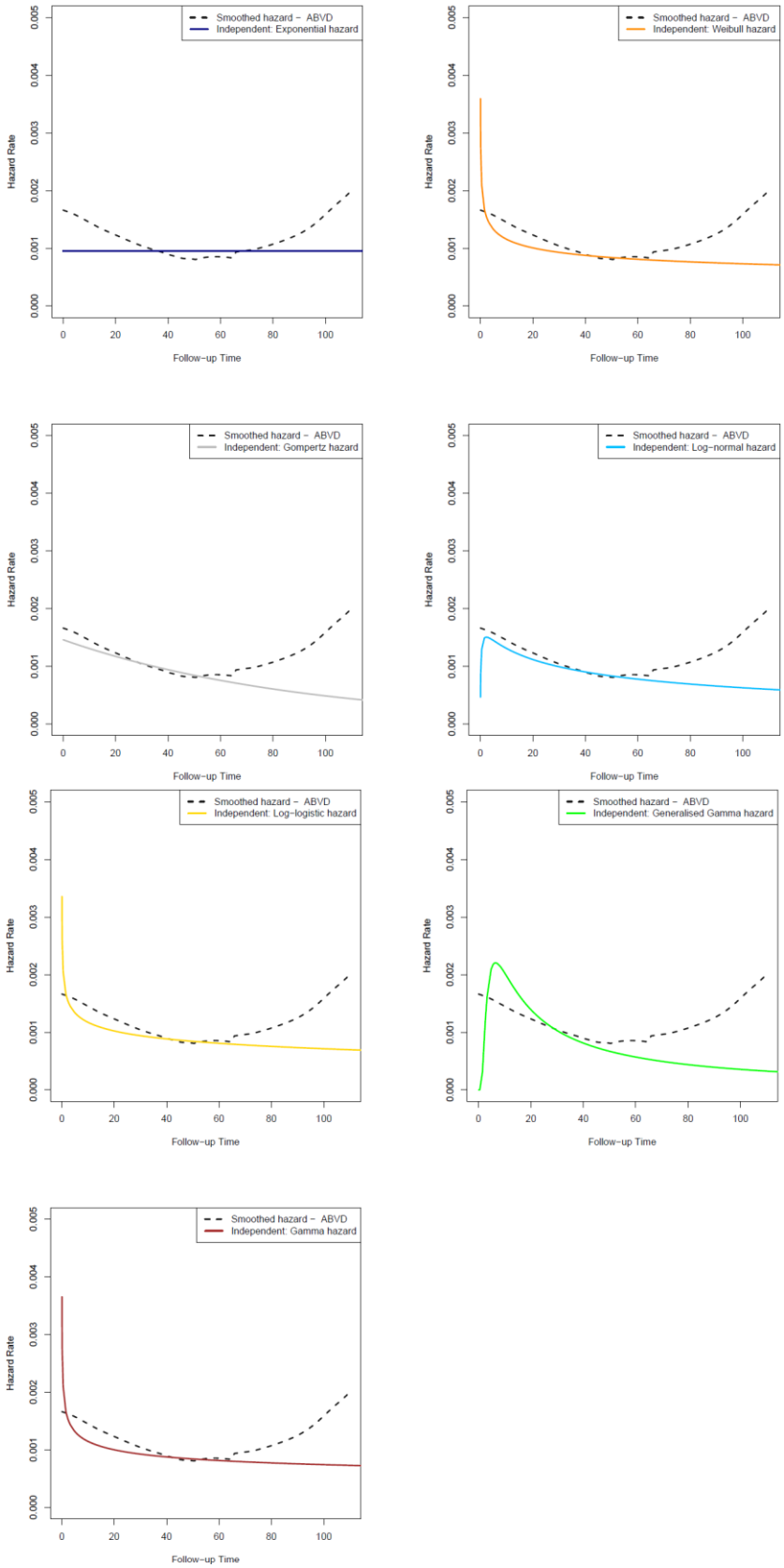
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 66: OS independent standard parametric models AIC and BIC values | ABVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	622	7	627	1
Weibull	622	5	631	5
Lognormal	620	2	629	2
Loglogistic	622	4	631	4
Gompertz	621	3	630	3
Generalised Gamma	619	1	632	7
Gamma	622	6	631	6

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 64: Comparison of predicted independent standard parametric models and observed hazards for OS | ABVD (<60-years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 65 presents the extrapolated independent MCM parametric curves for A+AVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 67 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 66.

Figure 65: OS independent MCM parametric models | A+AVD (<60-years)

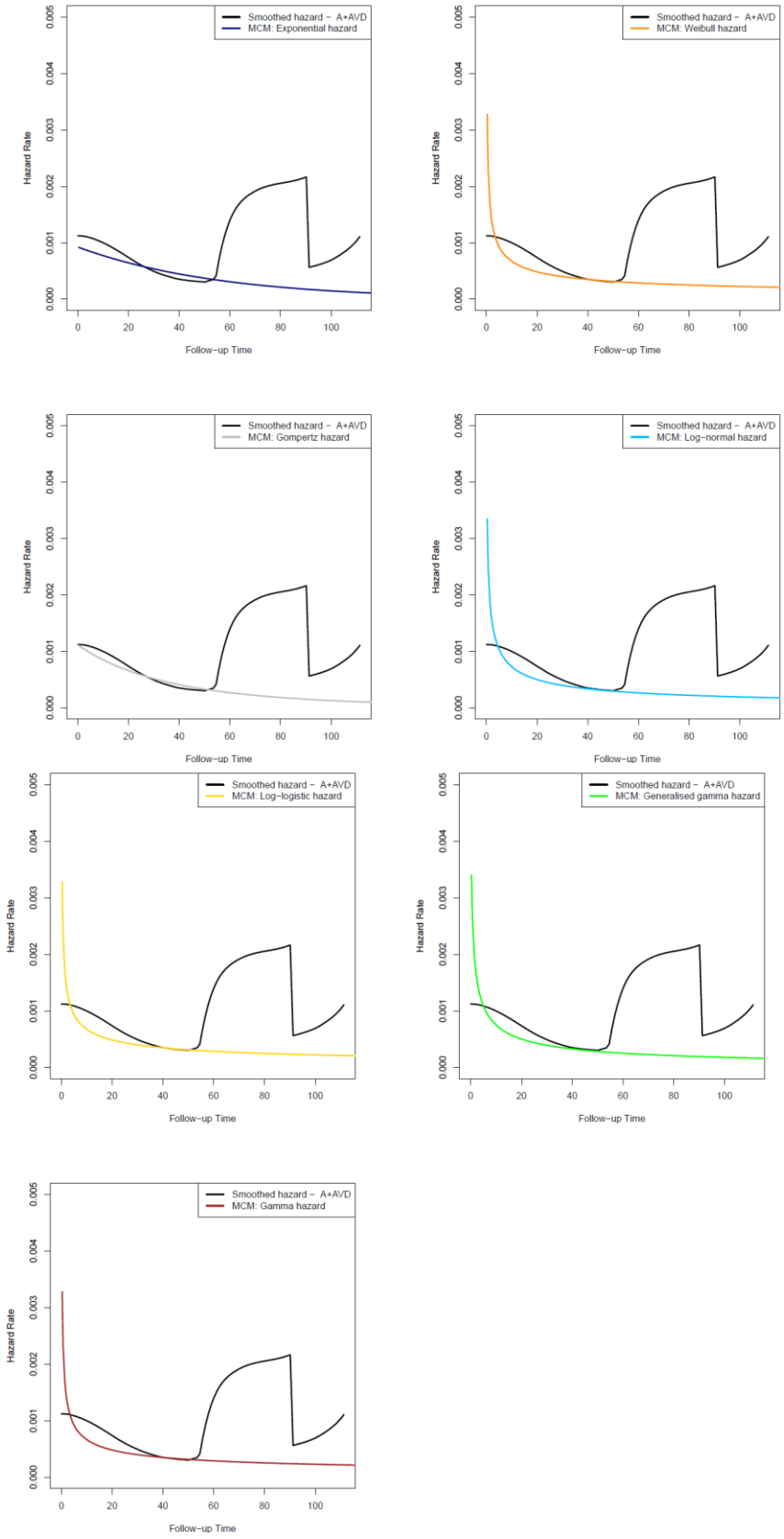
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 67: OS independent MCM parametric models AIC and BIC values | A+AVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	363	6	372	4
MCM: Weibull	359	3	372	3
MCM: Lognormal	359	1	372	1
MCM: Loglogistic	359	4	372	5
MCM: Gompertz	364	7	377	6
MCM: Generalised Gamma	361	5	378	7
MCM: Gamma	359	2	372	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 66: Comparison of predicted independent MCM parametric models and observed hazards for OS | A+AVD (<60-years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 67 presents the extrapolated independent MCM parametric curves for ABVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 69 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 68.

Figure 67: OS independent MCM parametric models | ABVD (<60-years)

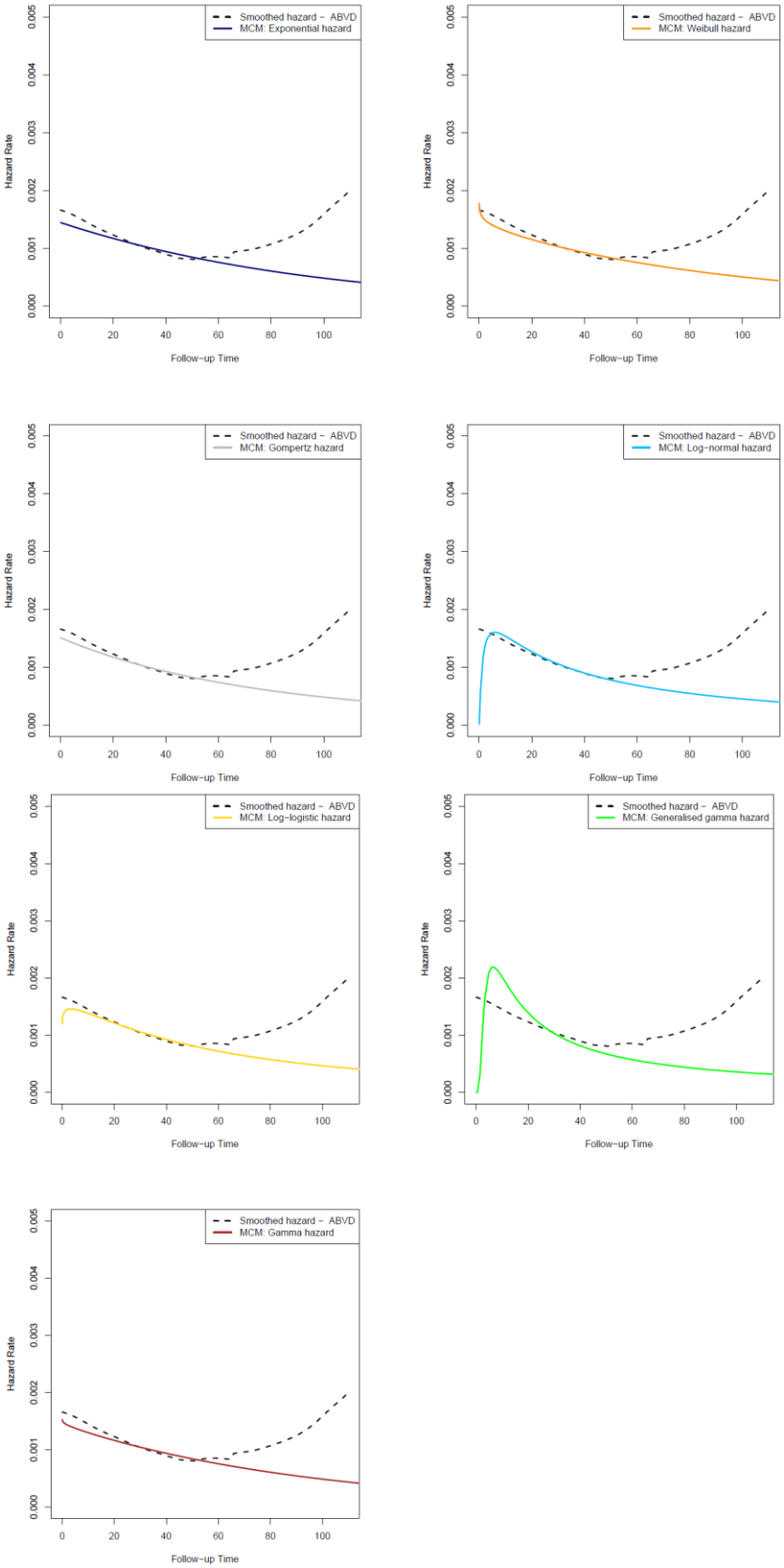
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 68: OS independent MCM parametric models AIC and BIC values | ABVD (<60-years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	621	3	630	1
MCM: Weibull	623	6	636	5
MCM: Lognormal	621	1	634	2
MCM: Loglogistic	623	4	636	3
MCM: Gompertz	623	5	636	4
MCM: Generalised Gamma	621	2	638	7
MCM: Gamma	623	7	636	6

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 68: Comparison of predicted independent MCM parametric models and observed hazards for OS | ABVD (<60-years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 69 presents the extrapolated independent one-knot spline parametric curves for A+AVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 69 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 70.

Figure 69: OS independent one-knot splines parametric models | A+AVD (<60-years)

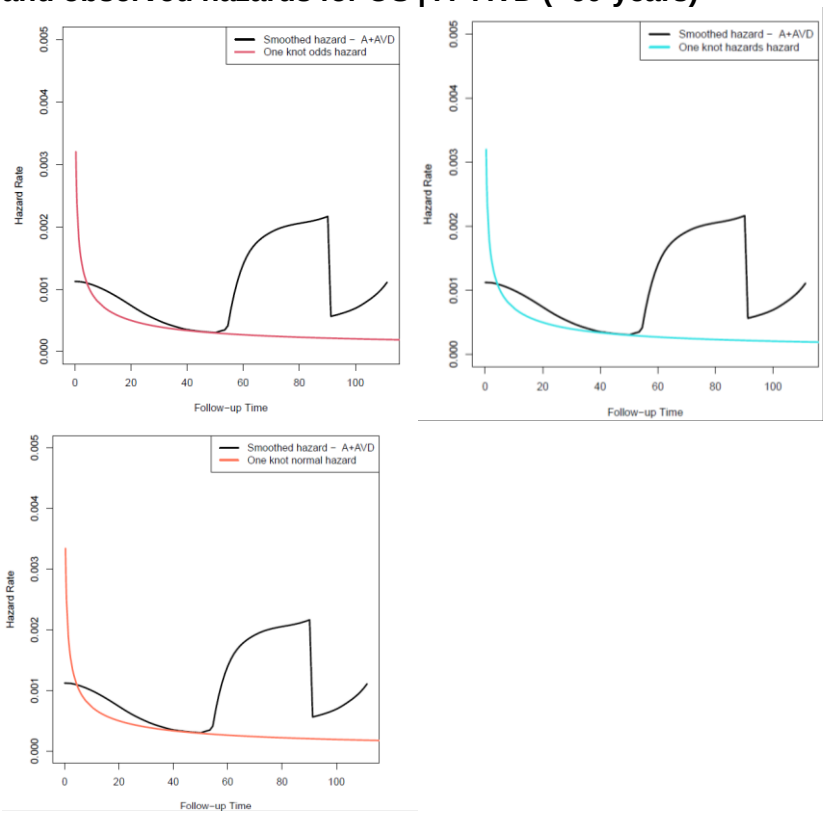
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 69: OS independent one-knot splines parametric models AIC and BIC values | A+AVD (<60-years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	359	3	372	3
One-knot hazard	359	2	372	2
One-knot normal	359	1	372	1

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 70: Comparison of predicted independent one-knot splines parametric models and observed hazards for OS | A+AVD (<60-years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 71 presents the extrapolated independent one-knot splines parametric curves for ABVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 70 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 72.

Figure 71: OS independent one-knot splines parametric models | ABVD (<60-years)

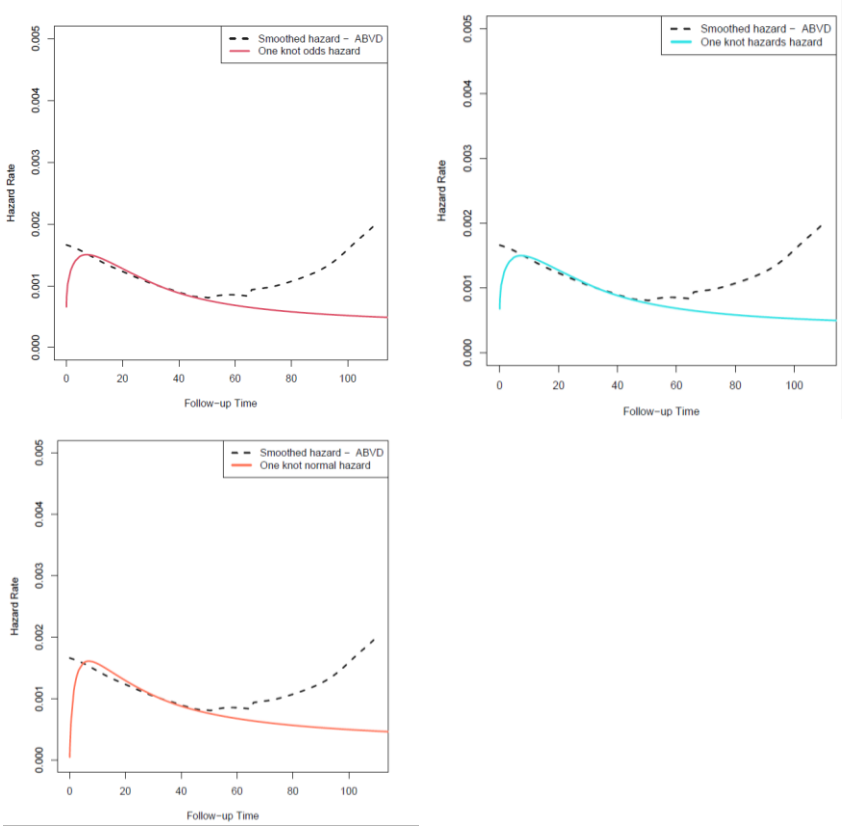
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 70: OS independent one-knot splines parametric models AIC and BIC values | ABVD (<60-years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	622	3	635	3
One-knot hazard	622	2	635	2
One-knot normal	621	1	634	1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 72: Comparison of predicted independent one-knot splines parametric models and observed hazards for OS | ABVD (<60-years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival.

Age subgroup ≥60 years

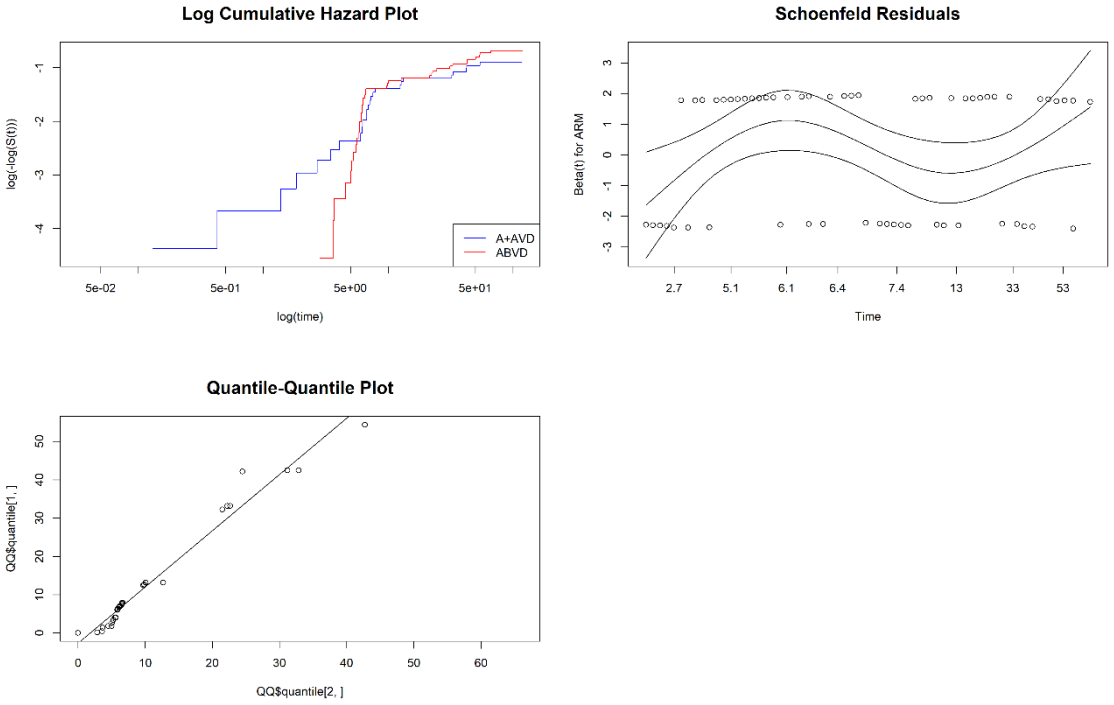
PFS

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS are presented in Figure 73. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.5967. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold.

Additionally, the log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold (Figure 73). Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case.

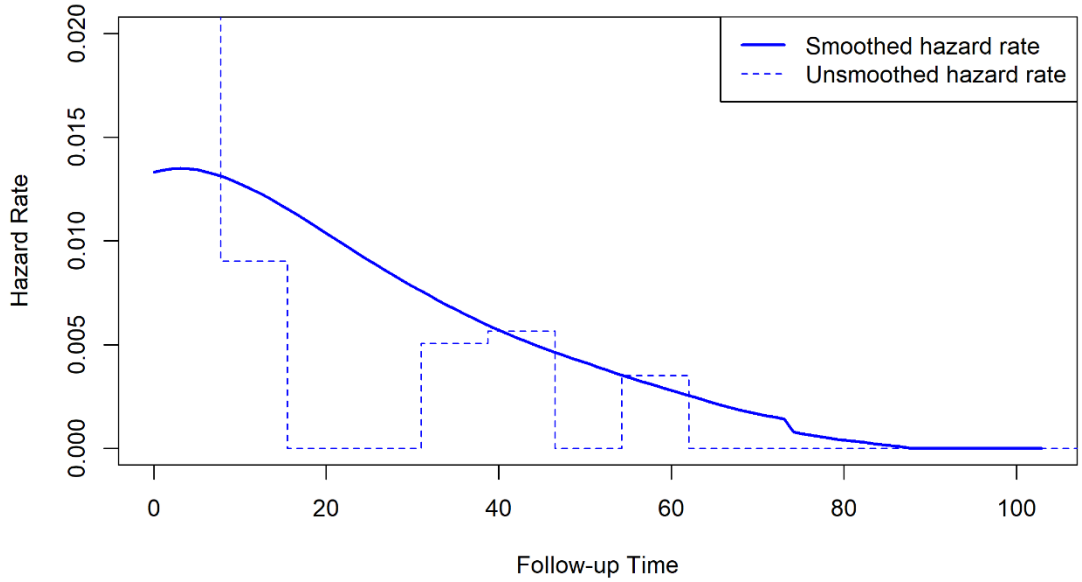
The shape of the observed hazards shown in the hazard plots are similar for A+AVD and ABVD; Figure 74 and Figure 75 for A+AVD and ABVD, respectively.

Figure 73: PFS proportional hazards and accelerated failure time tests (≥60 years)



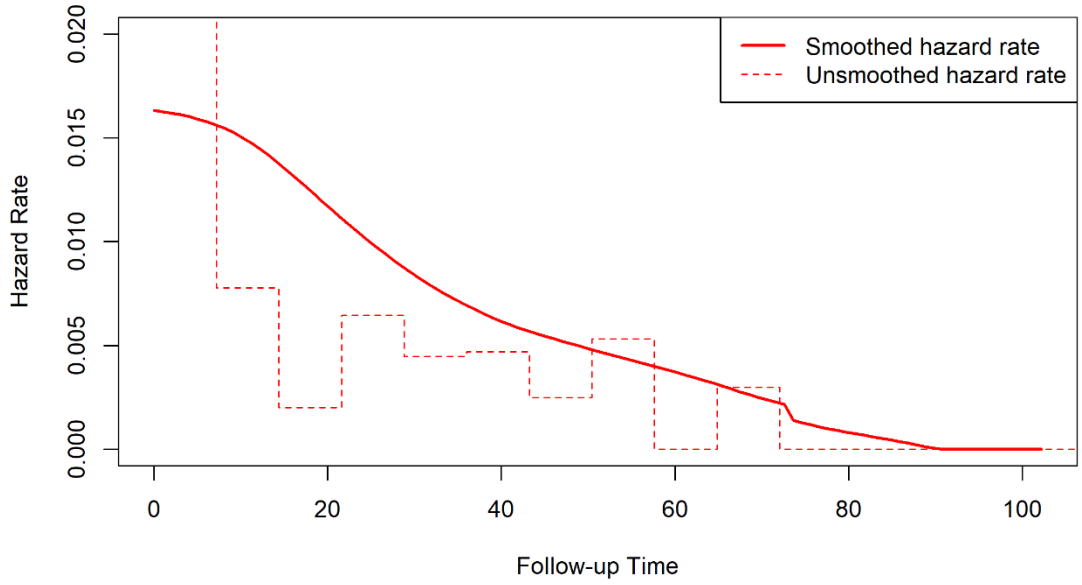
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 74: Observed hazards | A+AVD | PFS per INV (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

Figure 75: Observed hazards | ABVD | PFS per INV (≥60 years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 76 presents the extrapolated independent standard parametric curves for A+AVD, excluding adjusted background mortality across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 71 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 77.

Figure 76: PFS independent standard parametric models | A+AVD (≥60 years)

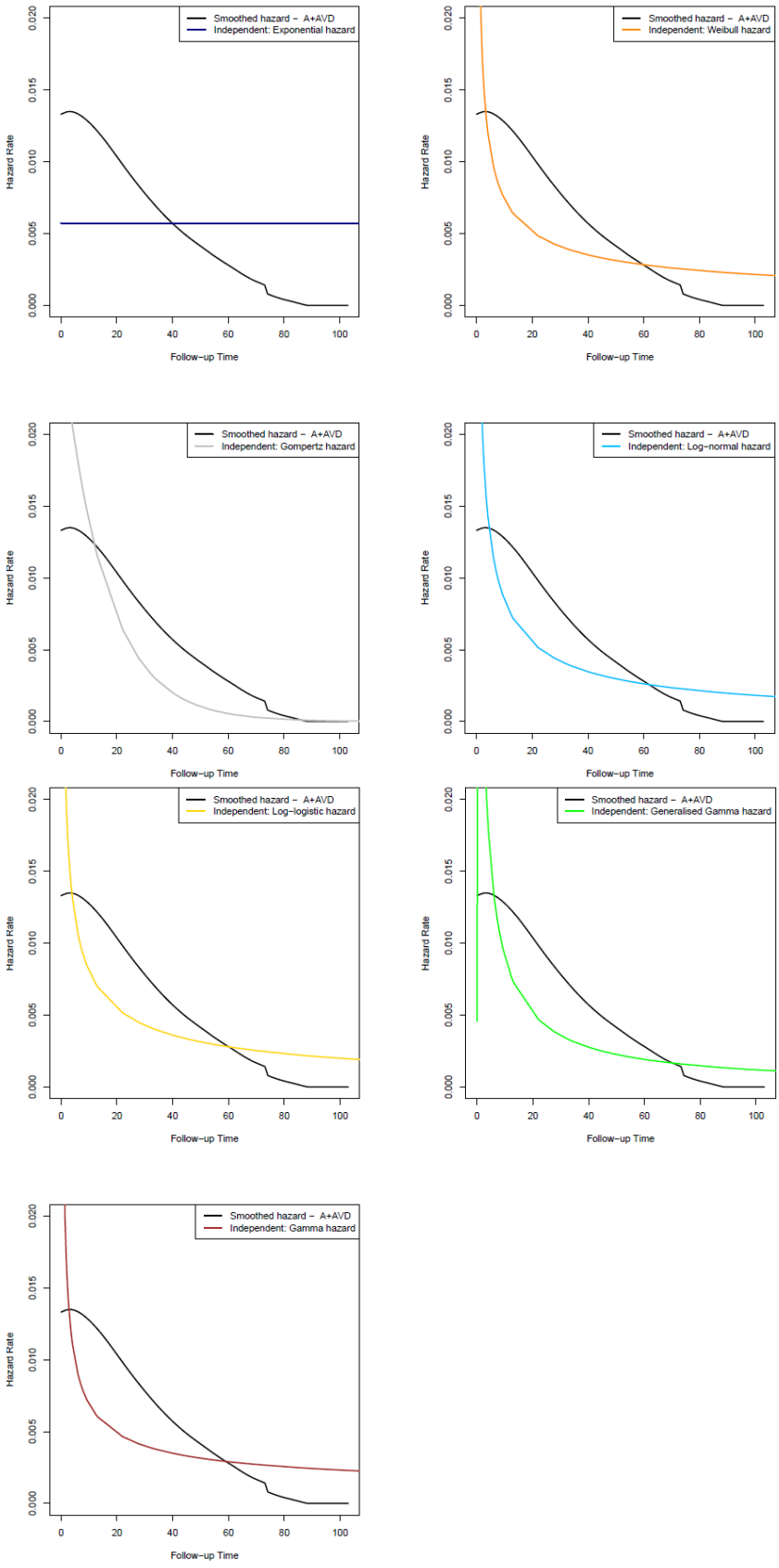
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 71: PFS independent standard parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	310	7	313	7
Weibull	288	5	293	5
Lognormal	284	3	289	2
Loglogistic	286	4	291	4
Gompertz	277	1	282	1
Generalised Gamma	283	2	290	3
Gamma	289	6	294	6

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 77: Comparison of predicted independent standard parametric models and observed hazards for PFS | A+AVD (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 78 presents the extrapolated independent standard parametric curves for ABVD, excluding adjusted background mortality, across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 72 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 79.

Figure 78: PFS independent standard parametric models | ABVD (≥60 years)

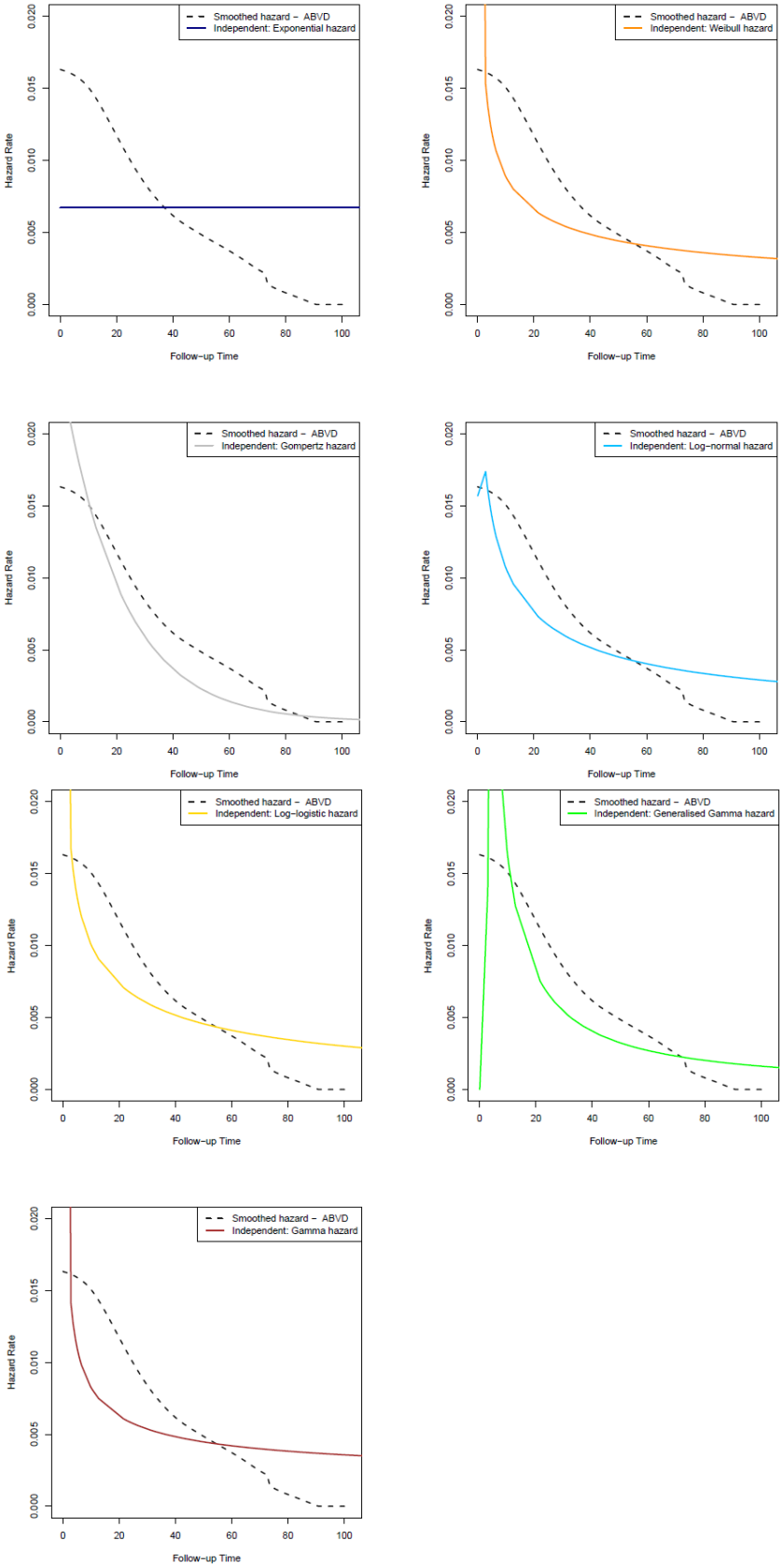
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 72: PFS independent standard parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	446	7	449	7
Weibull	430	5	435	5
Lognormal	421	3	427	3
Loglogistic	426	4	431	4
Gompertz	411	2	417	2
Generalised Gamma	395	1	403	1
Gamma	432	6	438	6

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 79: Comparison of predicted independent standard parametric models and observed hazards for PFS | ABVD (≥60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 80 presents the extrapolated independent MCM parametric curves for A+AVD, excluding adjusted background mortality, across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 73 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 81.

Figure 80: PFS independent MCM parametric models | A+AVD (≥60 years)

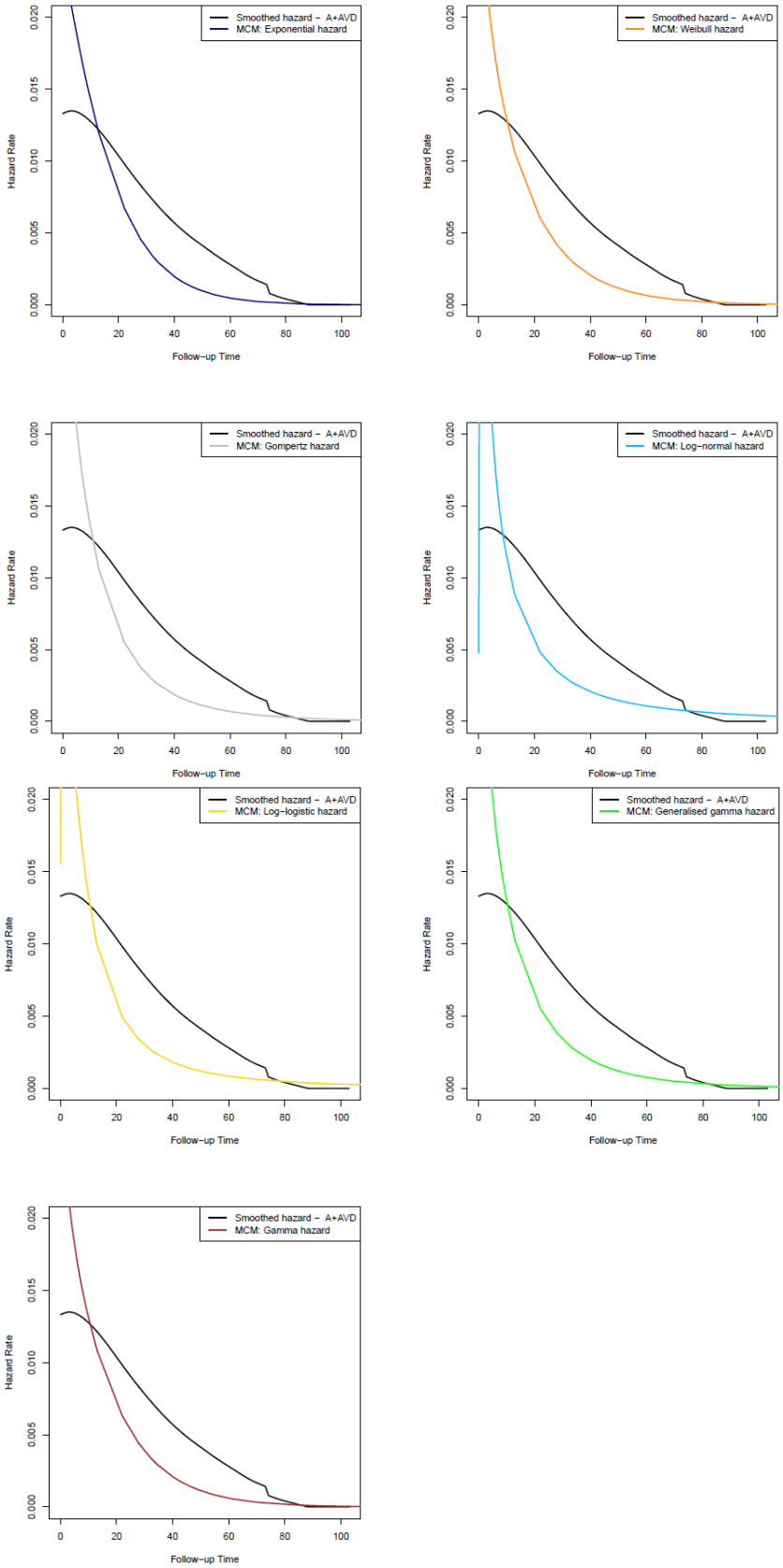
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 73: PFS independent MCM parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	278	1	283	1
MCM: Weibull	279	4	286	4
MCM: Lognormal	280	6	287	6
MCM: Loglogistic	278	2	285	2
MCM: Gompertz	278	3	286	3
MCM: Generalised Gamma	281	7	290	7
MCM: Gamma	279	5	287	5

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 81: Comparison of predicted independent MCM parametric models and observed hazards for PFS | A+AVD (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 82 presents the extrapolated independent MCM parametric curves for ABVD, excluding adjusted background mortality, across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 74 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 83.

Figure 82: PFS independent MCM parametric models | ABVD (≥60 years)

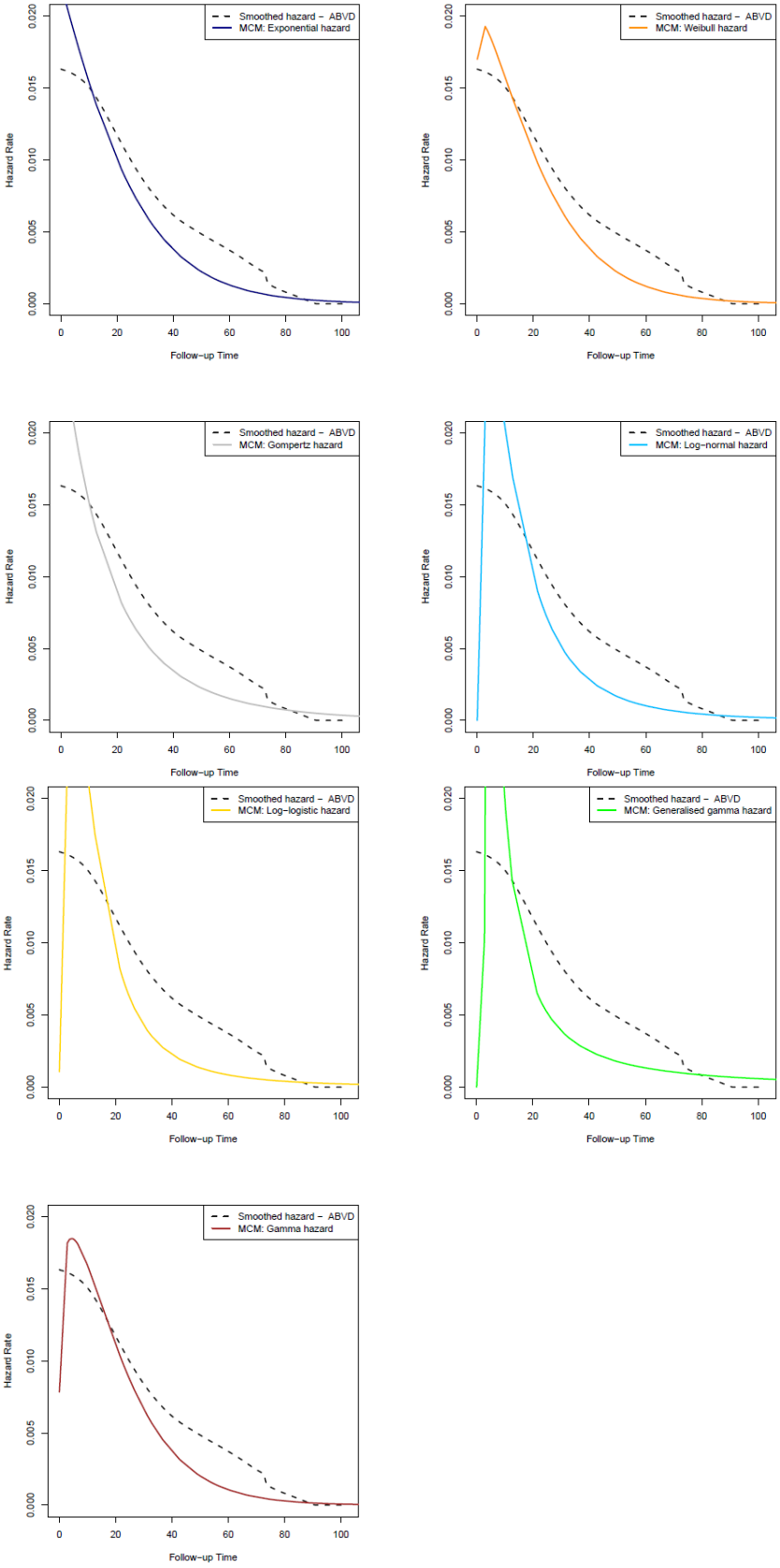
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 74: PFS independent MCM parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	412	4	417	4
MCM: Weibull	414	7	422	7
MCM: Lognormal	404	2	412	2
MCM: Loglogistic	406	3	414	3
MCM: Gompertz	413	6	421	6
MCM: Generalised Gamma	392	1	403	1
MCM: Gamma	413	5	421	5

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 83: Comparison of predicted independent MCM parametric models and observed hazards for PFS | ABVD (≥60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 84 presents the extrapolated independent one-knot spline parametric curves for A+AVD, excluding adjusted background mortality, across a 20-year time horizon. Note: the one-knot normal was unable to converge. Therefore, this is not presented. The corresponding AIC and BIC values are presented in Table 75 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 85.

Figure 84: PFS independent one-knot splines parametric models | A+AVD (≥60 years)

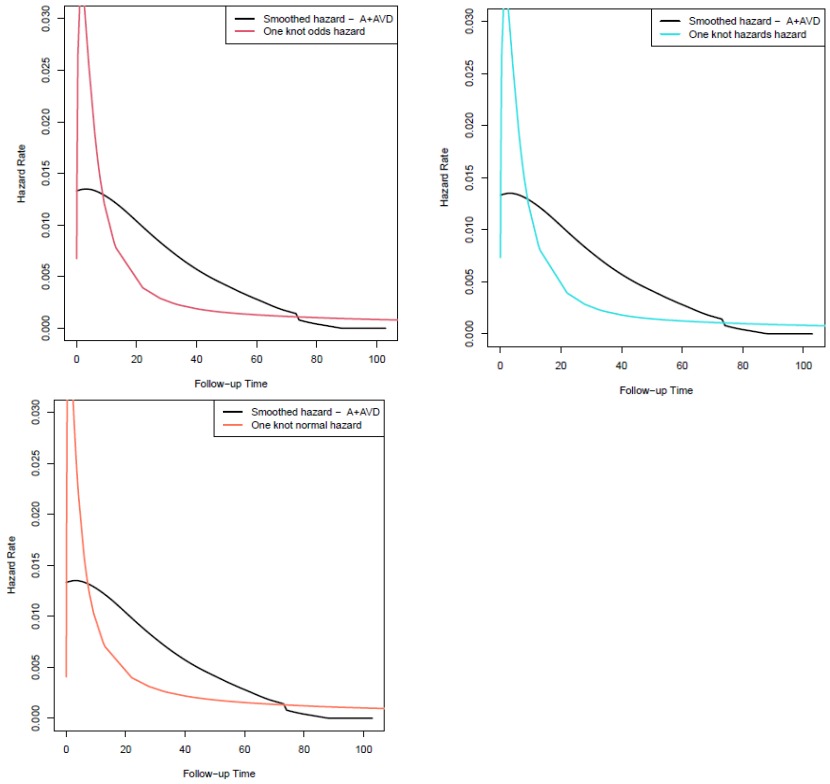
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 75: PFS independent one-knot splines parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	280	2	287	2
One-knot hazard	279	1	287	1
One-knot normal	282	3	289	3

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 85: Comparison of predicted independent one-knot splines parametric models and observed hazards for PFS | A+AVD (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 86 presents the extrapolated independent one-knot splines parametric curves for ABVD, excluding adjusted background mortality across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 76 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 87.

Figure 86: PFS independent one-knot splines parametric models | ABVD (≥60 years)

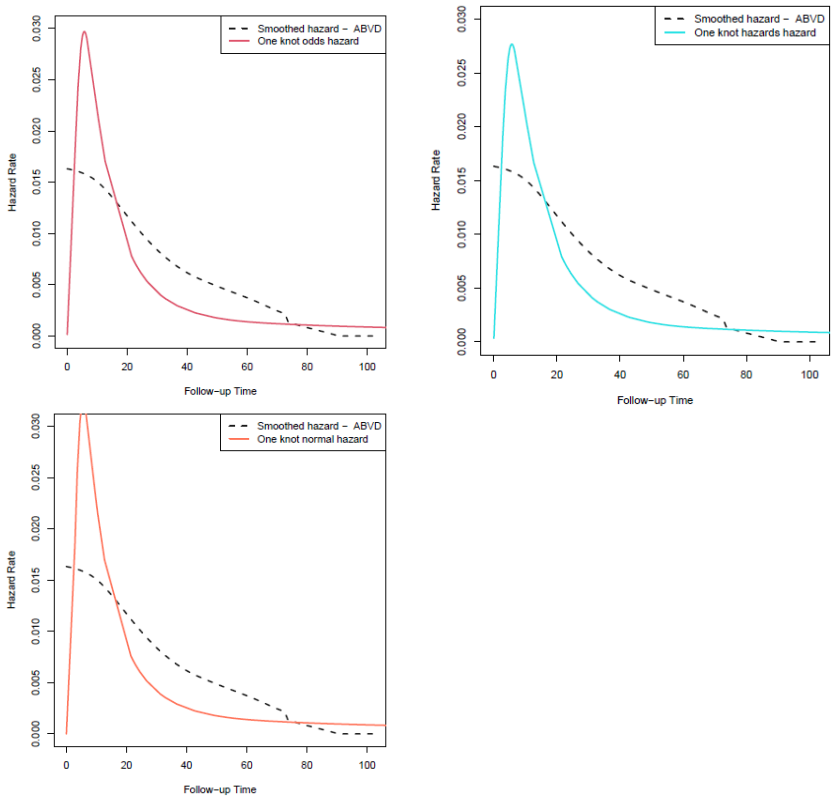
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival

Table 76: PFS independent one-knot splines parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	400	2	408	2
One-knot hazard	402	3	409	3
One-knot normal	397	1	405	1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 87: Comparison of predicted independent one-knot splines parametric models and observed hazards for PFS | ABVD (≥60 years)



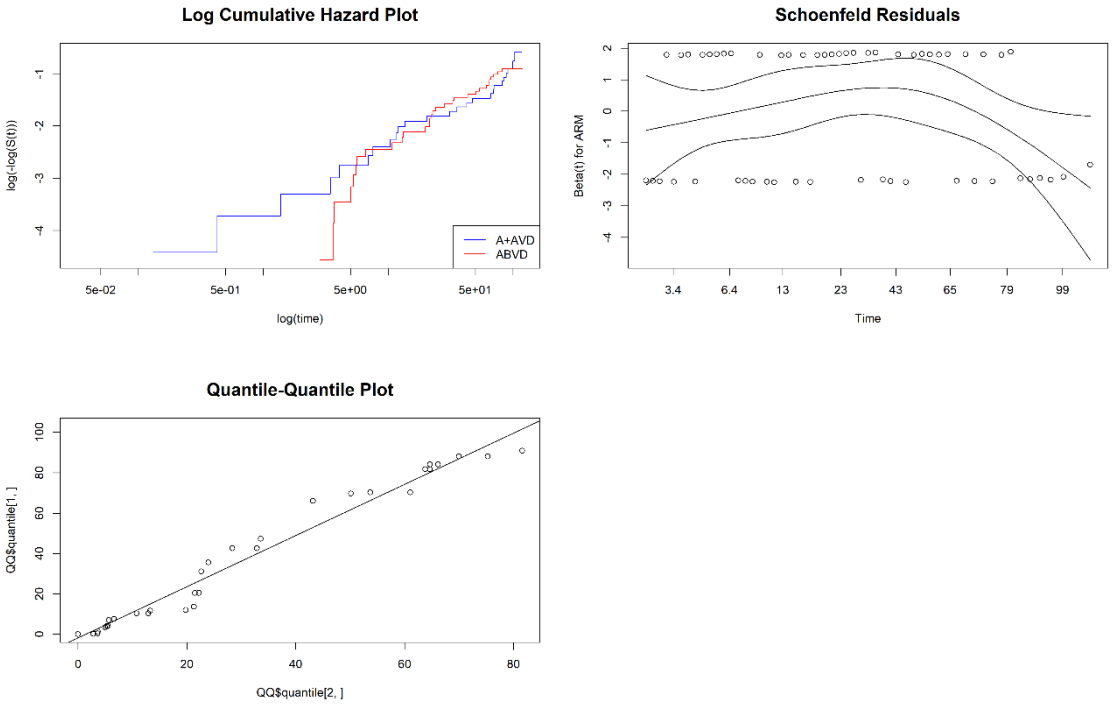
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

OS

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for OS are presented in Figure 88. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.5436. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold.

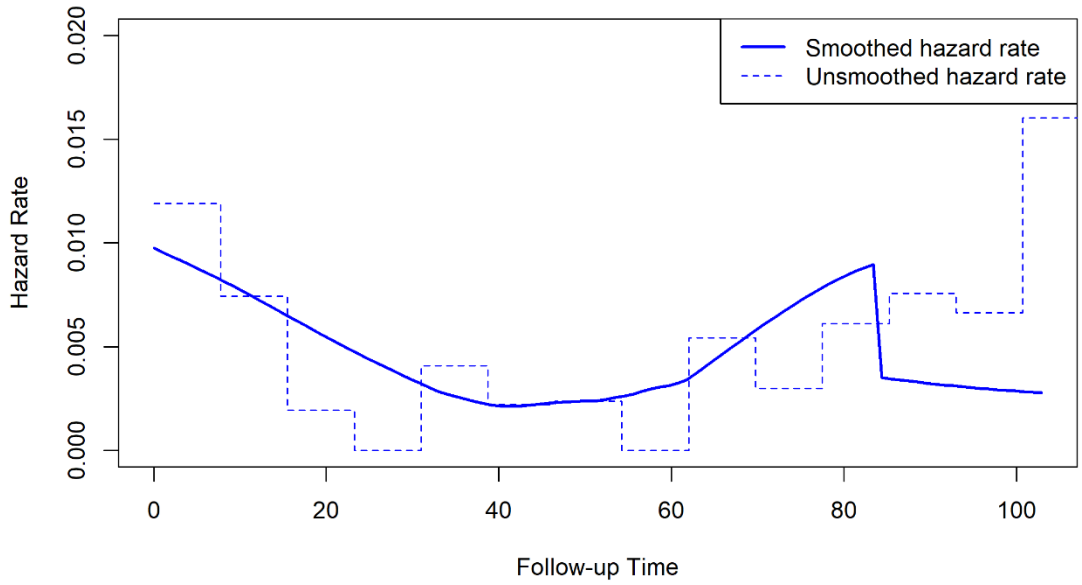
Additionally, the log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold (Figure 88). Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case. The shape of the observed hazards shown in the hazard plots are similar for A+AVD and ABVD; Figure 89 and Figure 90 for A+AVD and ABVD, respectively.

Figure 88: OS proportional hazards and accelerated failure time tests (≥60 years)



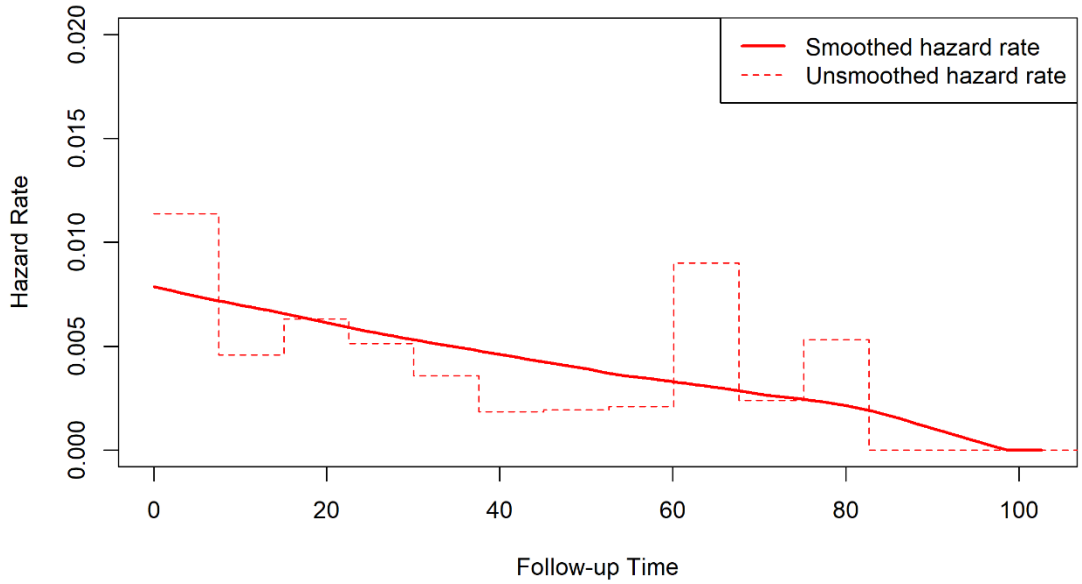
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival.

Figure 89: Observed hazards | A+AVD | OS (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 90: Observed hazards | ABVD | OS (≥60 years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 91 presents the extrapolated independent standard parametric curves for A+AVD, excluding adjusted background mortality across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 77 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 92.

Figure 91: OS independent standard parametric models | A+AVD (≥60 years)

[redacted]

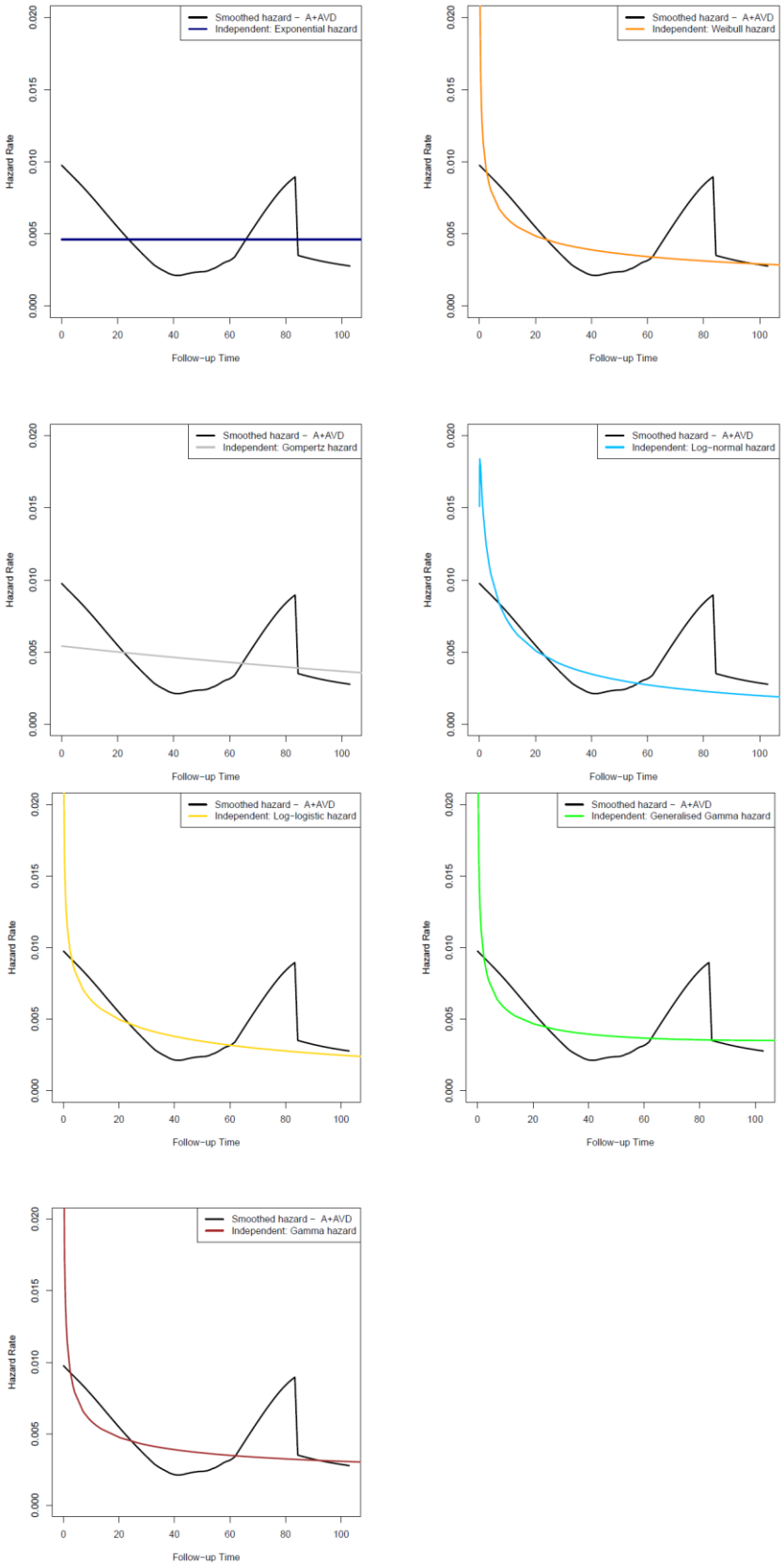
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 77: OS independent standard parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	321	6	323	3
Weibull	318	2	323	2
Lognormal	321	5	326	5
Loglogistic	319	3	324	4
Gompertz	323	7	328	7
Generalised Gamma	319	4	326	6
Gamma	318	1	323	1

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 92: Comparison of predicted independent standard parametric models and observed hazards for OS | A+AVD (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 93 presents the extrapolated independent standard parametric curves for ABVD, excluding adjusted background mortality across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 78 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 94.

Figure 93: OS independent standard parametric models | ABVD (≥60 years)

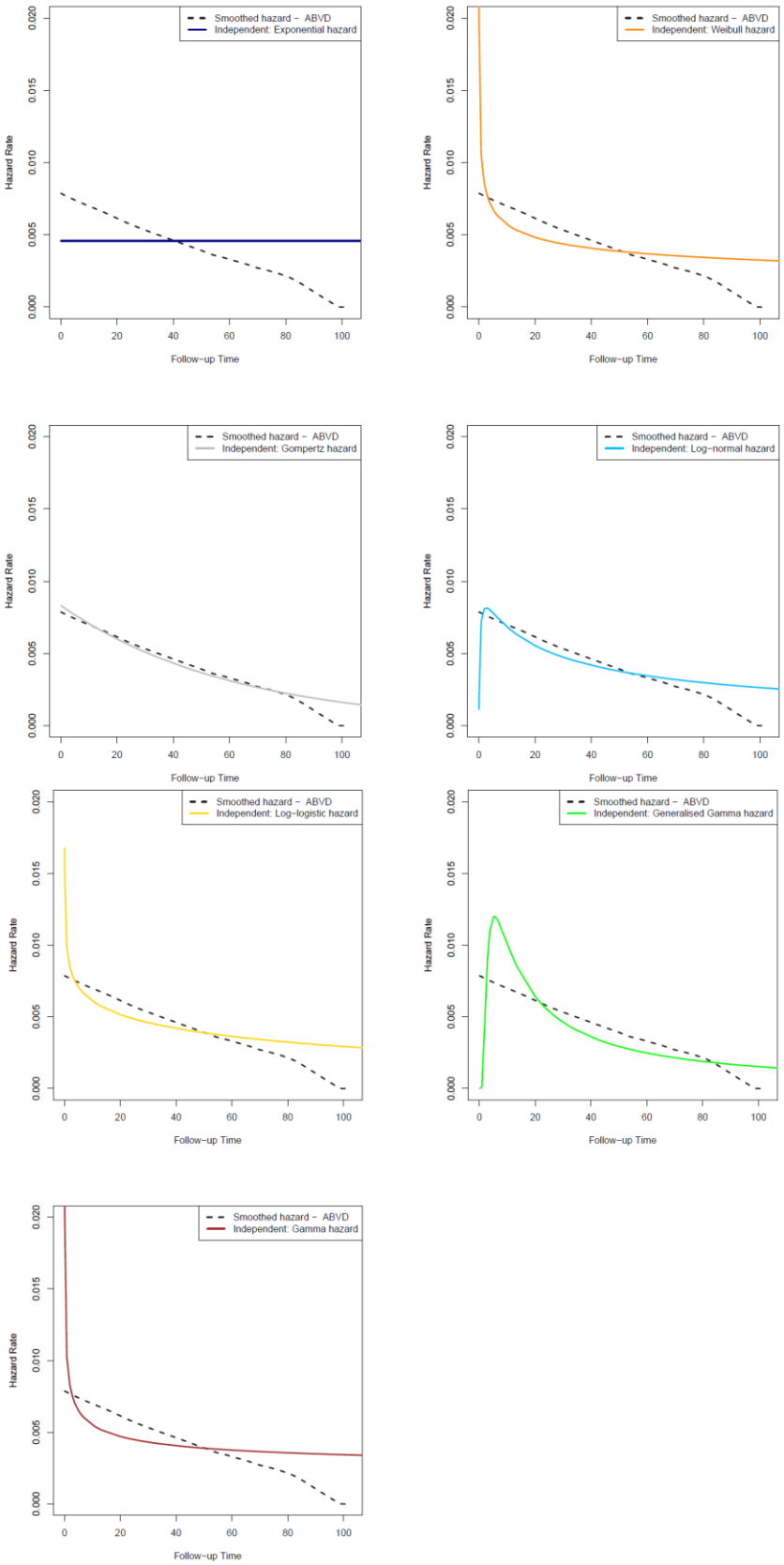
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 78: OS independent standard parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	385	7	388	3
Weibull	384	5	389	6
Lognormal	381	2	386	1
Loglogistic	383	4	388	4
Gompertz	382	3	387	2
Generalised Gamma	381	1	389	5
Gamma	385	6	390	7

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 94: Comparison of predicted independent standard parametric models and observed hazards for OS | ABVD (≥60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 95 presents the extrapolated independent MCM parametric curves for A+AVD, excluding adjusted background mortality across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 79 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 96.

Figure 95: OS independent MCM parametric models | A+AVD (≥60 years)

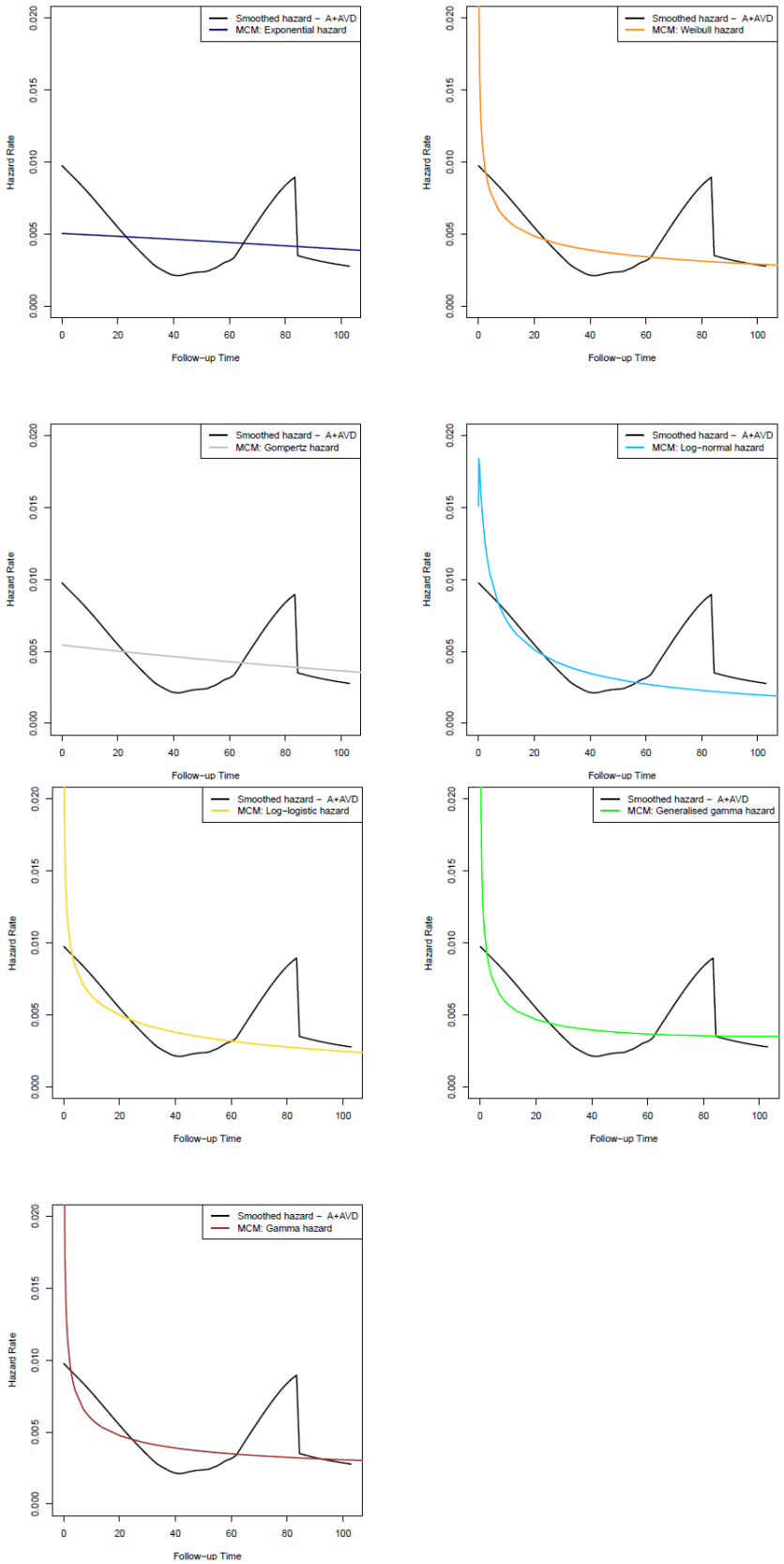
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 79: OS independent MCM parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	323	6	328	3
MCM: Weibull	320	2	327	2
MCM: Lognormal	323	5	330	5
MCM: Loglogistic	321	3	328	4
MCM: Gompertz	325	7	332	7
MCM: Generalised Gamma	321	4	331	6
MCM: Gamma	320	1	327	1

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 96: Comparison of predicted independent MCM parametric models and observed hazards for OS | A+AVD (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 97 presents the extrapolated independent MCM parametric curves for ABVD, excluding adjusted background mortality across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 80 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 98.

Figure 97: OS independent MCM parametric models | ABVD (≥60 years)

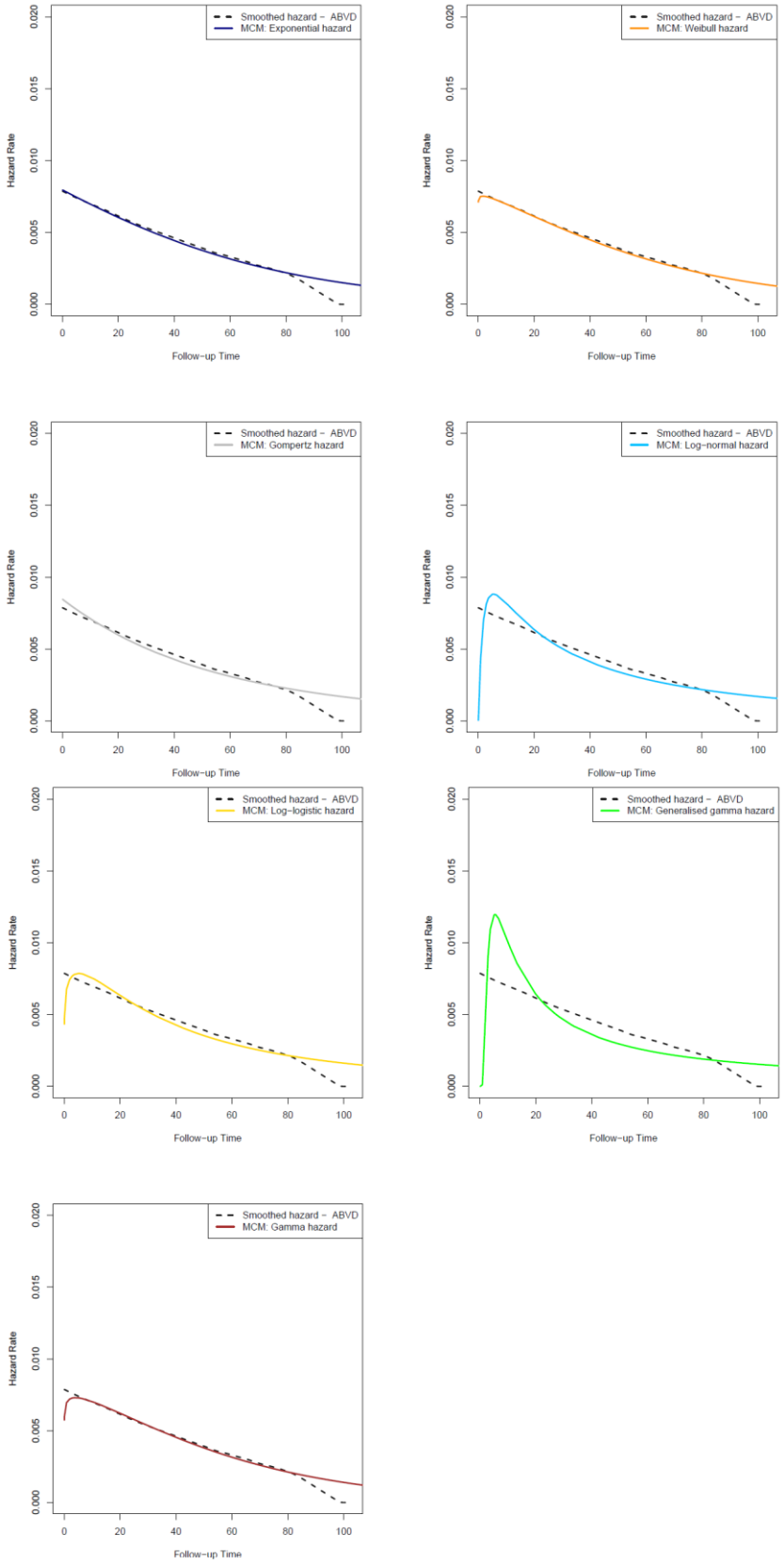
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 80: OS independent MCM parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	382	1	387	1
MCM: Weibull	384	7	392	6
MCM: Lognormal	382	2	390	2
MCM: Loglogistic	383	4	391	3
MCM: Gompertz	384	5	392	4
MCM: Generalised Gamma	383	3	393	7
MCM: Gamma	384	6	392	5

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

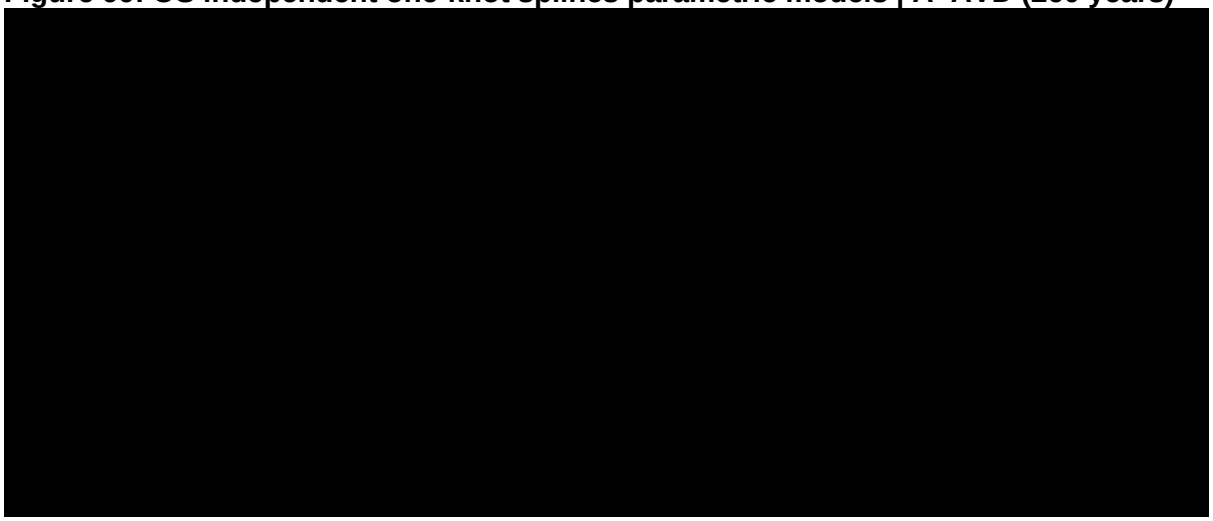
Figure 98: Comparison of predicted independent MCM parametric models and observed hazards for OS | ABVD (≥60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 99 presents the extrapolated independent one-knot spline parametric curves for A+AVD, excluding adjusted background mortality across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 81 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 100.

Figure 99: OS independent one-knot splines parametric models | A+AVD (≥60 years)



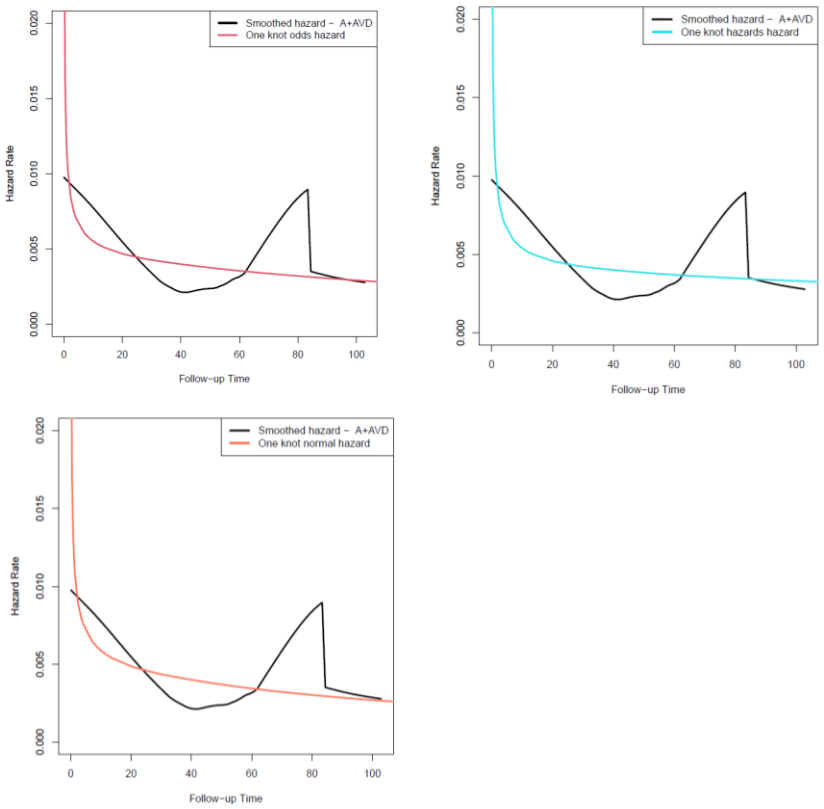
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 81: OS independent one-knot splines parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	320	2	328	2
One-knot hazard	320	1	327	1
One-knot normal	321	3	328	3

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 100: Comparison of predicted independent one-knot splines parametric models and observed hazards for OS | A+AVD (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 101 presents the extrapolated independent one-knot splines parametric curves for ABVD, excluding adjusted background mortality across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 82 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 102.

Figure 101: OS independent one-knot splines parametric models | ABVD (≥60 years)

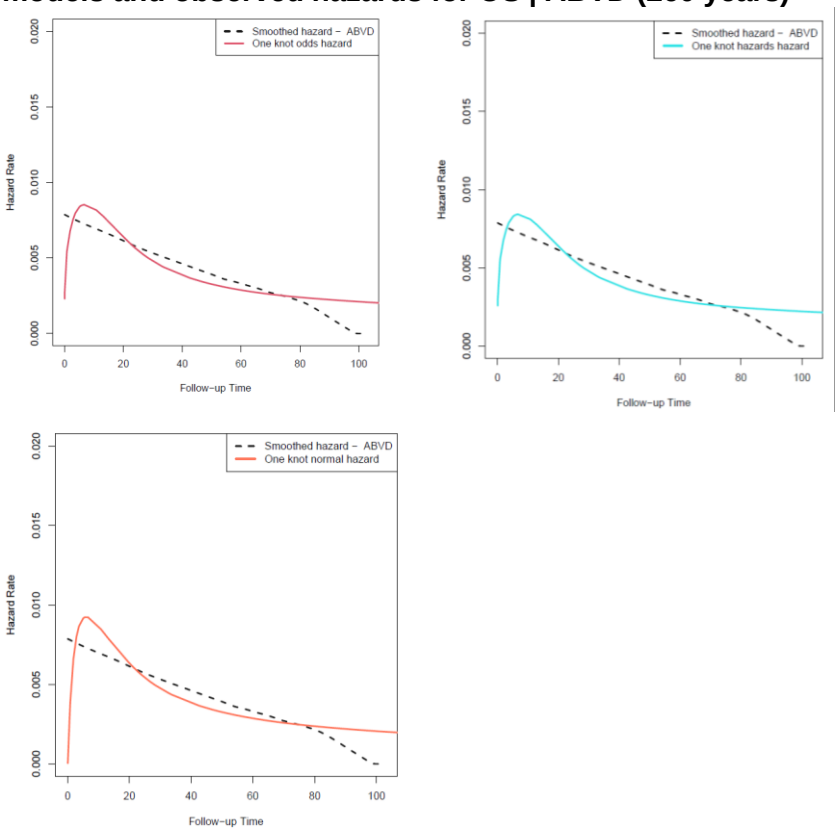
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival

Table 82: OS independent one-knot splines parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	383	2	391	2
One-knot hazard	383	3	391	3
One-knot normal	382	1	390	1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 102: Comparison of predicted independent one-knot splines parametric models and observed hazards for OS | ABVD (≥60 years)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

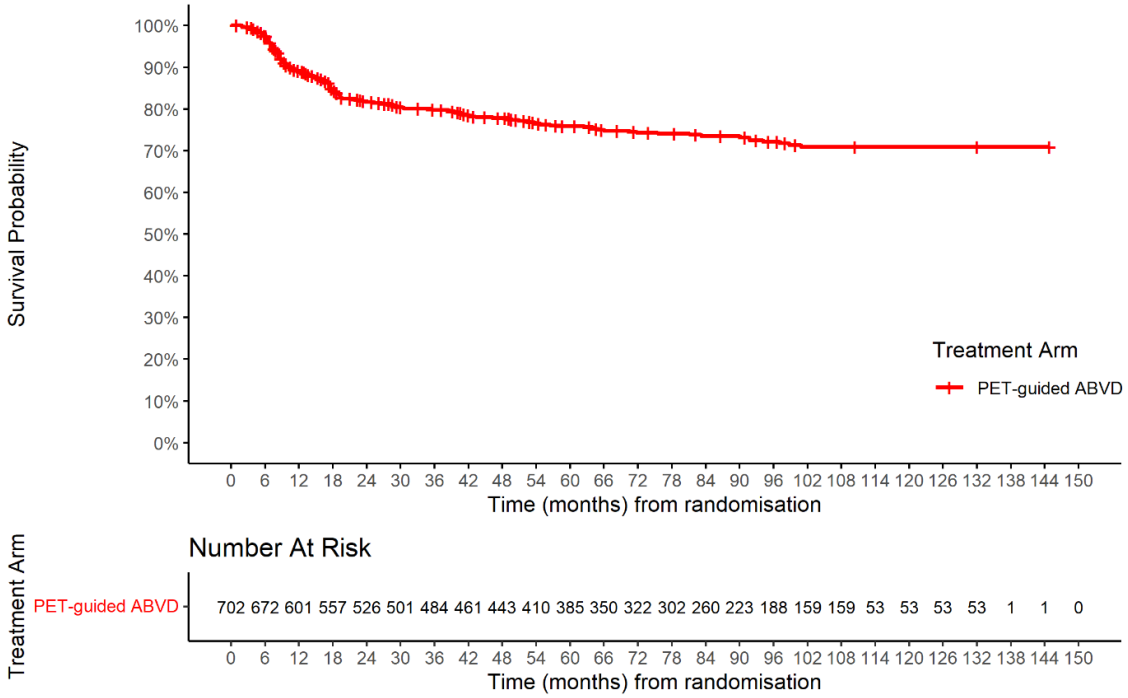
Stage III/IV subgroup from the RATHL study

In response to the EAG's question B2, parametric curves have been fit to the digitised PFS and OS data from the Stage III/IV subgroup from the RATHL study used in the MAICs.

PFS

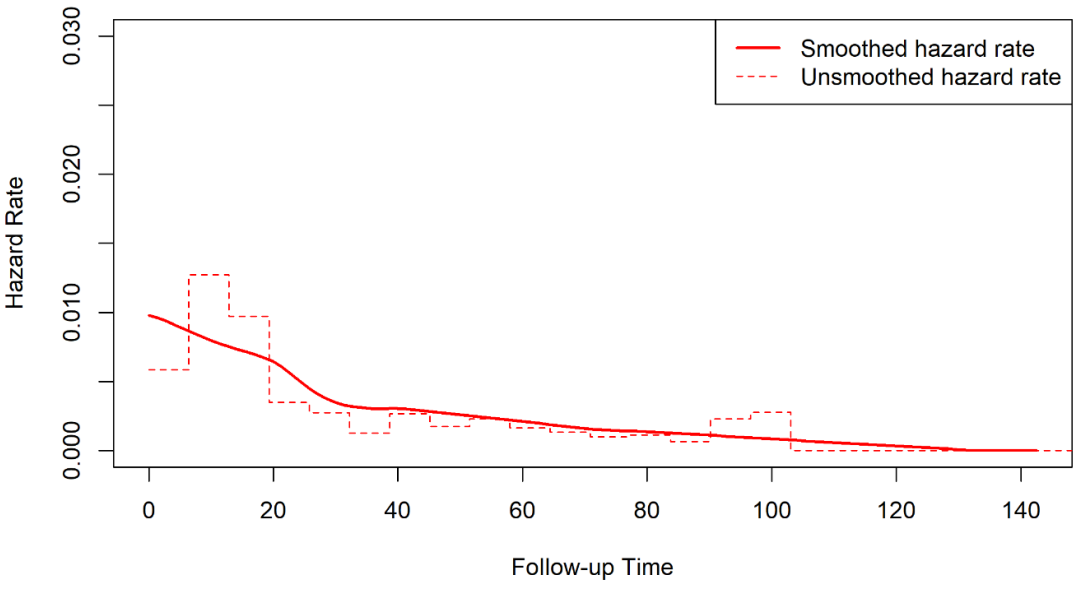
Figure 103 presents the digitised Kaplan-Meier data. The corresponding hazard plot is presented in Figure 104.

Figure 103: PFS digitised Kaplan-Meier data | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Figure 104: PFS observed hazards | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

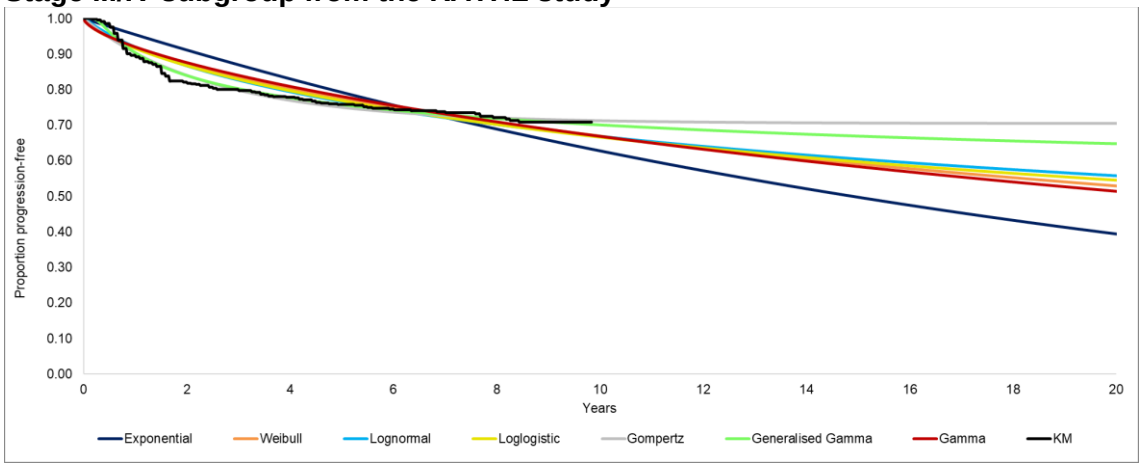


Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Figure 105 presents the extrapolated independent standard parametric curves for PET-adapted ABVD, excluding adjusted background mortality for a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 83 and the

comparisons of predicted hazards vs. observed hazards are presented in Figure 106.

Figure 105: PFS independent standard parametric models | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



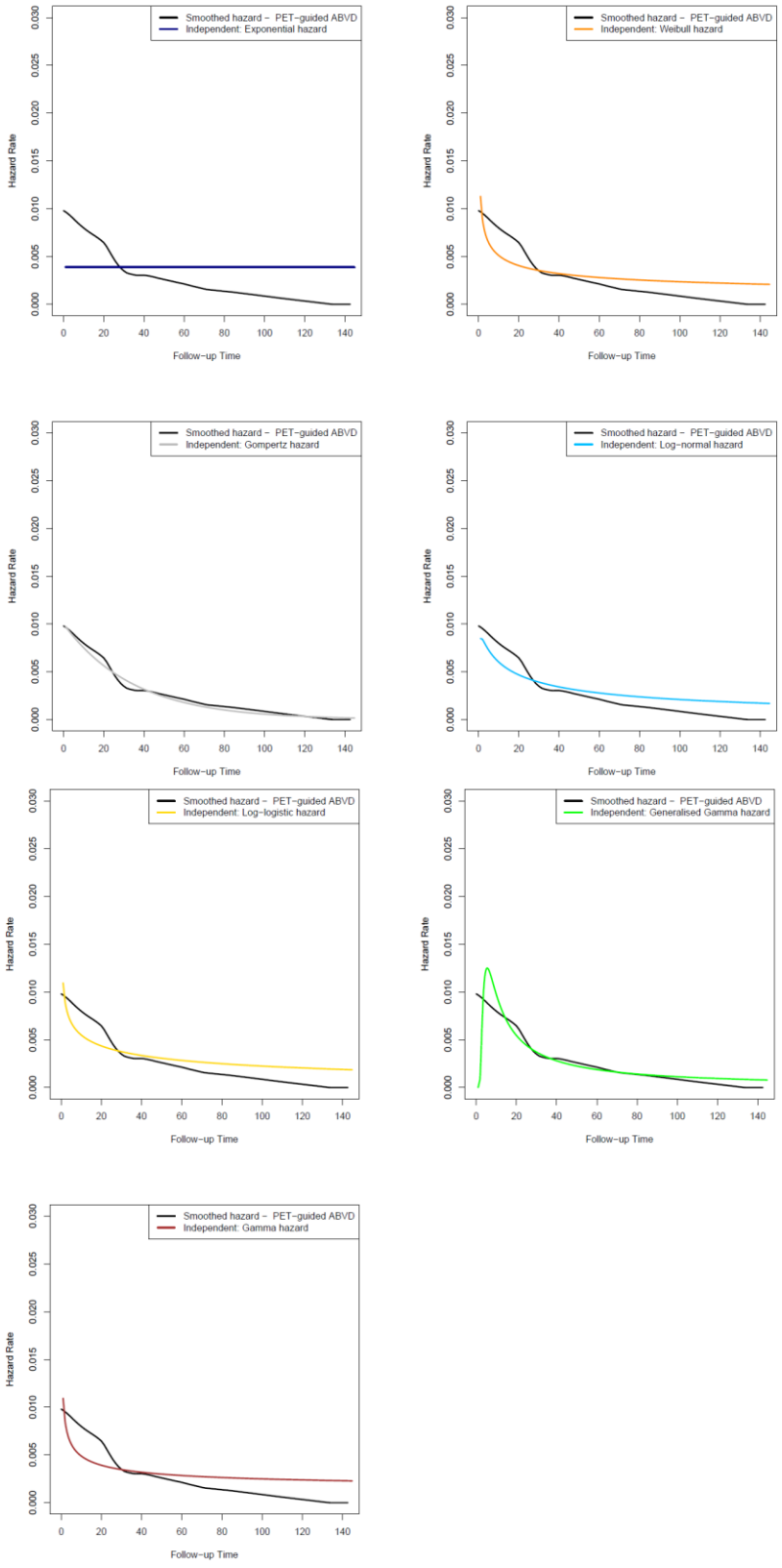
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Table 83: PFS independent standard parametric models AIC and BIC values | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	2295	7	2299	7
Weibull	2256	5	2265	5
Lognormal	2225	3	2234	3
Loglogistic	2246	4	2255	4
Gompertz	2205	2	2214	2
Generalised Gamma	2164	1	2177	1
Gamma	2261	6	2270	6

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PET, positron emission tomography; PFS, progression-free survival

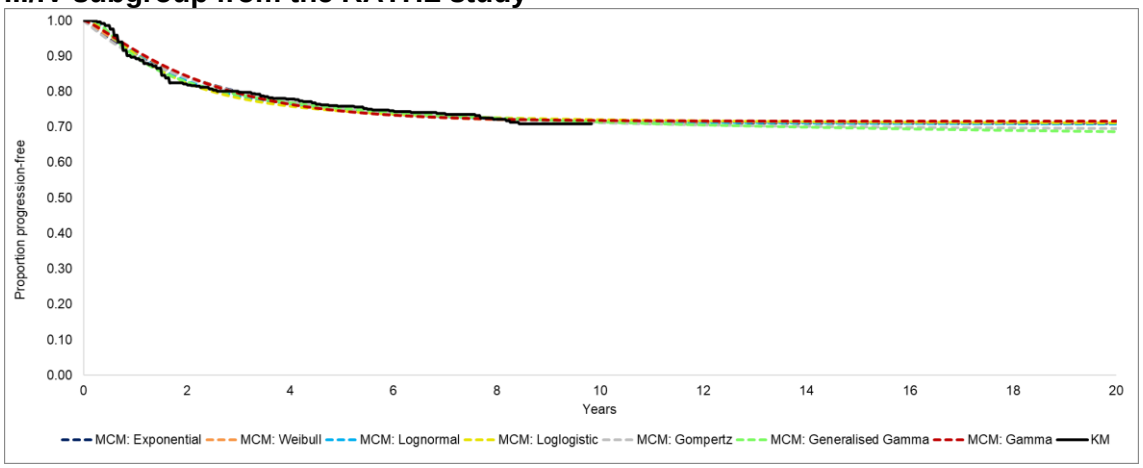
Figure 106: Comparison of predicted independent standard parametric models and observed hazards for PFS | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Figure 107 presents the extrapolated independent MCM parametric curves for PET-adapted ABVD, excluding adjusted background mortality, for a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 84 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 108.

Figure 107: PFS independent MCM parametric models | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



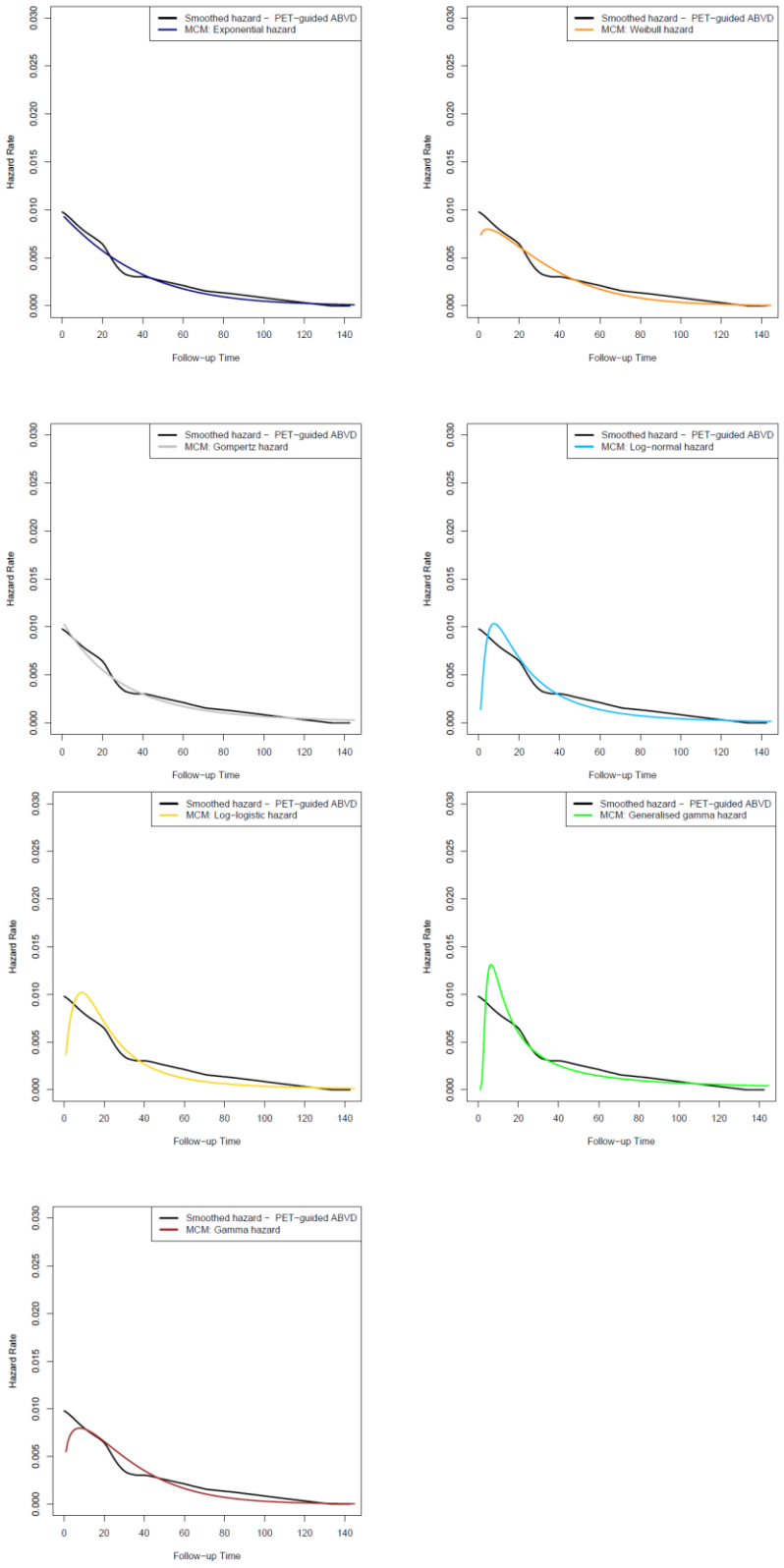
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PET, positron emission tomography; PFS, progression-free survival

Table 84: PFS independent MCM parametric models AIC and BIC values | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	2205	5	2215	4
MCM: Weibull	2205	7	2219	7
MCM: Lognormal	2173	2	2186	2
MCM: Loglogistic	2181	3	2195	3
MCM: Gompertz	2205	6	2219	6
MCM: Generalised Gamma	2161	1	2179	1
MCM: Gamma	2201	4	2215	5

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

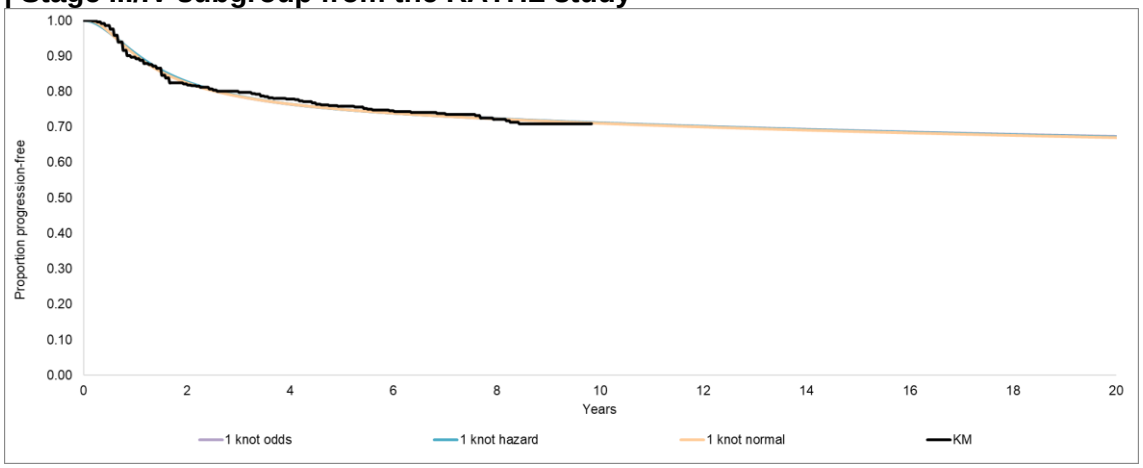
Figure 108: Comparison of predicted independent MCM parametric models and observed hazards for PFS | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PET, positron emission tomography; PFS, progression-free survival

Figure 109 presents the extrapolated independent one-knot spline parametric curves for PET-adapted ABVD, excluding adjusted background mortality, across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 85 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 110.

Figure 109: PFS independent one-knot spline parametric models | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



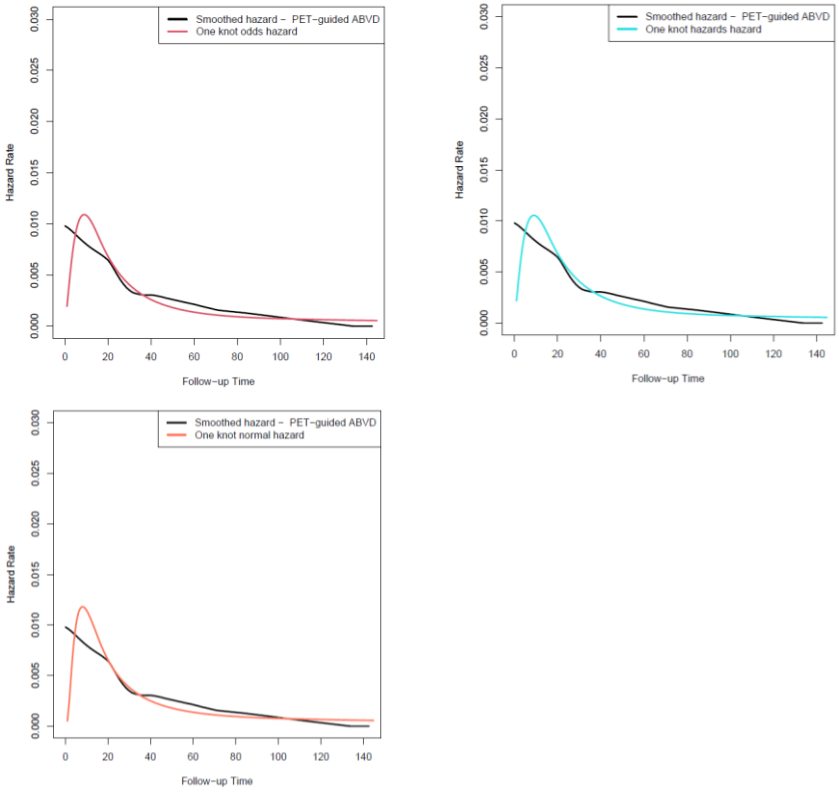
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Table 85: PFS independent MCM parametric models AIC and BIC values | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	2167	2	2181	2
One-knot hazard	2169	3	2183	3
One-knot normal	2160	1	2174	1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

Figure 110: Comparison of predicted independent one-knot spline parametric models and observed hazards for PFS | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

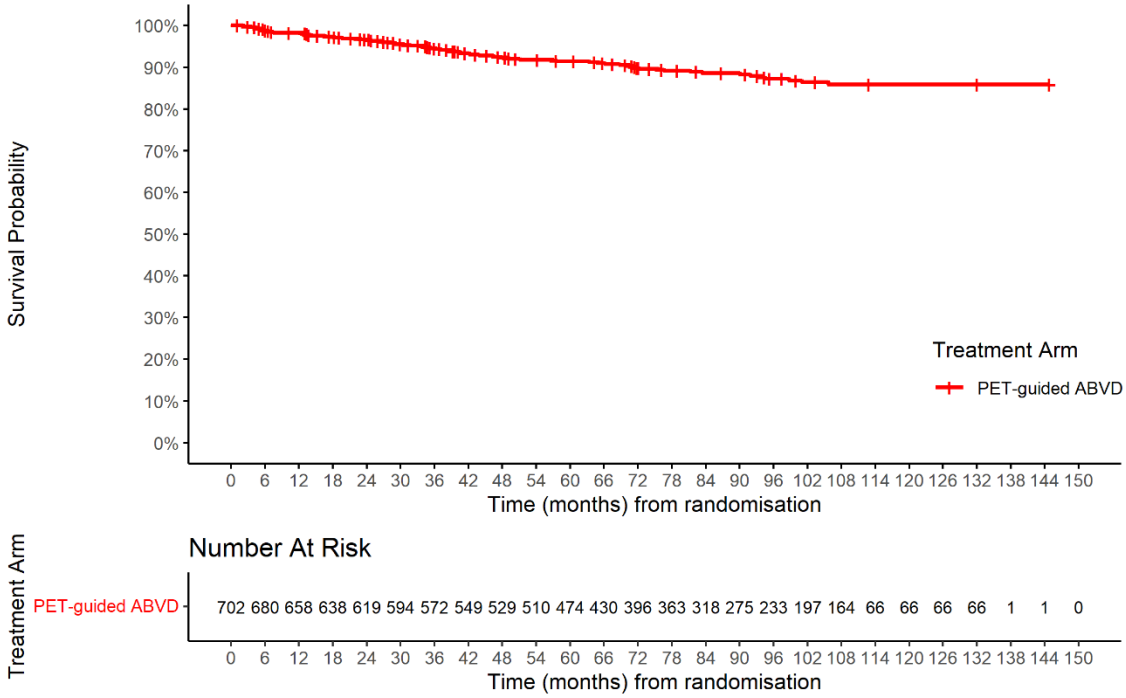


Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

OS

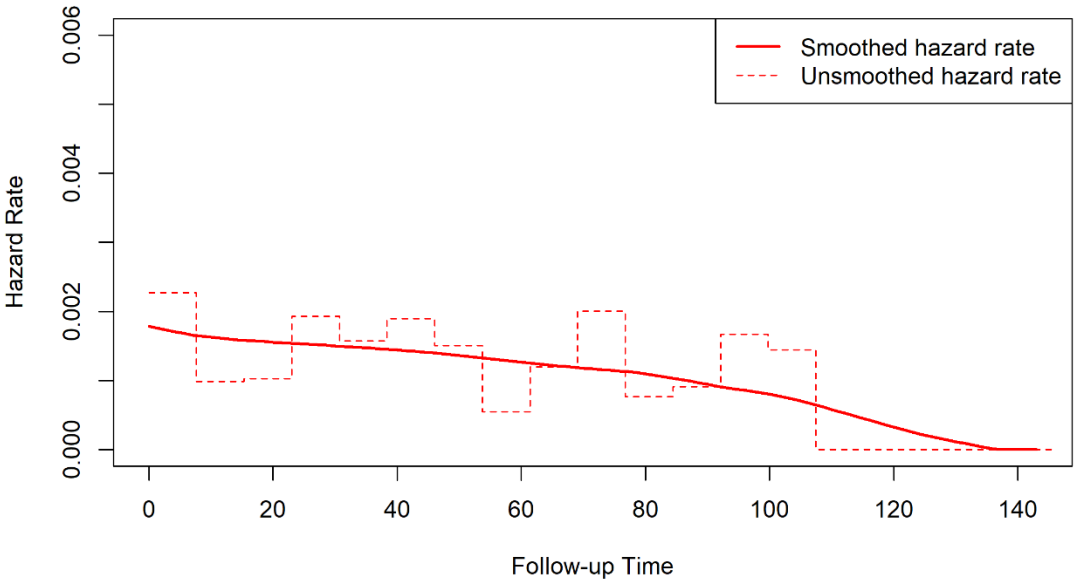
Figure 111 presents the digitised Kaplan-Meier data. The corresponding hazard plot is presented in Figure 112.

Figure 111: OS digitised Kaplan-Meier data | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Figure 112: OS observed hazards | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

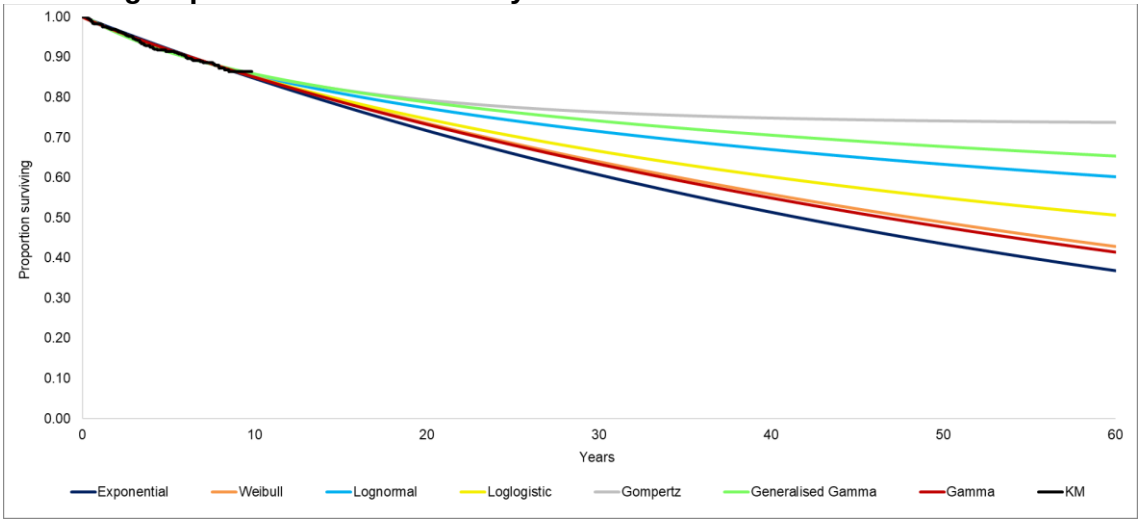


Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Figure 113 presents the extrapolated independent standard parametric curves for PET-adapted ABVD, excluding adjusted background mortality, for a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 86 and the

comparisons of predicted hazards vs. observed hazards are presented in Figure 114.

Figure 113: OS independent standard parametric models | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



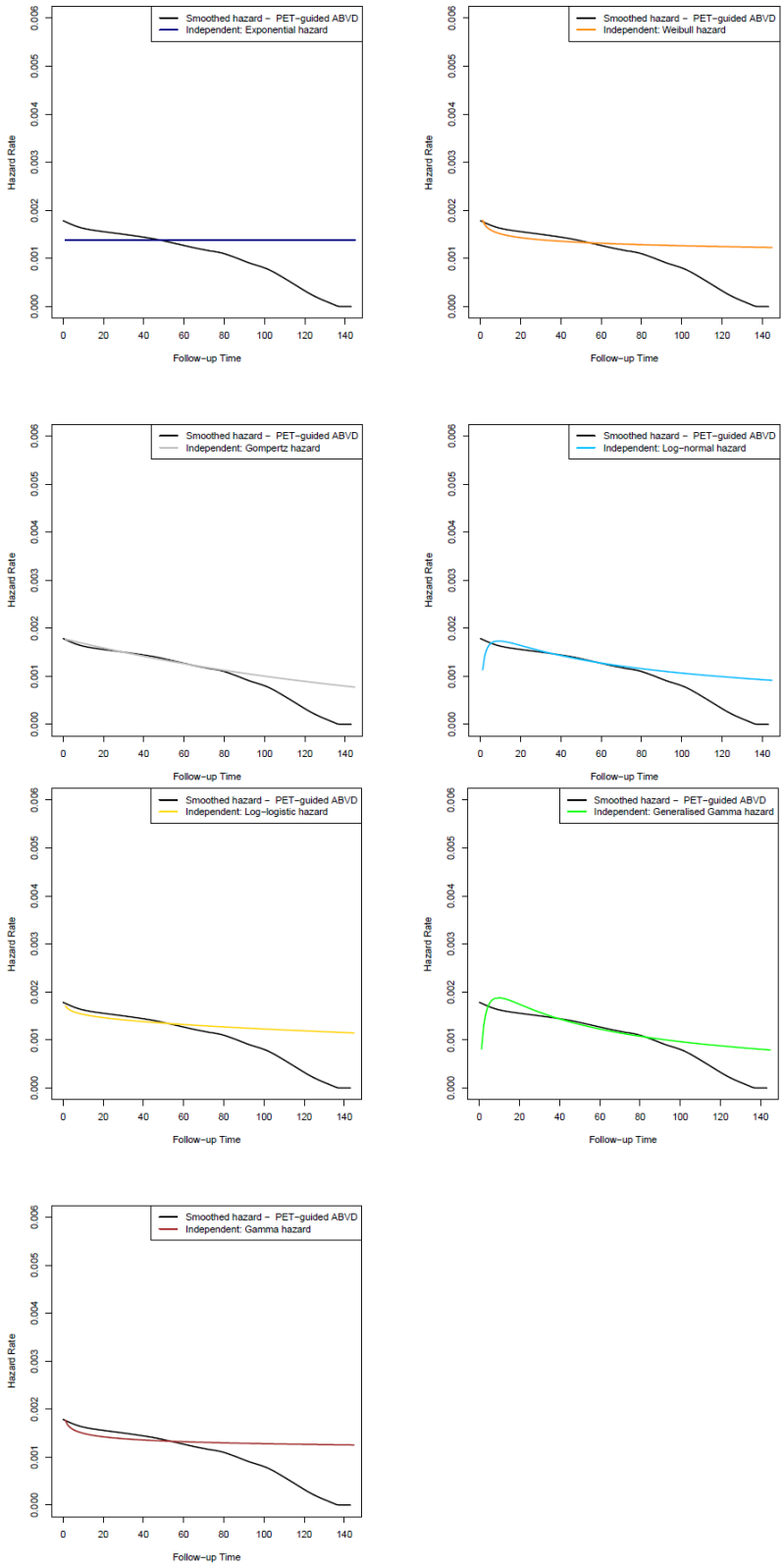
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Table 86: OS independent standard parametric models AIC and BIC values | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	1109	3	1113	1
Weibull	1110	6	1119	5
Lognormal	1107	1	1116	2
Loglogistic	1110	5	1119	4
Gompertz	1108	2	1118	3
Generalised Gamma	1109	4	1122	7
Gamma	1110	7	1119	6

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PET, positron emission tomography; OS, overall survival

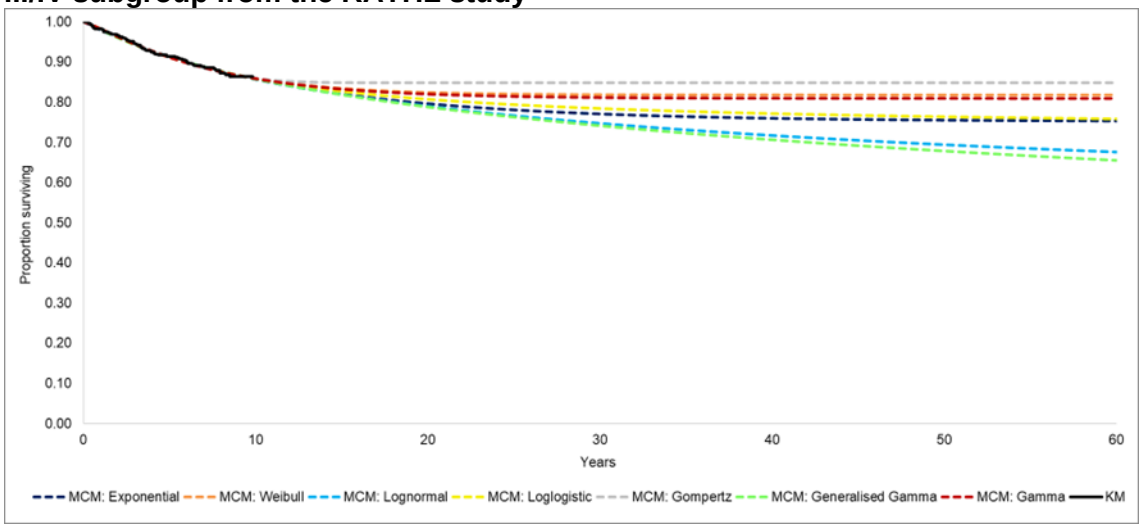
Figure 114: Comparison of predicted independent standard parametric models and observed hazards for OS | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Figure 115 presents the extrapolated independent MCM parametric curves for PET-adapted ABVD – excluding adjusted background mortality – across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 87 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 116.

Figure 115: OS independent MCM parametric models | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



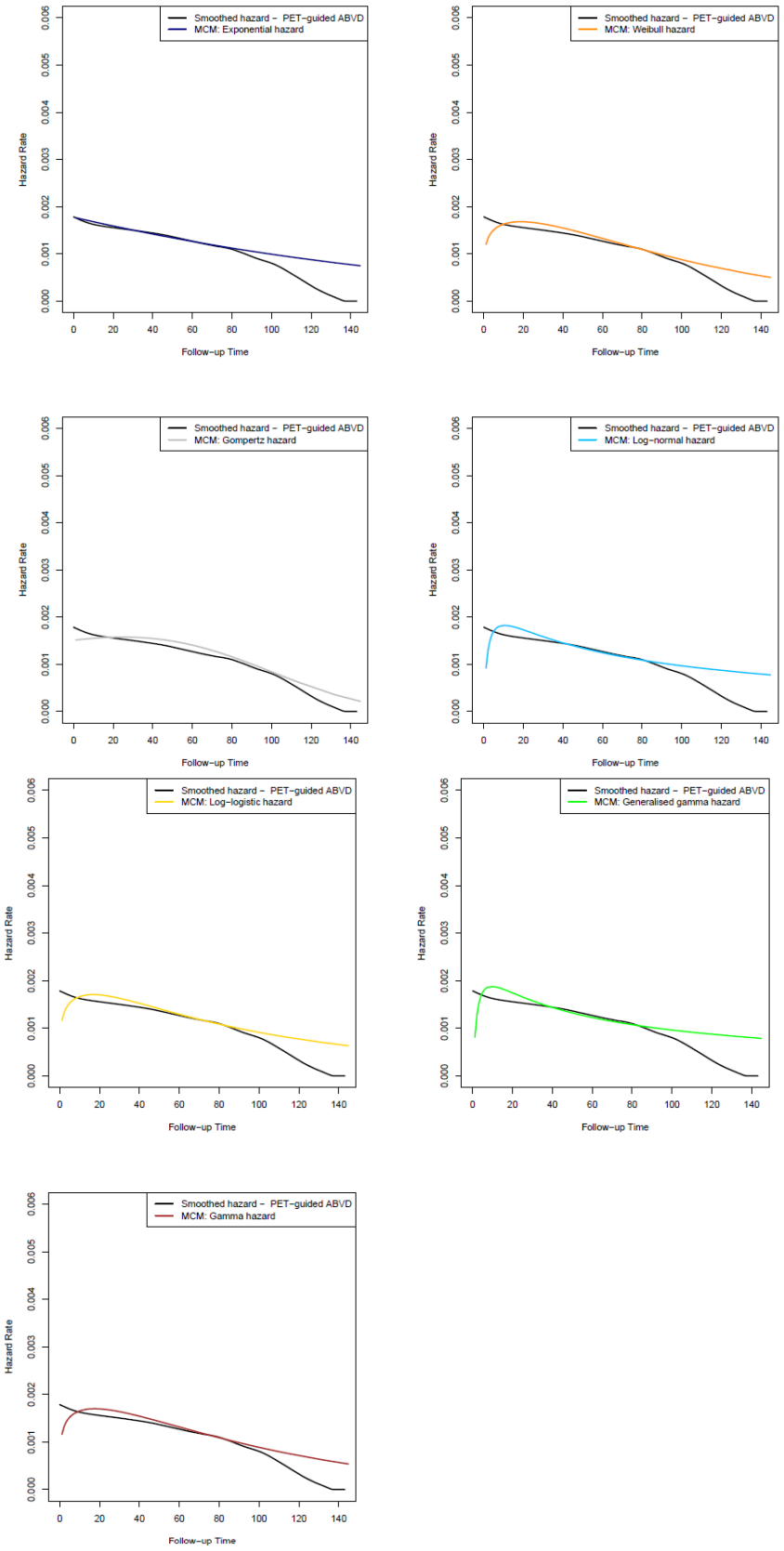
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PET, positron emission tomography; OS, overall survival

Table 87: OS independent MCM parametric models AIC and BIC values | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1108	1	1118	1
MCM: Weibull	1110	4	1123	4
MCM: Lognormal	1109	2	1123	2
MCM: Loglogistic	1110	5	1123	5
MCM: Gompertz	1110	6	1123	6
MCM: Generalised Gamma	1111	7	1129	7
MCM: Gamma	1110	3	1123	3

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

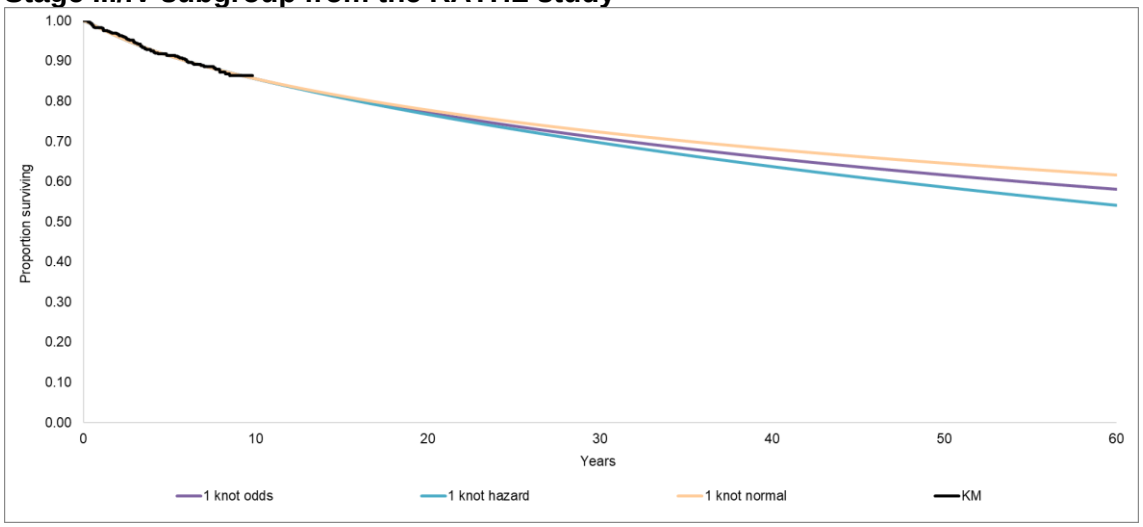
Figure 116: Comparison of predicted independent MCM parametric models and observed hazards for OS | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PET, positron emission tomography; OS, overall survival

Figure 117 presents the extrapolated independent one-knot spline parametric curves for PET-adapted ABVD, excluding adjusted background mortality, for a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 88 and the comparisons of predicted hazards vs. observed hazards are presented in Figure 118.

Figure 117: OS independent one-knot spline parametric models | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



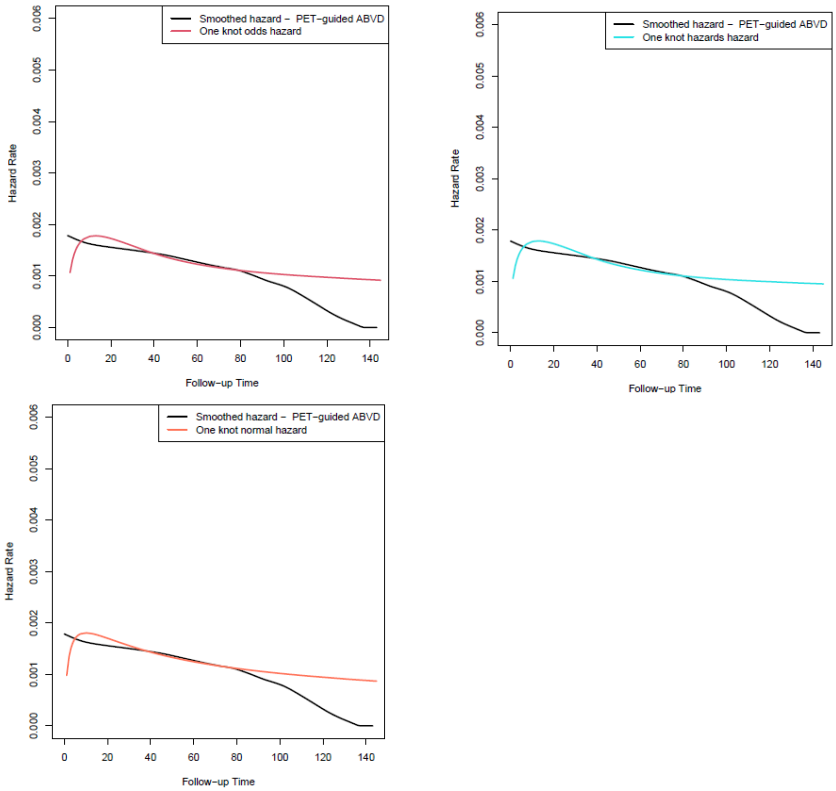
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Table 88: OS independent MCM parametric models AIC and BIC values | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	1110	2	1124	2
One-knot hazard	1110	3	1124	3
One-knot normal	1109	1	1123	1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 118: Comparison of predicted independent one-knot spline parametric models and observed hazards for OS | PET-adapted ABVD | Stage III/IV subgroup from the RATHL study



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival, progression-free survival

MAIC-weighted A+AVD data

In response to the EAG's question A3 and B2, parametric curves have been fit to the MAIC-weighted A+AVD PFS and OS data from the ECHELON-1 study – a full description of the MAIC is provided in the response to A3.

PFS

Figure 119 compares the MAIC-weighted A+AVD PFS (weighted based on mean age, IPS 3–7, ECOG ≥1, Stage IV, male gender, and presence of B-symptoms) with the digitised PET-adapted ABVD data (unadjusted) from RATHL – aligning with Figure 103.

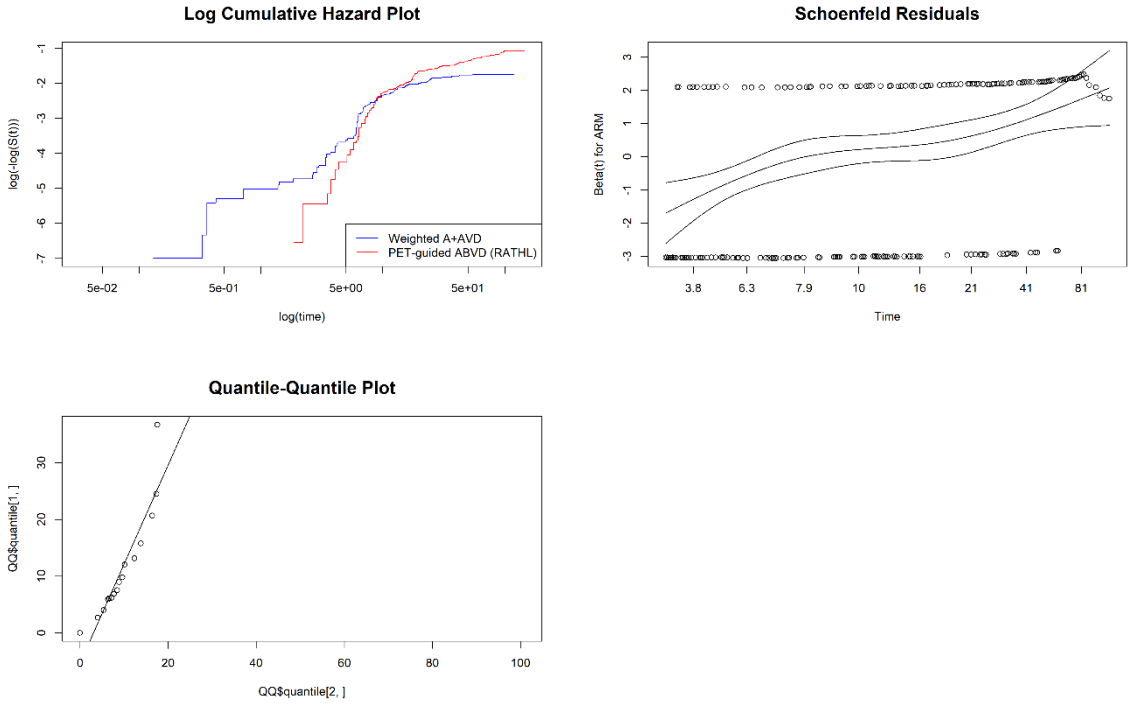
Figure 119: PFS MAIC-weighted A+AVD Kaplan-Meier data from ECHELON-1 compared to the digitised PET-adapted ABVD data from RATHL (unadjusted)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for PFS are presented in Figure 120. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption is likely violated, with a p-value of <0.001. Additionally, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold.

The log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may hold (Figure 120). Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case.

Figure 120: PFS MAIC-weighted A+AVD Kaplan-Meier data from ECHELON-1 compared to the digitised PET-adapted ABVD data from RATHL (unadjusted) | proportional hazards and accelerated failure time tests



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 121 presents the extrapolated independent standard parametric curves for the MAIC-weighted A+AVD, excluding adjusted background mortality for a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 89.

Figure 121: PFS independent standard parametric models | MAIC-weighted A+AVD | ECHELON-1

[redacted]

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Table 89: PFS independent standard parametric models AIC and BIC values | MAIC-weighted A+AVD | ECHELON-1

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	1154	7	1159	7
Weibull	1092	5	1100	5
Lognormal	1078	3	1087	3
Loglogistic	1088	4	1097	4
Gompertz	1023	1	1031	1
Generalised Gamma	1058	2	1072	2
Gamma	1094	6	1103	6

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PET, positron emission tomography; PFS, progression-free survival

Figure 122 presents the extrapolated independent MCM parametric curves for the MAIC-weighted A+AVD, excluding adjusted background mortality, for a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 90.

Figure 122: PFS independent MCM parametric models | MAIC-weighted A+AVD | ECHELON-1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PET, positron emission tomography; PFS, progression-free survival

Table 90: PFS independent MCM parametric models AIC and BIC values | MAIC-weighted A+AVD | ECHELON-1

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1022	6	1031	4
MCM: Weibull	1017	3	1030	3
MCM: Lognormal	1027	7	1040	7
MCM: Loglogistic	1016	1	1029	1
MCM: Gompertz	1021	5	1035	5
MCM: Generalised Gamma	1018	4	1036	6

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Gamma	1016	2	1029	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 123 presents the extrapolated independent one-knot spline parametric curves for the MAIC-weighted A+AVD, excluding adjusted background mortality, across a 20-year time horizon. The corresponding AIC and BIC values are presented in Table 91.

Figure 123: PFS independent one-knot spline parametric models | MAIC-weighted A+AVD | ECHELON-1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; PFS, progression-free survival

Table 91: PFS independent MCM parametric models AIC and BIC values | MAIC-weighted A+AVD | ECHELON-1

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	1026	2	1040	2
One-knot hazard	1026	1	1039	1
One-knot normal	1041	3	1054	3

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression-free survival

OS

Figure 124 compares the MAIC-weighted A+AVD OS (weighted based on mean age, IPS 3–7, ECOG ≥1, Stage IV, male gender, and presence of B-symptoms) with the digitised PET-adapted ABVD data (unadjusted) from RATHL – aligning with Figure 111.

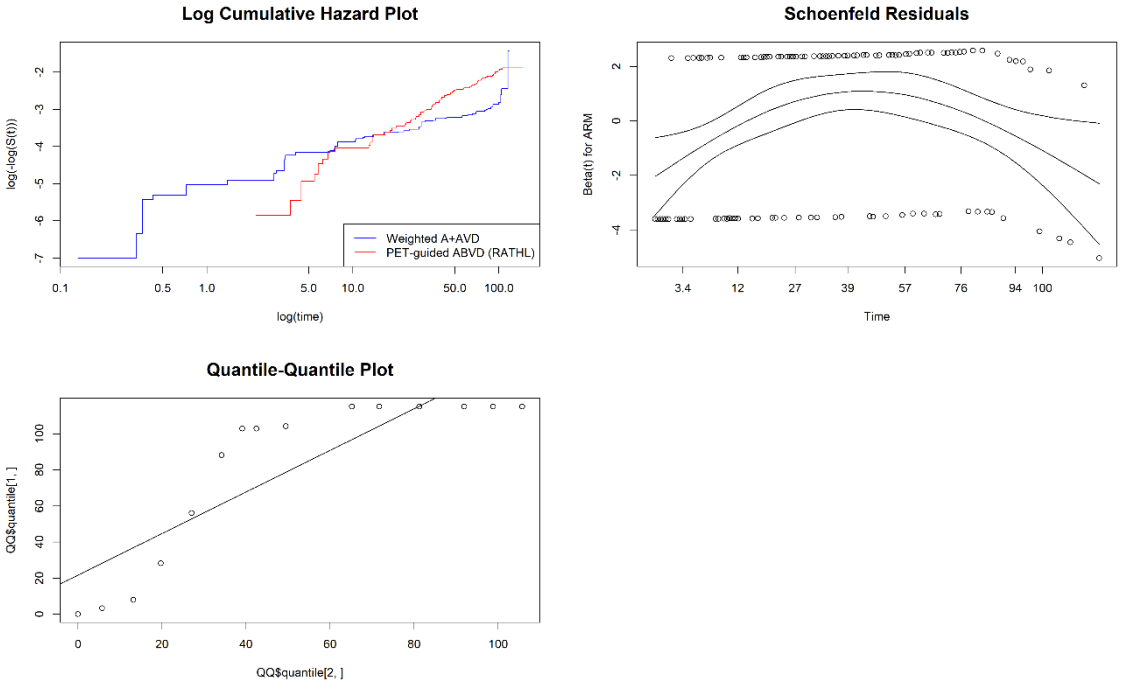
Figure 124: OS MAIC-weighted A+AVD Kaplan-Meier data from ECHELON-1 compared to the digitised PET-adapted ABVD data from RATHL (unadjusted)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Plots assessing the validity of the proportional hazards and accelerated failure time assumptions for OS are presented in Figure 125. The Schoenfeld residuals and the Grambsch–Therneau test indicate that the proportional hazards assumption may hold, with a p-value of 0.1803. However, the log-cumulative hazard plots show a clear crossing of curves. Therefore, the assumption of proportional hazards was not considered to hold.

The log-cumulative hazard plots are not straight lines – indicating that more flexible parametric modelling methods should be considered. The quantile-quantile plot indicates that the accelerated failure time assumption may also be violated (Figure 125). Based on this, and as the proportional hazards assumption was shown to be violated, independent models were pursued in the base case.

Figure 125: OS MAIC-weighted A+AVD Kaplan-Meier data from ECHELON-1 compared to the digitised PET-adapted ABVD data from RATHL (unadjusted) | proportional hazards and accelerated failure time tests



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival.

Figure 126 presents the extrapolated independent standard parametric curves for the MAIC-weighted A+AVD, excluding adjusted background mortality for a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 92.

Figure 126: OS independent standard parametric models | MAIC-weighted A+AVD | ECHELON-1

[redacted]

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Table 92: OS independent standard parametric models AIC and BIC values | MAIC-weighted A+AVD | ECHELON-1

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	465	7	469	6
Weibull	453	3	462	3
Lognormal	453	1	462	1
Loglogistic	453	4	462	4
Gompertz	463	6	472	7
Generalised Gamma	455	5	469	5
Gamma	453	2	462	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PET, positron emission tomography; OS, overall survival

Figure 127 presents the extrapolated independent MCM parametric curves for the MAIC-weighted A+AVD, excluding adjusted background mortality, for a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 93.

Figure 127: OS independent MCM parametric models | MAIC-weighted A+AVD | ECHELON-1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PET, positron emission tomography; OS, overall survival

Table 93: OS independent MCM parametric models AIC and BIC values | MAIC-weighted A+AVD | ECHELON-1

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	463	6	472	5
MCM: Weibull	455	3	469	3
MCM: Lognormal	455	1	469	1
MCM: Loglogistic	455	4	469	4

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Gompertz	464	7	477	7
MCM: Generalised Gamma	457	5	475	6
MCM: Gamma	455	2	469	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 128 presents the extrapolated independent one-knot spline parametric curves for the MAIC-weighted A+AVD, excluding adjusted background mortality, across a 60-year time horizon. The corresponding AIC and BIC values are presented in Table 94.

Figure 128: OS independent one-knot spline parametric models | MAIC-weighted A+AVD | ECHELON-1

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography; OS, overall survival

Table 94: OS independent MCM parametric models AIC and BIC values | MAIC-weighted A+AVD | ECHELON-1

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	455	3	469	3
One-knot hazard	455	1	469	1
One-knot normal	455	2	469	2

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Subgroup-specific inputs

Table 95 to Table 99 presents the inputs used in the age <60 years and ≥60 years subgroup analyses detailed in Question B1.

Table 95: Baseline characteristics for age subgroups (ECHELON-1)

	<60 years	≥60 years
Age (years)	[redacted]	[redacted]
Proportion male	[redacted]	[redacted]
Body weight (kg)	[redacted]	[redacted]
BSA (m2)	[redacted]	[redacted]
Baseline utility score	[redacted]	[redacted]
Receipt of G-CSF (ref: no)	[redacted]	[redacted]
IPS risk factor 0	[redacted]	[redacted]
IPS risk factor 1	[redacted]	[redacted]
IPS risk factor 2	[redacted]	[redacted]
IPS risk factor 3	[redacted]	[redacted]
IPS risk factor 4	[redacted]	[redacted]
IPS risk factor 5	[redacted]	[redacted]
IPS risk factor 6	[redacted]	[redacted]
IPS risk factor 7	[redacted]	[redacted]

Abbreviations: BSA, body surface area; kg, kilogram.

Table 96: Grade ≥3 drug-related TEAEs | ≥5% of all patients | ECHELON-1

	<60 years		≥60 years	
	A+AVD	ABVD	A+AVD	ABVD
N	579	561	83	98
Anaemia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; N, number; TEAE, treatment-emergent adverse events

Table 97: Duration of therapy and dose intensity

	Mean number of treatment cycles		RDI	
	<60 years	≥60 years	<60 years	≥60 years
A+AVD				
Brentuximab vedotin	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Vinblastine	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
ABVD				
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]

	Mean number of treatment cycles		RDI	
	<60 years	≥60 years	<60 years	≥60 years
Bleomycin	[redacted]	[redacted]	[redacted]	[redacted]
Vinblastine	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; RDI, relative dose intensity.

Table 98: Assumptions for concomitant medications

	% receiving A+AVD		% receiving ABVD	
Treatment	**<60 years**	**≥60 years**	**<60 years**	**≥60years**
Anti-infectives				
Acyclovir	[redacted]	[redacted]	[redacted]	[redacted]
Levofloxacin	[redacted]	[redacted]	[redacted]	[redacted]
Pain management				
Oxycodone	[redacted]	[redacted]	[redacted]	[redacted]
Tramadol	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Table 99: Patients who receive at least one subsequent treatment from ECHELON-1

	ECHELON-1; A+AVD		ECHELON-1; ABVD-based treatment	
	<60-years	≥60-years	<60-years	≥60-years
Patients with at least one subsequent therapy, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
ASCT, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
Brentuximab vedotin monotherapy, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
alloSCT or donor lymphocyte infusion, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
Multiagent chemotherapy, % (n)	[redacted]	[redacted]	[redacted]	[redacted]
Radiation, % (n)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant

Additional information on subsequent treatment distributions

Figure 129: Subsequent treatment distributions (clinical opinion) | A+AVD

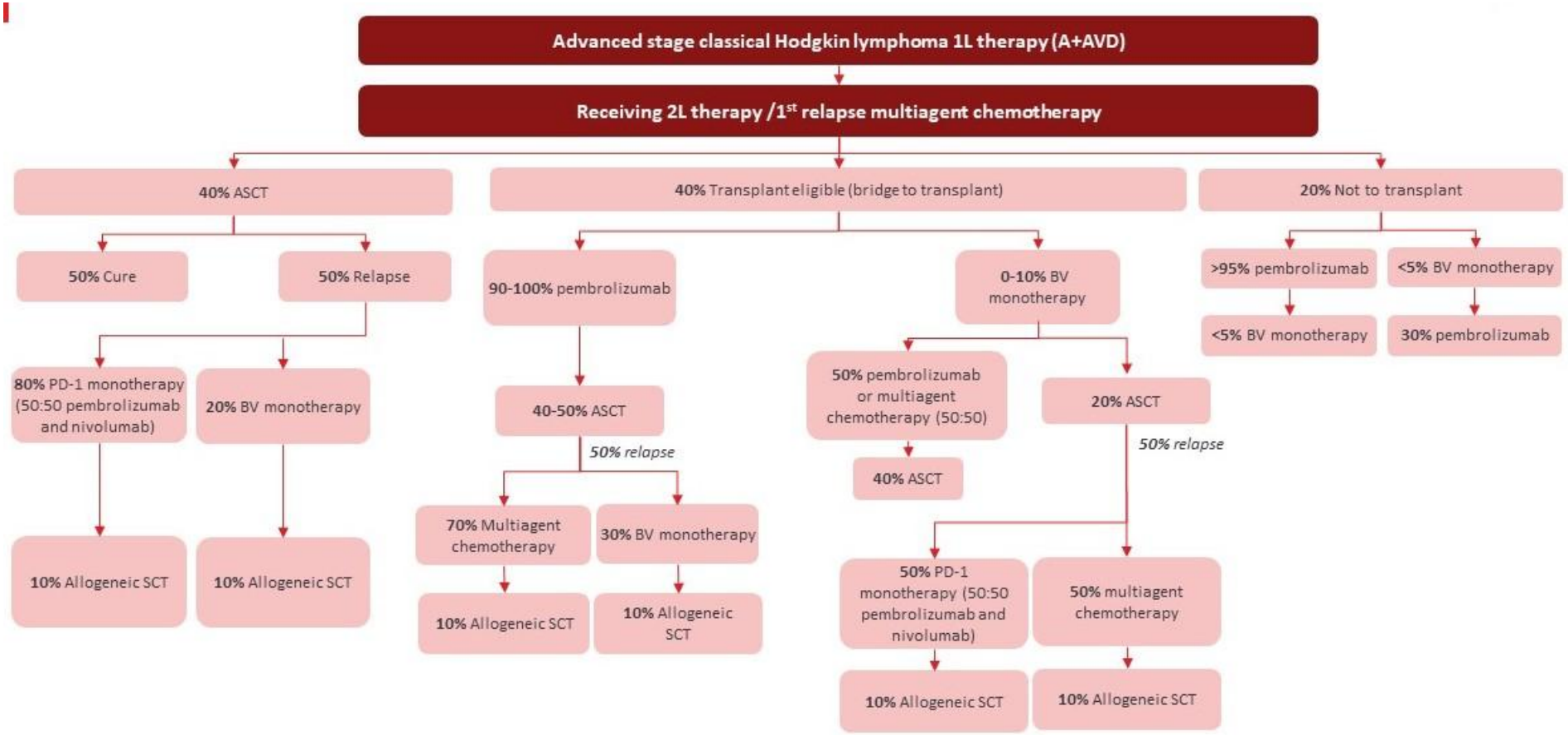
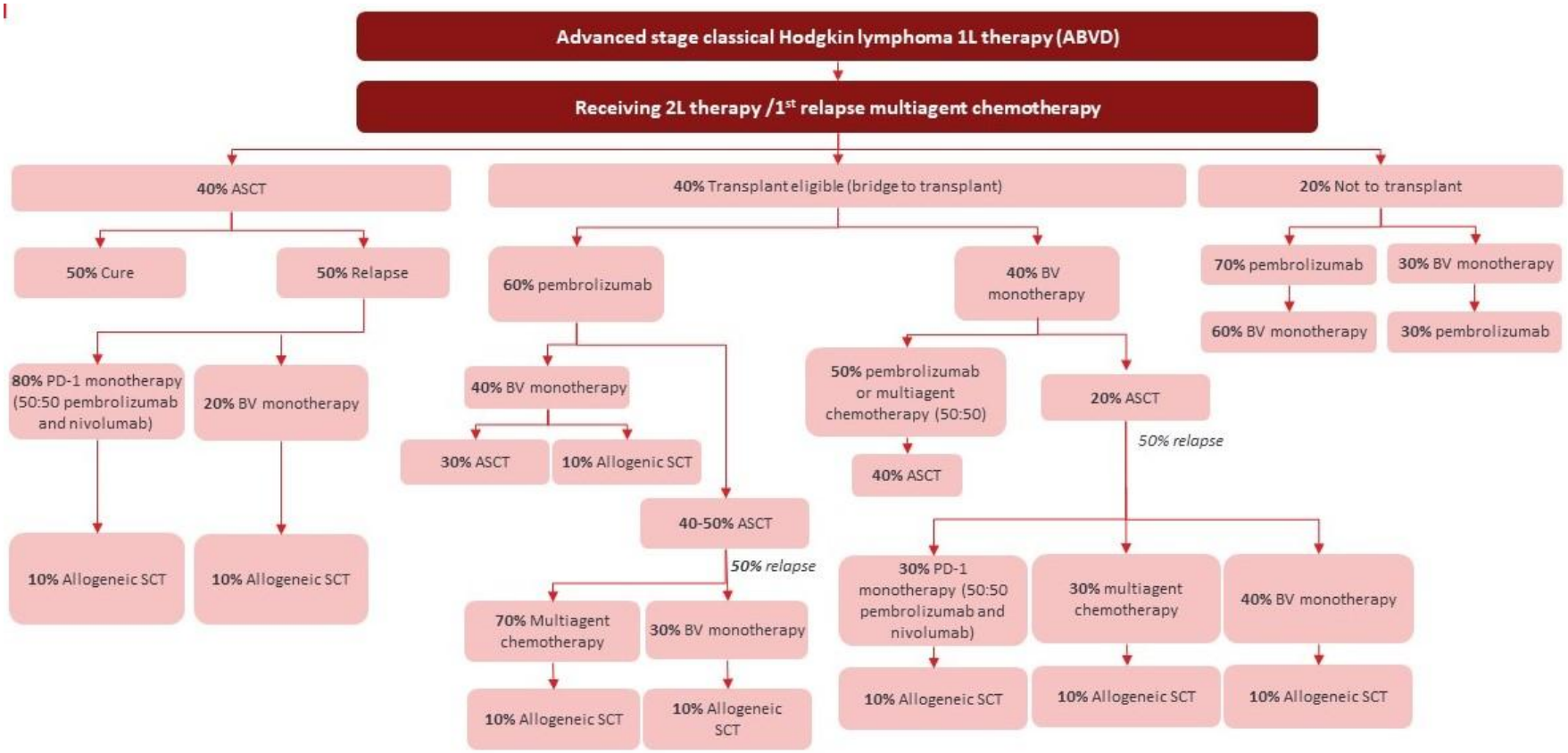


Figure 130: Subsequent treatment distributions (clinical opinion) | ABVD



NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including Review of TA594) [ID6334]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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**

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
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. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. 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. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Funding received in 2023 Takeda - £15,000 (contributed towards our National Conference and publications including Lymphoma Matters magazine) Accord Healthcare Limited - none Hospira - none Janssen-Cilag Ltd - none Kyowa Kirin Ltd - £10,000 (contributed towards our Healthcare Professional project lead) Medac GmbH - none Pfizer Limited - none Seacross Pharmaceuticals Ltd - none Teva Pharma B.V. - none
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with classical Hodgkin lymphoma.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lymphoma is a type of blood cancer, where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The difference is due to abnormal cells called Reed-Sternberg cells found in HL. HL affects less people than NHL but there are still around 2100 people diagnosed with it every year. It can be diagnosed at any age but mostly in people aged between 15 and 34, and those over 60. It is the most common cancer in young people aged between 15 and 24 in the UK. There are two types of HL: classical HL (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Most people have classical Hodgkin lymphoma. Classical Hodgkin lymphoma usually starts with swollen lymph nodes which cause painless swellings in the neck or just above the collar bone, they can also be felt in the armpit or groin. Many people also have these swollen lymph nodes inside their chest. These can cause pain in the chest, cough or shortness of breath, *"…having a bad cough for months. I was told it was a smoker's cough and my chest pains were stress from work".* About a quarter of patients will also have fevers, drenching sweats especially at night and unexplained weight loss. They may also complain about itching or fatigue. Fatigue is a symptom that our patient group find particularly troublesome and difficult to endure. Due to the variety and vagueness of a lot of the symptoms of cHL people can go weeks or months, and often have to see healthcare professionals multiple times, before they are finally diagnosed. One of our patients described her difficult journey to diagnosis, *"My lymphoma was found very late… No one thought to check my symptoms (cough for months, weight loss, night sweats, pain in chest and back) could have been related to cancer".* This is why many people are diagnosed in later stages. As well as the immediate difficulties of living with cHL and enduring treatment, patients often have to live with the long-term effects of the illness as described by this patient, *"The long-term effects of Lymphoma have had a profound effect on my life. I am now disabled and unable to work. I also cannot have children now".* Due to the rapidly developing symptoms, and then the burden of current treatments, patients often have to rely heavily on their family and friends. This can be in the form of emotional support, or with practical things such as getting to appointments or dealing with financial issues. One spouse explained how she was fortunate that her

	workplace allowed her to be flexible with her hours to look after her husband, but that it was still a very difficult time, *"Your world stops after your loved one has been given a diagnosis of cancer*". They also have to witness the struggle that their loved one is going through, which is incredibly difficult: *"It has been extremely hard for my family and friends to see everything I have been through".* *"My husband coped by trying to pretend none of it was happening which put a strain on our marriage".*

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with cHL, even in stages III or IV, usually receive first-line treatment with the aim of cure and long-term remission. It usually responds well to treatment, and most people are cured. Advanced cHL (stage III and IV) is usually treated with chemotherapy in the form of 6 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), or 4 to 6 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and dacarbazine (escBEACOPDac). If there are any remaining areas of lymphoma after chemotherapy, people may have radiotherapy. People over 60 are less likely to be able to endure these intense regimens, and so gentler chemotherapy regimens and more radiotherapy are often used. The chemotherapy may be in the form of chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP) or doxorubicin, vinblastine and dacarbazine (AVD). Although usually successful, the current treatment options have a large physical and emotional impact on patients. They can experience nausea, vomiting, bowel changes and fatigue along with a whole host of other side effects. People are often not able to work or look after their dependents, and in fact become dependent on others. One patient described to us how she had to move back in with her parents as her husband was working two jobs to support them. Becoming completely dependent on others can be incredibly difficult. Unfortunately, 20-30% of people with advanced HL will have cHL which does not respond to first line treatment (refractory) or comes back after treatment (relapse). These patients will often be treated with a course of salvage chemotherapy, and then if fit enough, a stem cell transplant. This is a very intensive treatment requiring prolonged hospital stays. Not everyone is fit enough for this. Also, even if cured, people can experience long term effects of the treatment, which acts as a constant reminder of the experience. Our patients have described brain fog, memory issues, and extreme fatigue. One long-term impact of note is the lung damage that can occur from the bleomycin in ABVD regimen, *“It was decided that I would have AVD as bleomycin could cause lung damage and I only had one lung”.* These short and long-time effects can really impact on a patient’s quality of life and mental wellbeing. Some patients describe how their lives have completely changed since the diagnosis and treatment., *“Adjusting to my life how it is now has been a major challenge…I suffered emotionally a great deal”.* This psychological impact is something that really cannot be underestimated, and often has just as great, if not a greater, long-term impact than the physical.

	"My mum had to come round each day to get me out of bed as I would wake up crying, upset at my life and not wanting to wake up and deal with another day." One unfortunate long term side-effect of the current chemotherapy regimens is infertility, and as a large number of those affected by cHL are young, this has the potential to impact many people: *"My husband has had to come to terms with the fact I can no longer have children and that we will go through rest of our lives together childless."* *"We are currently going through the assisted fertility pathway, but there are no guarantees of children".*
8. Is there an unmet need for patients with this condition?	Our patients feel that there is always a need for more treatment options which are easy to administer and well tolerated. The current chemotherapy regimens such as ABVD are effective in most people but they are not always suitable for all. One of our patients was unable to have ABVD due to damage to her lungs and was offered brentuximab on compassionate grounds. She feels strongly that it saved her life and therefore feels that it should be an option for all.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Brentuximab is an antibody-drug conjugate where an anticancer drug is connected to an antibody. The antibody binds to a molecule on the cancer cell, therefore taking the antibody direct to it's target making it a targeted treatment. Targeted treatments are currently only available in the treatment for cHL for people who have not responded to first line treatments. Brentuximab is intended to be given alongside doxorubicin, vinblastine and dacarbazine (AVD) as an alternative to bleomycin. It is given intravenously on days 1 and 15 of each 28 day treatment cycle. It is to be given in an outpatient setting after AVD is given. A number of our patients with cHL who we questioned have been treated with brentuximab and have experienced its advantages, *"After brentuximab was added into my chemo regime I went into remission… I feel I would not be alive if I had not had brentuximab".* Our patients feel that is especially advantageous for those with later stage disease, and a more complicated disease where current treatment methods are not suitable, or indeed possible. Our patients also felt that brentuximab had the potential to have less side effects than current treatments. One patient described how they tolerated brentuximab based chemotherapy well and had very little in the way of side effects. This meant they were able to work throughout and were not dependent on their loved ones which has both practical and emotional benefits. This same patient started with bleomycin as a component of ABVD but when it had a significant impact on their oxygen levels they were switched to brentuximab and were very grateful for this.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Our patients could see no disadvantages of 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.	Our patients felt that brentuximab would benefit those patients with more complex disease who could not have the current treatment options. One patient was able to have brentuximab privately and so felt there was a currently a disadvantage to those people who were not able to do this.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our patients could not think of any potential equality issues.

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.	• **Classical HL is a serious illness which has a number of short and long term impacts** • **Current treatment options can cause side effects such as infertility and, lung and breathing problems** • **Brentuximab is easily administered, and could be given alongside AVD chemotherapy** • **Brentuximab would give a viable option for patients who are unable to tolerate ABVD chemotherapy** • **Our patients described experiencing very few side effects of brentuximab**

Thank you for your time.

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Single Technology Appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

Clinical expert statement

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The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating previously untreated late-stage classical Hodgkin lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Cathy Burton
2. Name of organisation	Leeds Teaching Hospitals NHS Trust
3. Job title or position	Consultant Haematologist
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 previously untreated late-stage classical Hodgkin lymphoma? ☐ A specialist in the clinical evidence base of previously untreated late-stage classical Hodgkin lymphoma or the 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 did not submit one, I do not 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
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for previously untreated late-stage classical Hodgkin lymphoma ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cure of the condition
9. 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)	Attainment of complete response (CR) or complete metabolic response (CMR)
10. In your view, is there an unmet need for patients and healthcare professionals in previously untreated late-stage classical Hodgkin lymphoma?	Yes
11. How is previously untreated late-stage classical Hodgkin lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Patient are currently treated with ABVD in a RATHL trial approach, ie 2 cycles of ABVD, then an interim PET scan is performed. If CMR on interim PET, then treatment is de-escalated to AVD. If not CMR, either continue with ABVD or escalate to escBEACOPDac. The alternative approach is to treat with escBEACOPDac from outset. Again PET scan performed after 2 cycles and if CMR, 4 cycles of escBEACOPDac are given in total. If not CMR, 6 cycles are given. The alternative to this is the AHL2011 approach, which de-escalates to 4 cycles of ABVD if in CMR after 2 cycles of escBEACOPDac (less commonly used approach). The latter approach (escBEACOPDac) is more intensive so is favoured for the TYA or younger adult patients (less than 50 years) and those with a high prognostic score, eg stage 3-4 disease, high LDH, avoid radiotherapy etc. Front line BSH guidelines Practice varies across UK – some more commonly use ABVD, most institutions give escBEACOPDac to younger, high IPI patients but not at all centres The technology would allow the substitution of bleomycin (which causes lung toxicity and should be avoided in most patients over 60years) by brentuximab. Therefore would improve on the treatment option of ABVD and there may also

	be patients who are borderline for escBEACOPDac whom instead would receive A+AVD.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It would be used in a similar way for advanced HL, ie MDT and patient discussion about merits of individual treatments and the best treatment option for the individual patient. Healthcare resource similar – outpatient administration, should be less lung toxicity so possibly reduced impact on respiratory services, more neutropenia so more G-CSF use Used in secondary care Minimal investment, nurses familiar with giving brentuximab, pharmacy set up required in individual trusts but also fully familiar with drugs
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	In the Echelon-1 trial published in NEJM in 2022, a total of 664 patients were assigned to receive A+AVD and 670 to receive ABVD. At a median follow-up of 73.0 months, 39 patients in the A+AVD group and 64 in the ABVD group had died. The 6-year overall survival estimates were 93.9% in the A+AVD group and 89.4% in the ABVD group. Progression-free survival was longer with A+AVD than with ABVD. Fewer patients in the A+AVD group than in the ABVD group received subsequent therapy, including transplantation, and fewer second cancers were reported with A+AVD (in 23 vs. 32 patients). There has not been a direct comparison between A=AVD and escBEACOPDac. More patients had peripheral neuropathy with A+AVD than with ABVD, but this resolved for most patients. Less lung toxicity with A+AVD and adding in G-CSF meant infection risk comparable. Less risk of second cancers with A+AVD compared with escBEACOPDac.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not compared with general population. More effective for patients in 50-70 years who cannot receive escBEACOPDac and better than ABVD
15. 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 to current practice
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not required as based on trial data, clinical use
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No should be assessed in QALY
18. 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?	Increases treatment options/unmet need for those patients not deemed fit for escBEACOPDac, with improved survival outcomes compared with ABVD

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Peripheral neuropathy can be increased but usually resolves. Use of G-CSF mitigates against infective complications. Less lung toxicity.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do 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?	UK patients entered into Echelon 1 trial so reflects practice. Long term follow up data from trial shows both PFS and more importantly OS benefit of A+AVD. Survival data for advanced HL is already good so to show a further benefit with treatment in terms of survival is important and impressive for these patients. This treatment is aiming for cure with no further treatment including transplant being required. No additional A/E.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Comparable between trial and real world – no concerns.
23. For people who have peripheral neuropathy for 6 years with no resolution of symptoms, would the condition be considered as lifelong, or could resolution still be achieved?	Could further improve after 6 years but if has lasted that long likely to be left with some residual neuropathy.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into	No groups disadvantaged.

account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Patients who received A+AVD for the treatment of stage III or IV Hodgkin's lymphoma in the Echelon-1 trial had a progression free and overall survival advantage over those who received ABVD
2. Intention of treatment is cure and improved outcome with A+AVD reduces need for additional treatment including transplant
3. Substitution of brentuximab for bleomycin reduces the incidence of lung toxicity
4. A+AVD is less toxic with less second cancers and has less impact on fertility than escBEACOPDac
5. Increased incidence of peripheral neuropathy was seen with A+AVD but in the vast majority of patients this resolved without significant sequalae

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Part 1: Treating previously untreated late-stage classical Hodgkin lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Graham Collins
2. Name of organisation	Oxford University Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist and Lymphoma lead clinician Deputy chair of UK Lymphoma Study Group
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 previously untreated late-stage classical Hodgkin lymphoma? ☐ A specialist in the clinical evidence base of previously untreated late-stage classical Hodgkin lymphoma or the 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 did not submit one, I do not 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

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for previously untreated late-stage classical Hodgkin lymphoma ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim for the vast majority of patients is cure of the disease.
9. 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)	Any improvement in the rate of cure (i.e. a rise in the plateau of the progression free survival curve) is clinically meaningful. Ideally this would also be reflected by an improvement in overall survival, although this doesn't have to be the case as patients with relapsed disease can also be cured with the appropriate treatment albeit with intensive therapy.
10. In your view, is there an unmet need for patients and healthcare professionals in previously untreated late-stage classical Hodgkin lymphoma?	Yes. - Whilst cure rates are high with current treatment, those who are not cured (and if fit enough) have to undergo intensive therapy including a stem cell transplant, to try to cure relapsed disease. This is psychologically and emotionally very difficult for patients and disruptive to their work and family life (most patients with Hodgkin lymphoma are young). Furthermore the approach is toxic and associated with significant late effects such as reduced fertility, second cancers and increased risk of heart disease. - For older patients (defined for Hodgkin lymphoma as 60 years of age or older) the chance of cure is reduced. This is partly due to biological differences in the Hodgkin lymphoma but also partly due to older patients not being able to tolerate the more intensive first line regimens (such as escalated BEACOPP) which are associated with increased cure rates. At relapse they are also less likely to be able to tolerate a stem cell transplant making it more likely they will die of the disease.

11. How is previously untreated late-stage classical Hodgkin lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Treatment dose vary from centre to centre and differs according to the age and fitness of the patient. However there are 2 main regimens used: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or escalated BEACOPDac (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, predniolsone and dacarbazine) 1. Young (<60y), fit patients - 6 cycles of ABVD like chemotherapy remains a standard in many centres. It cures about 75% of patients with advanced stage disease. Usually the so-called 'RATHL' approach is adopted, named after the investigator-initiated UK NCRI RATHL study. Patients receive 2 cycles of ABVD then an interim PET scan. If the PET scan is negative (i.e. an excellent response), 4 more cycles are given without the bleomycin – 4xAVD); if the PET scan is positive (residual active lymphoma on the scan) then either patients continue on ABVD or they receive more intensive chemotherapy in the form usually of 4 cycles escalated BEACOPDac. For all advanced stage patients, this approach still resulted in a cure rate of around 75%. This approach is of benefit over 6x ABVD for all, as there is a slight reduction in toxicity of dropping the bleomycin in the majority of patients who are interim PET negative. However those who are interim PET positive had a rather disappointing cure rate, raising the question of how effective the 'escalation' component of this approach actually is. I should add, some large centres in the UK still give 6 cycles of ABVD with no PET adaptation, as standard. - 4-6 cycles of escalated BEACOPDac. The German Hodgkin study group established escalated BEACOPP as a more effective treatment than ABVD albeit with more side effects which initially limited its use outside of Germany. The British group decided to switch the procarbazine to dacarbazine (forming escalated BEACOPDac) in an attempt to reduce the impact on fertility and retrospective studies suggests this maybe the

	case. So in England escalated BEACOPDac has replaced escapated BEACOPP. The current way of using this regimen is to give 2 cycles then an interim PET. If negative 2 more cycles; if positive 4 more cycles with an option of radiotherapy if there are PET avid areas at the end. This approach cures around 90% of patients. However there are more short and longer term toxicities and it is contra-indicated in patients 60y and older. It is also used cautiously (if at all) in patients over 50y and even younger if they have co-morbidities. The choice of ABVD or escalated BEACOPDac in young fit patients is complex and involves shared decision making as well as centre preference. Many centres would advise a 'higher risk' patient (international prognostic score of 3+) to have escalated BEACOPDac. However others would advise all advanced stage fit patients to receive escalated BEACOPDac. On the other extreme, some other centres advise ABVD for all advanced patients, even when young and fit. 2. Older (60y+) patients (may include younger with comorbidities) - Bleomycin lung toxicity is more frequent in older patients. Many centres would give ABVD 2 cycles to 'fitter' older patients. However most would then continue with 4 cycles of AVD (no bleomycin) irrespective of what the PET scan shows. For those patients over the age approximately of 70y, most centres would not give bleomycin at all so patients would receive 6 cycles of AVD. There is however no real 'standard' in these patients. Other regimens include ACOPP (doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone). - For patients who are not fit for an anthracycline (e.g. with cardiac comorbidities), options sadly are not very good at all. A regimen such as ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone) or DECC

	(Iomustine, etoposide, chlorambucil and dexamethasone) maybe used but with the expectation that cure rates are low. Overall for patients aged 60-70, the chance of cure is around 60-65%; for patients aged over 70 this falls to around 50%.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	As the ECHELON-1 trial compared AVD+brentuximab with ABVD, I would expect AVD+brentuximab to largely replace the use of ABVD in those advanced stage patients who would otherwise get ABVD. I would not expect it to replace all patients who would otherwise receive escalated BEACOPDac although some patients may prefer to use AVD+brentuximab instead due to its slightly lower treatment intensity and superiority over ABVD. As older patient are unable to receive escalated BEACOPDac, I would expect AVD+BV to be used in older patients particularly although they would still need to be anthracycline fit. Compared with ABVD, AVD+brentuximab is similar in its administration (brentuximab is a simple 30m infusion). All patients received primary prophylaxis with filgrastim which is an additional supportive measure as this is not used for most patients receiving ABVD / AVD. Peripheral neuropathy is more common with AVD+brentuximab and this may delay return to work for some patients. However there is no current effective treatment so it would not particularly increase healthcare resource utilisation. The technology would be administered in haematology / oncology day treatment units in a hospital setting. No investment would be needed to introduce the technology.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I do expect a meaningful clinical benefit based on the ECHELON-1 study. For those patients who would otherwise get an ABVD/AVD approach I expect that use of AVD+brentuximab would: - Increase their chance of cure (in ECHELON 1 there was a significant increase in progression-free survival with AVD-brentuximab and a reduction in use of subsequent treatment) - Increase their overall survival. This was observed in the ECHELON 1 study and was a surprising result as it is uncommon to see an overall survival advantage in Hodgkin lymphoma studies due to the relative effectiveness of subsequent treatments.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I think the technology would be more impactful for older patients as they would otherwise be getting an ABVD approach.
15. 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)	- Delivery of AVD+brentuximab is very similar to ABVD with no significant increase in chair time - Primary prophylaxis with GCSF is mandated with AVD+brentuximab - There is an increased rate of peripheral neuropathy which clinicians and patients will need to be alert to. Protocols will need to specify dose reductions and discontinuation of BV and / or vinblastine when there is onset or worsening of peripheral neuropathy - No additional monitoring with scans will be needed. - We would expect to see LESS bleomycin lung with AVD+brentuximab as it is a bleomycin-free regimen.

	- In Echelon-1 there was more neutropenic sepsis with AVD+brentuximab although this was reduced when mandatory GCSF use with introduced.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As above, clinicians and patients will need to be alert to the need to monitor clinically for peripheral neuropathy and make the necessary dose adjustments as and when it arises.
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The main benefit is QoL is related to increased cure rate, as quality of life is largely linked to remission status.
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	AVD+brentuximab provides an incremental benefit in the outcomes for the first line treatment of advanced stage classical Hodgkin lymphoma. It results in improved cure rates and overall survival compared to ABVD. For older patients it offers a 'bleomycin free' regimen.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	1. Peripheral neuropathy. This is more common with AVD+brentuximab. Grade 3 is potentially disabling and so careful clinical monitoring needs to happen as patients receive this, with appropriate dose reductions built into the protocol. Grade 3 peripheral neuropathy was uncommon in Echelon-1 but grade 2 can also be problematic for a patient. Happily all studies so far with brentuximab

	show a reduction in grade, or resolution, of peripheral neuropathy with time after treatment for most patients. 2. Sepsis. This was more common with AVD+brentuximab until mandatory primary prophylaxis with GCSF was built into the protocol. GCSF should therefore be used with this regimen. However centres are used to educating patients on this use with other regimens and patients rarely find it difficult to use.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do 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?	The main issue here is that not all centres use 6x ABVD as standard of care. 1. The RATHL approach is described above. The RATHL study showed that omitting the bleomycin for cycle 3-6 in those who were interim PET negative was a little less toxic and was as effective as continuing with ABVD. It was however no more effective in terms of cure rate. For those who were interim PET positive, escalation to escalated BEACOPP was associated with a disappointing progression free survival. Overall then there is no suggestion that the outcome of the RATHL study is better (in terms of PFS and OS) than that of 6x ABVD for advanced stage patients. 2. Escalated BEACOPDac. The German Hodgkin study group, and the EORTC group have shown cure rates with escalated BEACOPP of around 90% for advanced stage disease. Whilst there is no study comparing AVD+brentuximab with escalated BEACOPP, it would be expected that AVD+brentuximab would not be superior to escalated BEACOPP / escalated BEACOPDac in terms of PFS and OS. For those patients who are deemed by their clinician to be suitable for this more intensive approach I would not therefore expect AVD+brentuximab to replace this approach. However some patients may elect a slightly less intensive regimen which shown to be superior to ABVD even if it perhaps less effective than escalated BEACOPDac.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. How do data on real-world experience compare with the trial data?	AVD+brentuximab is not available in England or the devolved nations so there is no UK based real world data. I am aware of a study by Steiner et al (2023) Blood Adv. They retrospectively analysed the outcome of 179 US patients treated with AVD-BV in the 'real world'. The focus of the study was to see if dose reductions of BV was associated with worse outcome. The 12 month PFS was 90% and no association of outcome with cumulative dose of BV was seen. Overall this study confirmed high efficacy of AVD-BV and was reassuring to clinicians that dose reductions due to toxicity do not appear to have a major impact on outcome.
23. For people who have peripheral neuropathy for 6 years with no resolution of symptoms, would the condition be considered as lifelong, or could resolution still be achieved?	Peripheral neuropathy generally improves slowly over several years. However if it is persisting at 6 years I would not expect further improvement. Do I would consider it life long at this stage.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	None that I am aware of.

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The aim of first line treatment in Hodgkin lymphoma is cure.

AVD+brentuximab does increase cure (PFS) and overall survival compared with ABVD providing a significant, incremental benefit.

In England, an ABVD/AVD approach remains standard for many patients especially those who are older.

Escalated BEACOPDac is another standard regimen which is the most effective so far described and probably more effective than AVD+brentuximab but it is not suitable for all due to its high intensity and some centres use very little of it.

Peripheral neuropathy is one of the main side effects which would need to be monitored carefully and dose adjustments made as required.

Thank you for your time.

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Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report.
Vicky Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections.
Nicole Downes	Critical appraisal of the company's submission and critical appraisal of the clinical evidence.
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.
Sophie Ip	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

A	Brentuximab vedotin
A+AVD	Brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
ADC	Antibody–drug conjugate
AE	Adverse event
AFM	Alternative frontline medication
AIC	Akaike Information Criterion
ALCL	Anaplastic large cell lymphoma
AlloSCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukaemia
ARDS	Acute respiratory distress syndrome
ASCT	Autologous stem cell transplantation
AUC	Area under curve
AVD	Doxorubicin, vinblastine, dacarbazine
BEACOPDac	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone
BEACOPP-14	14-day bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone regimen
BIC	Bayes Information Criterion
BNF	British National Formulary
BSA	Body surface area
BSH	British Society for Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CDF	Cancer Drugs Fund
CI	Confidence interval
COMP	Committee for Orphan Medicinal Products
CR	Complete remission
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
DCO	Data cutoff
DLBCL	Diffuse large B-cell lymphoma
DS	Deauville score
DSU	Decision support unit
EAG	External assessment group
ECDRP	European Commission Decision Reliance Procedure
ECOG	Eastern Cooperative Oncology Group

EMA	European Medicines Agency
eMIT	Electronic marketing information tool
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of treatment
Esc	Escalated
ESMO	European Society of Medical Oncology
EAG	External Assessment Group
FACIT	Functional Assessment of Chronic Illness Therapy
FACT/GOG-NTx	Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity subscale
G-CSF	Granulocyte-colony-stimulating factor
GHSG	German Hodgkin Study Group
HCRU	Healthcare resource utilisation
HDCT	High-dose chemotherapy
HF	Heart failure
HL	Hodgkin lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HRS	Hodgkin and Reed-Sternberg
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent data and safety monitoring committee
ILD	Interstitial lung disease
INV	Investigator
IPS	International Prognostic Score
IQR	Interquartile range
IRF	Independent review facility
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
LTFU	Long-term follow up
LY	Life year
LYG	Life year gained
MAIC	Matched adjusted indirect comparison
MCM	Mixture cure models
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Multidimensional Fatigue Inventory
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimally important difference

MMAE	Monomethyl auristatin E
NA	Not applicable
NE	Not estimable
NICE	National Institute of Health and Care Excellence
NHS	National Health Service
NMB	Net monetary benefit
ORR	Overall response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD	Progressive disease
PET	Positron emission tomography
PET2	Positron emission tomography after cycle 2
PFS	Progression-free survival
PMN	Peripheral motor neuropathy
PN	Peripheral neuropathy
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PTFU	Post-treatment follow-up
PVLE	Present value lifetime earnings
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life questionnaire
QoL	Quality of life
RATHL	Response-Adapted Therapy for advanced Hodgkin Lymphoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
R/R	Relapsed or refractory
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SoC	Standard of care
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document

TTO	Time trade-off
VAS	Visual analogue scale
VHD	Valvular heart disease
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WHO	World Health Organization
WPAI:CG	Work Productivity and Activity Impairment Caregiver questionnaire
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs; Section 1.4).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (Section 2 onwards).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Clinical data for ABVD not reflective of current standard care in UK clinical practice	2.2.1, 2.3.3
2	Bimodal age patient population not adequately accounted for in the model	4.2.3
3	Use of a spline model for OS survival modelling	4.2.6
4	Use of different standardised mortality ratios for A+AVD and ABVD	4.2.7
5	Life-long peripheral neuropathy not included in the model	4.2.8

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; EAG, External Assessment Group; OS, overall survival; UK, United Kingdom.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the use of a mixed cure model (MCM) to extrapolate the ECHELON-1 survival data, the application of the same standardised mortality ratio to both treatment arms and the inclusion of peripheral neuropathy as an adverse event of interest in the model.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Decreasing the probability of disease progression, in this case, the recurrence of Hodgkin's lymphoma;
- Increasing the rate of patient survival; and
- Increasing the probability of adverse events.

Overall, the technology is modelled to affect costs by:

- Being more costly than the comparator;
- Fewer patients requiring subsequent treatments;
- Fewer patients requiring treatment administrations;
- Fewer patients requiring monitoring and follow up care; and
- More patients requiring adverse event treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- Weighting the ICER based on the age groups predominantly impacted by HL;
- The standardised mortality ratios (SMR) applied to A+AVD and ABVD;
- The choice of OS extrapolation model and curve; and
- The inclusion of patients with potentially lifelong peripheral neuropathy.

1.3 Summary of the EAG's key issues

Table 2. Issue 1: Clinical data for ABVD not reflective of current standard care in UK clinical practice

Report section	2.2.1, 2.3.3
Description of issue and why the EAG has identified it as important	The company has used the clinical efficacy data for six-cycle ABVD from the ECHELON-1 trial to inform ABVD in the economic model, but both the company and the EAG's clinical experts reported that the main comparator of relevance to UK clinical practice is PET-adapted ABVD. The EAG is thus concerned that the efficacy data used in the economic model may not be reflective of the efficacy of PET-adapted ABVD in UK clinical practice. The company conducted MAICs to support the decision to use the six-cycle ABVD comparator efficacy data in the model but the EAG considers the results of the MAICs to be unreliable. This is partly because the MAICs are unanchored and also because the assumption of proportional hazards was shown not to hold in the MAICs where full adjustment for all baseline characteristics was made. In addition to the concerns around the efficacy data, the EAG considers the safety data to also potentially be unreliable for both A+AVD and ABVD. This is because a large proportion of patients on A+AVD did not receive the now recommended primary prophylaxis with G-CSF from Cycle 1 and thus AEs may be higher in ECHELON-1 compared to that expected in clinical practice. However, the EAG also considers that there is potential issues with the

	safety data for ABVD used in the model. Of particular note, some of the comparator data (data from the RATHL trial) appear to be based on all TEAEs rather than drug-related TEAEs (ECHELON-1 data) and the escBEACOPP regimen used in the RATHL trial doesn't align with the escBEACOPDac regimen used in UK clinical practice. Despite the issues flagged above, the EAG agrees with the company that ECHELON-1 is the best available source of efficacy data for A+AVD and ABVD for use in the model at present. The EAG also does not consider it possible to predict the likely resulting direction of bias from the efficacy and safety data currently used in the company's economic model.
What alternative approach has the EAG suggested?	None. The EAG considers this issue to be unresolvable due to a lack of alternative data being available.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Direct head-to-head clinical data for A+AVD compared to PET-adapted ABVD in the relevant UK population is required to enable more reliable estimates of the efficacy and safety of A+AVD compared to current clinical practice. However, the EAG is not aware of any additional data that is currently available to enable a more reliable estimate of the efficacy or safety of A+AVD versus PET-adapted ABVD.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event; EAG, External Assessment Group; escBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; escBEACOPDac,escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, dacarbazine; G-CSF, granulocyte-colony-stimulating factor; MAIC, matched adjusted indirect comparison; PET, positron emission tomography; TEAE, treatment-emergent adverse event; UK, United Kingdom.

Table 3. Issue 2: Bimodal age patient population not adequately accounted for in the model

Report section	4.2.3
Description of issue and why the EAG has identified it as important	Previously untreated late-stage classical Hodgkin lymphoma affects the population bimodally, with 20–24 year and 75–79-year-olds being most likely to have the condition. As such, the EAG considers that the company's mean age based approach may not be appropriate, given the two patient populations predominantly impacted.
What alternative approach has the EAG suggested?	The company was requested to provide an age-weighted ICER using the <60 and ≥60-year-old patient subgroups in ECHELON-1 as a scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Accounting for the age subgroups led to an increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence required.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

Table 4. Issue 3: Use of a spline model for OS survival modelling

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company have extrapolated the A+AVD and ABVD OS KM survival data using a spline model in contrast to the MCM used to model PFS. The company's clinical and health economic advisors unanimously agreed that

	the MCMs provided the best approach given the goal of treatment (i.e. cure), outcomes observed in ECHELON-1, and expectations in UK clinical practice which the EAG agrees with. The company's justification for the spline model is that under probabilistic conditions implausible cure fractions may be calculated; however, the EAG considers that some of the MCM models provide a good visual and statistical fit in addition to robust probabilistic cure fractions. As such, the EAG considers that OS should be modelled using a MCM.
What alternative approach has the EAG suggested?	As OS MCMs were explored in company scenario analysis, it was already possible to apply MCMs in the model and so no alternative approaches were suggested.
What is the expected effect on the cost-effectiveness estimates?	Modelling the OS survival data using a MCM led to an increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence required.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; EAG, External Assessment Group; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival.

Table 5. Issue 4: Use of different standardised mortality ratios for A+AVD and ABVD

Report section	4.2.7
Description of issue and why the EAG has identified it as important	In the company base case, separate SMRs have been applied to the A+AVD and ABVD mortality rates, with a higher SMR being assigned to ABVD (1.1) than A+AVD (1.05). This was based on the company's clinical expert opinion, and that A+AVD is more effective than ABVD, resulting in lower second malignancies and less exposure to subsequent treatment toxicities. Additionally, the company states that ABVD is a bleomycin containing treatment and therefore is associated with increased pulmonary toxicity. The EAG notes that the rates of second malignancies were broadly similar between treatments and that A+AVD patients were recorded as having more Grade ≥3 adverse events compared to ABVD in ECHELON-1. Furthermore, the EAG's clinical experts did not consider a difference in SMR clinically plausible. The EAG therefore considers that there is a lack of robust evidence to support differing SMR being applied and that applying the same SMR is more appropriate. The EAG notes that in the company base case, the ICER is most sensitive to the SMRs.
What alternative approach has the EAG suggested?	The EAG requested the company to present scenarios in which the SMR applied to background mortality was equal in both treatment arms, and to explore a range of alternative SMR values sourced from a review of the literature which the company conducted.
What is the expected effect on the cost-effectiveness estimates?	Applying the same SMR to each treatment arm led to an increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence required.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate.

Table 6. Issue 5: Life-long peripheral neuropathy not included in the model

Report section	4.2.8
Description of issue and why the EAG has identified it as important	While peripheral neuropathy was not originally included in the modelled adverse events, the EAG notes that 68 (10.3%) A+AVD patients in the arm and 11 (1.7%) ABVD patients reported one or more Grade ≥3 peripheral neuropathy events. At clarification a scenario including peripheral neuropathy was conducted; however, the EAG notes that the scenario assumed an adverse event duration calculated from patients whose peripheral neuropathy had resolved while 16 (2.4%) and 4 (0.6%) of A+AVD and ABVD patients had unresolved grade ≥3 peripheral neuropathy at last follow up. Median last follow up A+AVD patients was 356.7 weeks and 321.6 weeks for ABVD patients. The EAG therefore considers that a proportion of patients may have lifelong peripheral neuropathy, which is not captured in the company base case.
What alternative approach has the EAG suggested?	At clarification the EAG requested the company to conduct a scenario including peripheral neuropathy as an adverse event which the company conducted; however, potentially life-long peripheral neuropathy was not accounted for. The EAG therefore conducted a scenario analysis accounting for 2.4% and 0.6% of A+AVD and ABVD patients experience lifelong peripheral neuropathy.
What is the expected effect on the cost-effectiveness estimates?	The scenario led to a decrease in the incremental QALYs, given more A+AVD patients were recorded with Grade ≥3 or above peripheral neuropathy at last follow up.
What additional evidence or analyses might help to resolve this key issue?	Longer term peripheral neuropathy resolution status information for ECHELON-1 patients. In lieu of this, clinical expert opinion on whether peripheral neuropathy can be considered lifelong or not after more than six years having the condition with no resolution of symptoms.

Abbreviations: A+AVD, brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

1.4 Summary of EAG's preferred assumptions and resulting ICER

Table 7. Summary of EAG's preferred assumptions and resulting ICER

EAG preferred assumptions	Incremental costs	Incremental QALYs	ICER £/QALY (change from company base case
Company corrected base case	[redacted]	[redacted]	[redacted]
Applying the same SMR to both treatment arms (1.05)	[redacted]	[redacted]	[redacted]
Using the literature-based approach to calculate adverse event disutility	[redacted]	[redacted]	[redacted]

Using the EAG preferred adverse event disutilities and durations*	[redacted]	[redacted]	[redacted]
Applying treatment specific mean time to peripheral neuropathy resolution*	[redacted]	[redacted]	[redacted]
Accounting for patients with lifelong peripheral neuropathy*	[redacted]	[redacted]	[redacted]
Informing subsequent treatment proportions from company clinical expert opinions	[redacted]	[redacted]	[redacted]
5% of subsequent treatment patients receiving radiation*	[redacted]	[redacted]	[redacted]
Age-weighted ICER	[redacted]	[redacted]	[redacted]
Modelling long term OS and PFS using a MCM and the EAGs preferred distributions*	[redacted]	[redacted]	[redacted]

*Note: preferred assumption also includes previous listed preferred assumption.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival, PFS, progression free survival; QALY, quality-adjusted life-year

Table 8. EAG base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
A+AVD	[redacted]	20.11	[redacted]	-	-	-	-
ABVD	[redacted]	19.28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
A+AVD	[redacted]	20.09	[redacted]	-	-	-	-
ABVD	[redacted]	19.29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

Modelling errors identified and corrected by the EAG are described in Section 6.1 . For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.3.1.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of brentuximab vedotin (ADCETRIS®; Takeda) with doxorubicin, dacarbazine and vinblastine (A+AVD) in the treatment of adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma. The external assessment group (EAG) notes that the population specified in the National Institute for Health and Care Excellence (NICE) final scope (people with previously untreated late-stage classical Hodgkin lymphoma [HL])[1] has been adapted by the company to align with the anticipated marketing authorisation. Brentuximab vedotin (hereafter referred to as brentuximab) already has existing marketing authorisation (granted by the Medicines and Healthcare Products Agency [MHRA] on 6 February 2019) for previously untreated CD30+ Stage IV HL, in combination with doxorubicin, vinblastine and dacarbazine (AVD). In addition, the company has submitted a further application to the MHRA for marketing authorisation for brentuximab vedotin for adult patients with previously untreated CD30+ Stage III Hodgkin lymphoma (HL) in combination with AVD and is expecting this to be granted later in 2024. The EAG and the EAG's clinical experts consider the company's proposed population to be reasonable. Further critique on the company's adherence to the decision problem in the NICE final scope is provided in Section 2.3.

2.2 Background

Within Section B.1 of the CS, the company provides an overview of:

- brentuximab, including its mechanism of action, indications, dose and method of administration (Section B.1.2 of the CS);
- HL, including disease overview, diagnosis and staging, epidemiology and disease burden (Section B.1.3 of the CS).

Lymphoma is blood cancer that affects white blood cells of the lymphatic system, called lymphocytes.[2] It is divided into two main types: HL and non-HL.[2, 3] The malignant lymphocytes found in HL are referred to as Hodgkin Reed-Sternberg (HRS) cells.[4] HL is subdivided into classical HL and nodular lymphocyte-predominant HL, based on morphology and immunohistochemistry.[3, 4] The malignant HRS cell in classical HL exhibits a characteristic immunophenotypic pattern of CD30+,

CD15+, and CD45+.[4] Due to expression of CD30, classical HL is also referred to as CD30+ HL. The EAG notes that the population of interest for this single technology appraisal (STA) is classical HL and hereafter, classical HL will be referred to as CD30+ HL to align with the company submission (CS).

2.2.1 Treatment pathway and proposed positioning of A+AVD

The aim of first-line treatment for patients with Stage III or IV CD30+ HL is cure, without the need for additional therapy.[5] The company reported that the British Society for Haematology (BSH) guidelines, published in 2022, are those typically used in the UK to guide the treatment of previously untreated HL, along with local trust guidelines and protocols at each centre.[6, 7] For [redacted] (the population of relevance to this STA), the BSH guidelines recommend initiating treatment with either combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), or escalated treatment with bleomycin, etoposide, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine and prednisolone (escBEACOPP); in older patients or those with comorbidities, ABVD, AVD or alternative anthracycline-containing regimens are recommended.[6]

Procarbazine is associated with risks of gonadal and haematopoietic stem cell toxicity and the BSH guidelines suggest escBEACOPP with a dacarbazine substitution as a treatment alternative, hereafter referred to as escBEACOPDac.[6] The EAG understands from the CS and its clinical experts that escBEACOPDac is more frequently used than escBEACOPP in the UK, therefore only escBEACOPDac is discussed from here onwards.

Following the first two cycles of ABVD or escBEACOPDac, the BSH guidelines recommend PET-adapted treatment based on the findings of an interim PET scan (PET2).[6] The company reported that PET-adapted treatment is not used across all treatment centres in the UK but the EAG's clinical experts consider the PET-adapted approach to be the recommended approach in the UK and that it should be used by all UK treatment centres unless there is an individual patient specific reason as PET scans are widely available.

The company reported that the use of ABVD or escBEACOPDac as an initial treatment for CD30+ HL varies across the UK due to regional or centre-based preferences, and depends on multiple factors, including the patient's risk profile and the toxicity/efficacy balance of the recommended treatment regimens.[6, 7] Based on findings from an advisory board meeting, the company considered that ABVD tends to be used from the start in patients who are unsuitable or unwilling to accept the greater toxicity of up to six cycles of escBEACOPDac, or who do not require such an intensive regimen.[7] The

EAG's clinical experts agreed that this is broadly consistent with their experience in clinical practice in England.

In terms of the PET-adapted treatment strategies recommended by the BSH guidelines, for ABVD the recommended strategy is referred to as the RATHL approach.[6, 8] This is because it is based on the findings from the RATHL trial.[8] In summary, the RATHL trial approach is de-escalation to AVD or escalation to escBEACOPDac, depending on PET2 status, after two initial cycles of ABVD. The EAG notes that the RATHL trial used escalation to BEACOPP-14 or escBEACOPP rather than escBEACOPDac, but the EAG's clinical experts reported that the RATHL strategy is used in clinical practice with the substitution to escBEACOPDac and agreed with the company that efficacy is considered equivalent among the three different escalation drug combinations.

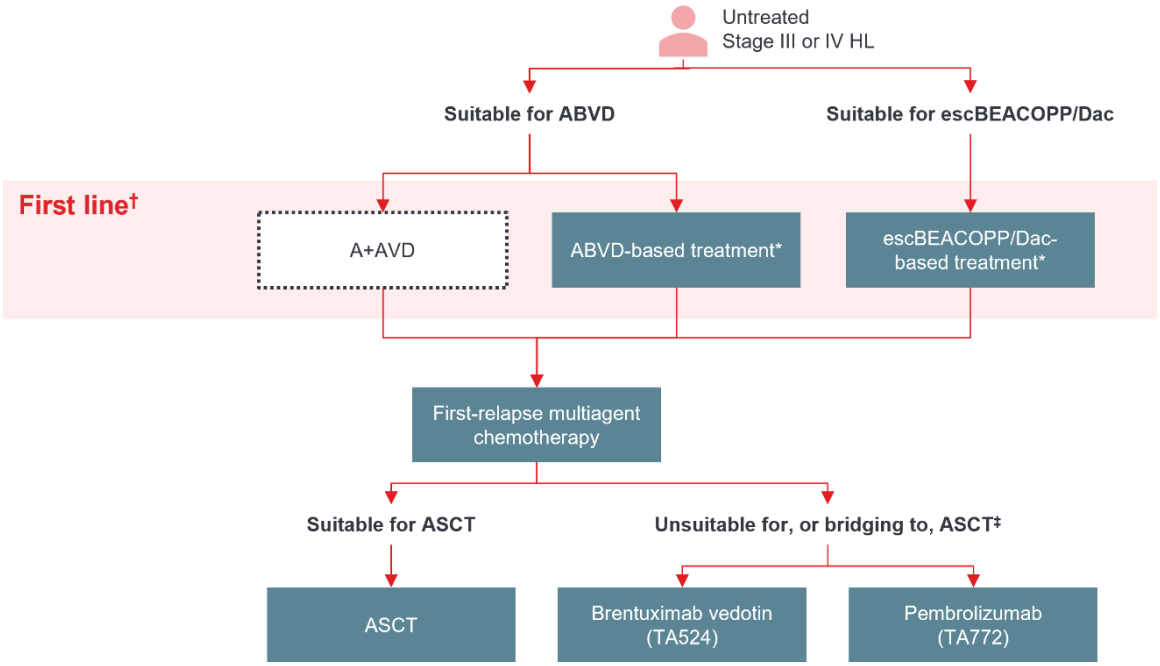
For patients starting with two cycles of escBEACOPDac, the treatment strategies are based on the HD18 trial[9] and the AHL2011 trial[10]. The HD18 trial recommended strategy is two additional cycles of escBEACOPDac in PET2-negative patients, or four additional cycles of escBEACOPDac in PET2-positive patients. The recommended strategy based on the AHL2011 trial is de-escalation to four cycles of ABVD or AVD in PET2-negative patients after two initial cycles of escBEACOPP.

The company reported that end of treatment radiotherapy may also be given following any of the treatment strategies but the EAG's clinical experts agreed with the company that it is not routinely used in all hospitals. In terms of follow-up, the company reported that patients are usually followed up for two years after the end of treatment and this is considered to be the timepoint within which the majority of relapses will occur. The EAGs clinical experts considered that while follow-up is likely to be more frequent for the first 2 years, patients may be followed up until 5 years before they are discharged.

2.2.1.1 Proposed positioning of A+AVD in therapy

The company's proposed positioning of A+AVD is for the treatment of previously untreated patients with CD30+ Stage III or IV HL who would otherwise be suitable for treatment with ABVD (Figure 1). The EAG notes that this proposed positioning of A+AVD is narrower than the NICE final scope as it limits the use of A+AVD to patients who would otherwise be eligible for treatment with ABVD and not those who would be treated with escBEACOPDac from the start. The EAG also notes that there is no escalation or de-escalation of treatment in response to PET2 in the current proposed positioning of A+AVD in contrast with how ABVD is used in clinical practice. Nevertheless, the EAG's clinical experts consider the company's proposed positioning of A+AVD in the treatment pathway to be reasonable.

Figure 1. Company overview of the current treatment pathway for untreated Stage III or IV CD30+ HL in England and Wales, and proposed positioning of A+AVD (reproduced from CS, Figure 3)



Dashed box denotes proposed place of A+AVD in therapy.
*Treatment may be PET-adapted (e.g. RATHL) or not PET-adapted. †Alternative treatment options (e.g. AVD, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone [ACOPP]) may be used in some patients where age or frailty precludes standard therapeutic options. ‡In transplant-naïve patients, treatment with pembrolizumab or brentuximab vedotin may be used as a bridge to ASCT.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplantation; CD30, cell membrane receptor 30; escBEACOPP/Dac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, prednisolone, procarbazine or dacarbazine; HL, Hodgkin lymphoma; PET, positron emission tomography; RATHL, *response-adapted therapy for advanced Hodgkin lymphoma;* TA, technology appraisal.
Sources: NICE 2021 (TA772 public committee slides);[11] British Society for Haematology guidelines;[6] Takeda, Medical Advisory Board (2023)[12].

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE[1], together with the company's rationale for any deviation from this, is provided in Table 9 below. Key differences between the decision problem addressed in the CS and the NICE final scope are discussed in greater detail in the sections that follow this table; the EAG considers that the main concerns are around the suitability of the comparator data used in the economic model.

Table 9. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with previously untreated late-stage classical Hodgkin lymphoma	[redacted]	The population was adjusted in line with the anticipated marketing authorisation.[1]	The EAG notes that the population detailed in the CS differs to that specified in the final scope issued by NICE but the EAG's clinical experts consider the population addressed by the company to be reasonable and note that it aligns with the anticipated marketing authorisation for brentuximab. The EAG also notes that the company's proposed positioning of brentuximab further narrows the population to those patients eligible for ABVD. This is discussed further in Section 2.3.3. In terms of the ECHELON-1 RCT, the EAG's clinical experts reported that the baseline characteristics of patients in the trial are broadly consistent with patients with [redacted] in the UK population. Please see Section 2.3.1 for further critique of the population.
Intervention	Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine	Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine	In line with the NICE final scope and marketing authorisation.[1]	The treatment regimen for brentuximab vedotin with doxorubicin, dacarbazine and vinblastine in the ECHELON-1 RCT is consistent with the anticipated MHRA marketing

				authorisation but the EAG notes that at present brentuximab only has marketing authorisation for use in patients with previously untreated CD30+ Stage IV HL, in combination with AVD. However, the company is expecting the MHRA to also grant approval for brentuximab vedotin for [redacted] and is expecting this to be granted [redacted]. See Section 2.3.2 below for further discussion.
Comparator(s)	Single or combination chemotherapy including but not limited to drugs such as doxorubicin, bleomycin, dacarbazine and vinblastine	Combination chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD-based regimens)	The proposed positioning of A+AVD is for the treatment of [redacted] who would otherwise be suitable for treatment with ABVD. In current UK clinical practice, patients suitable for treatment with ABVD will receive an ABVD-based regimen, either as six cycles or as per the PET-adapted RATHL approach.[6] While PET-adapted ABVD is commonplace across the UK, there are centres that do not use PET adaptation (i.e. treat with six cycles of ABVD rather than via the RATHL strategy).[7]	The EAG notes the company's positioning of A+AVD as a treatment for patients who would otherwise be suitable for ABVD and thus agrees that the comparator is an ABVD-based regimen. However, the EAG's clinical experts reported that the PET-adapted RATHL approach for ABVD is widely used in UK clinical practice and therefore the EAG is concerned that the company's estimate of 10% of patients using a standard unadjusted ABVD regimen may not accurately reflect UK clinical practice.

			Therefore, the comparator in the CEM is ABVD-based treatment, comprised of a weighted average of ABVD (six cycles) and PET-adapted ABVD, (10% and 90%, respectively, based on UK clinical expert feedback).	
Outcomes	The outcome measures to be considered include: • overall survival; • progression-free survival; • response rates; • adverse effects of treatment; • health-related quality of life.	As per the final scope, the submission considers the following outcomes: • overall survival; • progression-free survival; • response rates; • adverse effects of treatment; • health-related quality of life.	In line with the NICE final scope.[1]	The EAG considers the outcomes reported in the CS from ECHELON-1 to appropriately cover the outcomes specified in the final scope issued by NICE but the EAG notes that data from the final data cutoff were not provided in the clinical-effectiveness results section of the CS for the HRQL assessment using the EORTC QLQ-C30 or EQ-5D-3L tools. However, the EAG also notes that it is reported in the CS that the EQ-5D-3L data from the final data cut-off was used in the economic model. The EAG also notes that data on OS, PFS, HRQL and AE's from ECHELON-1 are used in the company's economic model. Further discussion of the outcomes is provided in Section 2.3.4.
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	The analysis performed is in line with the NICE reference case, and the NICE 2022 health technology evaluation manual; the economic analysis is a cost-utility analysis.	In line with the NICE reference case.	The EAG considers that the model evaluates the cost-effectiveness of treatments according to costs and QALYs with an ICER reported, in line with the NICE reference case.

	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, comparator and subsequent treatment technologies will be taken into account.	Costs and QALYs are considered over a lifetime horizon and will be conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The main output of the economic analysis is the incremental cost-effectiveness ratio (ICER). Certain subsequent treatments included in the economic analysis have confidential PASs in the form of simple discounts. The economic analysis has allowed for inclusion of these simple discounts for subsequent treatments, but the base case analysis reflects list prices for these treatments.		Appropriate time horizons have been assumed with an NHS and PSS perspective taken. The base cases reported reflect the list price of treatments, not including brentuximab vedotin which reflects the PAS price, with the discounts for relevant treatments included in the confidential appendix.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CD30, cell membrane receptor 30; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PSS, Personal Social Services; QALY, quality-adjusted life year.

2.3.1 Population

The population specified in the final scope issued by NICE is people with previously untreated late-stage classical Hodgkin lymphoma. The EAG notes that in the decision problem addressed in the CS the company has adapted the population to align with the anticipated wording of the marketing authorisation for brentuximab. The resulting population addressed in the CS is adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma, and based on feedback from its clinical experts, the EAG considers this to be reasonable. However, the EAG also notes that the population is further restricted by the company's positioning of brentuximab for patients eligible for ABVD. This restriction is discussed further in the critique of the comparators provided in Section 2.3.3 but the EAG considers it important to flag that it comprises a subgroup of the population of adult patients with previously untreated CD30+ Stage III or IV HL.

The ECHELON-1 trial[13] provides the key clinical safety and efficacy data for brentuximab in the CS and it was an international, open-label, randomised, Phase III randomised, controlled trial (RCT) of A+AVD (n=664) compared with ABVD (n=670). The trial was conducted across 218 sites in 21 countries and 154 of the 1334 enrolled patients were from Great Britain. ECHELON-1 enrolled treatment-naïve adults (aged ≥18 years) with histologically confirmed CD30+ Stage III or IV HL, and randomisation was stratified according to geographic region (Americas; Asia; Europe) and IPS risk factors (0–1; 2–3; 4–7). The EAG's clinical experts agreed with the company that the incidence of HL is bimodal with peaks at ages 20–24 years and 75–79 years, and the EAG considers the subgroup data by age <60 years and ≥60 years from ECHELON-1 of potential relevance (Section 3.3.5).[14, 15] The EAG's clinical experts also reported that the proportion of Stage III patients (36.3%) was slightly lower than expected in UK clinical practice and the proportion of Stage IV patients (63.7%) was slightly higher than expected. The EAG notes that data reported by Cancer Research UK on HL stage at diagnosis in England for 2021 indicate the split between Stage III and IV was 39.5% and 60.5%.[16]

The RATHL trial[17] (which provides comparator data for ABVD via the RATHL approach) was a prospective, RCT to determine whether the omission of bleomycin after negative findings on an interim PET-CT scan could yield a noninferior progression-free survival (PFS) rate at 3 years when compared with continued ABVD. The RATHL trial also followed-up the patients with positive findings on the interim PET-CT scan, for comparison with PFS in historical controls. Patients in the RATHL trial were recruited from sites across the United Kingdom, Italy, Australia, New Zealand, Norway, Sweden, and Denmark. The EAG's clinical experts considered the population in the Stage III and IV

subgroup of the RATHL trial to be potentially more representative of adult patients with previously untreated CD30+ Stage III or IV HL who are likely to be eligible for A+AVD than the population in the ECHELON-1 trial (see Appendix 8.1 for the baseline characteristics of the Stage III and IV subgroup from RATHL and for ECHELON-1). The EAG also notes that there was a [redacted] proportion of patients aged <60 years and ≥60 years in the Stage III and IV RATHL cohort ([redacted]% and [redacted]%, respectively) compared to in ECHELON-1 (86.1% and 13.9%, respectively).

In summary, the EAG considers the population addressed in the CS to be reasonable but also notes that the company's proposed positioning of A+AVD is for the treatment of previously untreated patients with CD30+ Stage III or IV HL who would otherwise be suitable for treatment with ABVD and that this is a subgroup of the population with previously untreated patients with CD30+ Stage III or IV HL.

2.3.2 Intervention

Brentuximab vedotin 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).[18, 19] Brentuximab selectively binds to the CD30 transmembrane cytokine receptor on malignant lymphoid cells and it ultimately results in cell death.

As discussed in Section 2.1, brentuximab is anticipated to be indicated for: the treatment of adult patients with previously untreated CD30+ Stage III or IV HL in combination with AVD. The EAG notes that brentuximab already has marketing authorisation for use in other places in the treatment pathway for HL, as well as for other types of lymphoma (see Table 2 in the CS for further details).

The recommended dose of brentuximab for the indication of interest for this appraisal is 1.2 mg/kg administered as an IV infusion over 30 minutes on days 1 and 15 of each 28-day cycle for six cycles.[20] In addition, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 (AVD) are required to be administered by IV infusion on the same days as brentuximab (A) for the six cycles. The treatment regimen for the A+AVD arm of the ECHELON-1 trial directly align with the recommended treatment dose and schedule.

The EAG notes that following the enrolment of approximately 70% of the study population for ECHELON-1, the independent data monitoring committee recommended that patients randomised to the A+AVD treatment arm received prophylactic growth factor support (granulocyte colony stimulating factor [G-CSF]) beginning with Cycle 1. The administration of prophylactic G-CSF was

subdivided into primary prophylaxis which was defined as G-CSF given by Day 5 of study treatment and secondary prophylaxis which was defined as the receipt of G-CSF at any time after Day 5 of Cycle 1. The EAG notes that only 83 patients (13%) in the A+AVD treatment arm of ECHELON-1 received G-CSF primary prophylaxis but in the summary of product characteristics (SmPC) for brentuximab, primary prophylaxis with growth factor support (G-CSF) beginning with the first dose, is recommended for all adult patients with previously untreated HL receiving combination therapy; i.e. A+AVD. The EAG therefore considers that most patients in UK clinical practice would be expected to receive prophylactic G-CSF and is therefore concerned that the use of G-CSF in ECHELON-1 does not reflect current recommendations for its use alongside A+AVD from Cycle 1. However, the EAG also notes that 81% of patients in the A+AVD arm received G-CSF during ECHELON-1.[21]

The trial protocol for ECHELON-1 required all patients to have a PET scan at the end of their second treatment cycle (PET2). Following the PET2 scan, patients were allowed to switch to an alternative frontline medication (AFM) at the investigators discretion and discontinue their randomised treatment. The EAG considers that although a higher proportion of patients switched to an AFM in the A+AVD arm of ECHELON-1 compared to in the ABVD arm, the proportion of patients switching was small across both trial arms (2% and 1%, respectively). The EAG notes from the clinical study report[22] that the most frequently reported AFM for the A+AVD patients was [redacted] was the most frequently reported AFM for ABVD patients. The company provide subgroup results for analyses of PFS and OS from ECHELON-1, with and without patients receiving AFM and these are discussed in Section 3.3.

2.3.3 Comparators

As discussed in Section 2.2.1, the company's proposed positioning of A+AVD is for use in patients who would otherwise be treated with ABVD and the EAG's clinical experts considered the company's proposed positioning of A+AVD in the treatment pathway to be reasonable. The EAG's clinical experts also reported that in UK clinical practice ABVD is typically given using the PET-adapted RATHL approach which comprises two cycles of ABVD followed by either escalation or de-escalation of treatment based on the findings of an interim PET scan (PET2): PET2-negative patients are subsequently de-escalated to treatment with AVD (four cycles) and PET2-positive patients would typically be escalated to receive treatment with escBEACOPDac (four cycles).[17] However, the company consider that not all UK centres use a PET-adapted approach, with some using a full

six cycles of ABVD, as per the comparator arm in ECHELON-1. The company therefore used a weighted average of ABVD treatment for six cycles (10%) and ABVD treatment via the PET-adapted RATHL approach (90%) in the economic analyses.

Similar to as noted above for the A+AVD arm of ECHELON-1, the EAG is concerned that the G-CSF usage in the ABVD arm does not reflect current UK clinical practice. Primary prophylaxis with G-CSF was given to 6.5% of patients in the ABVD treatment arm but the EAG notes that in UK clinical practice G-CSF would not be routinely used as a primary prophylactic treatment in ABVD treatment regimens for HL. However, the EAG also notes that in clinical practice some patients on ABVD would go on to receive escBEACOPDac following a positive PET2, in which case G-CSF is recommended.

The proportion of patients receiving six cycles ABVD and PET-adaptation was informed by the company's UK clinical experts and for the base case was 10% for six cycles of ABVD and 90% for PET-adapted RATHL approach with scenario analyses to explore alternative distributions. The EAG's clinical experts considered that generally all patients would be treated with the PET-adapted ABVD and therefore the EAG is concerned that the company base case may potentially overestimate the proportion of patients remaining on ABVD. The EAG also notes that the company has assumed that PFS and OS for ABVD-based treatment is the same irrespective of the approach. Specifically, the efficacy of the ABVD arm in ECHELON-1 was considered to be equivalent to ABVD administered via the PET-adapted approach. The company reported that this assumption was reached for reasons including the following:

- the de-escalated ABVD/AVD regimen demonstrating non-inferior 3-year PFS vs six cycles of ABVD in the RATHL trial;
- only a small proportion of patients in ECHELON-1 (7% and 9% in the A+AVD and ABVD treatment arms, respectively) being PET2 positive and potentially suitable for treatment escalation;
- the RATHL trial also comprising a minority of patients who were PET-positive after 2 initial cycles of ABVD (16% [excluding those with PET errors]) and subsequently escalated to escBEACOPP and concerns that this part of the trial was not randomised so it is unknown whether escalation leads to better outcomes than continuing therapy with either ABVD or AVD;
- unadjusted ITC and unanchored matched adjusted indirect comparison (MAIC) analyses conducted by the company which the company considered to demonstrate that six cycles of

ABVD as per ECHELON-1, was associated with comparable efficacy to PET-adapted ABVD as per RATHL; and

- clinical expert opinion at a 2024 access advisory board.[7]

The EAG is concerned that there is a lack of robust clinical effectiveness data to support the company's assumption of clinical equivalence between six-cycle ABVD and the PET-adapted ABVD RATHL approach. The EAG notes that the company provided an unanchored MAIC comparing the efficacy of the ABVD arm from ECHELON-1 with PET-adapted ABVD (RATHL approach) using the RATHL study in the CS, but the EAG is concerned about the face validity and generalisability of the findings from the MAIC analysis. This is because the results of the MAIC suggested a statistically significant benefit for OS with six-cycle ABVD compared to PET-adapted ABVD (RATHL) and the HR for INV-PFS also favoured treatment with six-cycle ABVD (although it did not reach statistical significance). The EAG notes that the six-cycle ABVD data includes patients who are PET2 positive and who may be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac. The EAG thus considers the results of the MAIC to contradict the findings in the RATHL trial of noninferiority for PFS and no significant difference for OS for de-escalated ABVD/AVD compared with six-cycle ABVD.

In response to clarification questions the company conducted an unanchored MAIC to provide a comparison of A+AVD (from ECHELON-1) with PET-adapted ABVD (RATHL approach) from the stage III and IV subgroup of the RATHL study but the EAG considers the results from this MAIC are likely to also be unreliable similar to for the MAIC of ABVD arm from ECHELON-1 versus PET-adapted ABVD from RATHL. In addition, the EAG notes that there is evidence to suggest the assumption of proportional hazards is violated. The EAG therefore agrees with the company that the most robust source of evidence for the comparison of A+AVD with ABVD is currently the ECHELON-1 trial, but the EAG is also concerned that the ABVD arm of ECHELON-1 does not accurately reflect the usage of PET-adapted ABVD in UK clinical practice. The EAG therefore considers the clinical efficacy of A+AVD versus PET-adapted ABVD to be uncertain and is concerned that the clinical efficacy data used in the cost effectiveness analyses may not accurately reflect outcomes in UK clinical practice.

Further critique of the MAICs and clinical efficacy results are provided in Section 3.3 and 3.4.

2.3.4 Outcomes

The outcomes specified in the final scope issued by NICE were:

- overall survival (OS);
- progression-free survival (PFS);
- response rates;
- adverse effects (AEs) of treatment; and
- health-related quality of life (HRQL).

The EAG notes that data for all of the outcomes listed in the final scope issued by NICE were reported in ECHELON-1 and relevant data were provided in the CS or its appendices. The EAG notes that there is a discrepancy in the latest data cutoff used for some of the analyses of outcome data from ECHELON-1 which is partly due to data availability; e.g. PFS as assessed by the independent review facility (PFS-IRF) is reported using the 20 April 2017 data cut-off because the IRF was disbanded 5 years after the trial initiation but the analysis of investigator assessed PFS (PFS-INV) is based on the final data cut-off of 11 March 2023. The EAG therefore focuses on the outcomes with data reported from the 11 March 2023 wherever possible.

The primary endpoint in ECHELON-1 was modified PFS per IRF and this was defined as the time from the date of randomisation to the date of the first of documentation of progressive disease, death due to any cause, or for patients who were confirmed non-complete responders per IRF, receipt of subsequent anticancer therapy for HL after completion of frontline therapy. The EAG's clinical experts reported that PFS defined as the time from the date of randomisation to the date of the first of documentation of progressive disease or death due to any cause is the definition typically used in clinical practice and modified PFS is not a standard outcome of interest. The EAG notes that PFS was also included as a prespecified exploratory endpoint in ECHELON-1 and that only PFS-INV is included in the economic model. The EAG therefore focuses on PFS-INV in this report but the results from the assessment of modified PFS per IRF and per INV at the 20 April 2017, primary endpoint data cutoff are available in the CS and its appendices.

Several different HRQL tools were used in ECHELON-1, with data reported using the EORTC QLQ-C30, Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea 10, the EQ-5D-3L questionnaire, and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity subscale (FACT/GOG-NTx). The EAG notes that HRQL was assessed during post-treatment follow-up (PTFU) up to 36 months after the end of treatment by EORTC QLQ-C30 and EQ-5D-3L only and that data from only the EQ-5D-3L were included in the economic model.[13] The EAG therefore only discusses the EQ-5D-3L results in detail in this report but further details on the HRQL results from

ECHELON-1 are available in the CS. The EAG also considers it important to highlight that the EQ-5D-3L data presented in the clinical effectiveness section of the CS (Section B.2.6.4.4) relate to the 20 April 2017 data cut rather than the final data-cut (01 June 2021) but it is reported in the cost-effectiveness section (Section B.3.4.1) that the results from the final data cut were used in the economic model. The EAG also considers that data from the EORTC QLQ-C30 assessments should also be available from the final data-cut and notes that these were not provided in the CS.

The reporting of response data in the CS included PET status after Cycle 2 with results for objective response rate and complete remission rate limited to the appendices of the CS. The EAG notes that the PET2 data used for ABVD in the economic model are taken from the RATHL study but given the relevance of PET2 status the EAG discusses the ECHELON-1 PET status after Cycle 2 results in Section 3.3.3. Reporting of the results of the other measures of response from ECHELON-1 are limited to the appendices of the CS and not discussed in this EAG report.

In summary, the EAG considers the outcomes reported in the CS to appropriately cover the outcomes specified in the final scope issued by NICE but the EAG notes that data from the final analyses were not provided in the CS for the HRQL assessment using the EORTC QLQ-C30 or EQ-5D-3L tools. However, the EAG also notes that it is reported in the CS that the EQ-5D-3L data from the final data cut-off was used in the economic model. Data from ECHELON-1 for OS, PFS-INV and Grade 3 or above treatment emergent adverse events (TEAEs) occurring in ≥5% of patients in either trial arm were also included in the company's economic model.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence reporting on the clinical efficacy, safety, tolerability, HRQoL and costs associated with first-line treatment of patients with advanced HL (defined as Stage IIB, III, or IV) to enable a comparison of A+AVD with PET-adapted ABVD (RATHL approach). Initial searches were conducted on 29 July 2016, followed by updates on 23 May 2018, 22 June 2022, and 19 and 27 December 2023; the December 2023 search dates correspond to searches for randomised controlled trial (RCT) and non-RCT data, respectively. Full details of the methodology and results of the SLR were provided in Appendix D of the CS. The EAG notes that only RCTs were included in the final SLR results and that the searches were broader than required for the final SLR inclusion criteria applied to address the NICE decision problem.

The company's SLR identified one RCT (23 publications) reporting effectiveness evidence for brentuximab vedotin: ECHELON-1 which included 1,334 patients with previously untreated CD30+ Stage III or IV HL, of whom 664 were treated with A+AVD and 670 were treated with six cycles of ABVD. For ABVD, the company considered only the RATHL trial (five publications), to be reflective of the use of ABVD in UK clinical practice. The RATHL trial was an RCT conducted in 1,201 patients with previously untreated advanced-stage classic HL (Stage IIb, III, and IV). ECHELON-1 is discussed further in Section 3.2 and the RATHL trial is discussed in Section 3.4.

In summary, the EAG considers the company SLR searches to be appropriate and unlikely to have missed any relevant RCTs for brentuximab or the RATHL approach ABVD. The EAG's clinical experts also reported that they considered the RATHL trial to provide the most appropriate comparator data on ABVD with regards to reflecting UK clinical practice although it was also acknowledged that the escalated treatment regimens used in the RATHL trial do not completely align with current UK clinical practice and the use of escBEACOPDac.

Table 10. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D	**The EAG considers the sources and dates searched to be reasonable and comprehensive.**

		Databases searched were as follows: • Embase®, 1980 to date of search via embase.com; • Ovid MEDLINE® In-Process & Other Non-Indexed Citations, 1946 to date of search; • the Cochrane Library (including the Cochrane Database of Systematic Reviews [Cochrane Reviews], 2005 to date of search, the Cochrane Central Register of Controlled Trials [CENTRAL], the HTA Database, the Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database [NHS EED]). In addition to the database searches, the following searches were also conducted: • hand searching of reference lists of included publications; • hand searching of conference proceedings to identify relevant abstracts from specific conferences not already identified in the electronic database searches; • hand searching of relevant HTA bodies; and • clinical trial registries (for details of ongoing/planned/completed RCTs). The database searches were originally conducted on 29 July 2016 and updated on 23 May 2018, on 22 June 2022, and 19 and 27 December 2023 (for randomised controlled trials [RCTs] and non-RCTs, respectively). The EAG notes that DARE and NHS EED were discontinued in 2015 and these databases were omitted from the searches run in the 2023 update but were included in the company's earlier searches.
Search strategies	Appendix D	**The EAG considers the search strategies used likely to be appropriate.** Search terms comprised a combination of terms for HL and the interventions of interest with an RCT study design filter applied to the searches of Medline and EMBASE. The search terms included a mixture of MeSH indexing and free-text terms.
Inclusion criteria	Appendix D	**The EAG considers the inclusion criteria for the SLR to be reasonable.** For inclusion, studies were required to comprise of newly diagnosed adult patients (≥18 years) with advanced HL. Interventions and comparators of interest were restricted to: • Brentuximab vedotin in combination with AVD; • 6x cycles of ABVD; and • PET-guided ABVD (i.e. treatment initiating with 2x cycles of ABVD, followed by PET adaptation). Study design for included studies was restricted to RCTs and studies were required to be published in English language.
Screening	Appendix D	**The EAG considers the methods for screening to be reasonable.** Records were screened by two independent analysts at both title and abstract review and full text review. It is reported that a third reviewer (senior analyst) was involved in the full text review where there was disagreement that could not be resolved by consensus but it is unclear if the third reviewer was also involved in the title and abstract reviewing stage. The EAG notes that an additional third screening stage was included after the full text review to narrow down the included studies to only those deemed relevant to the NICE decision problem.

		Results of the literature screening processes were summarised in a PRISMA diagram.
Data extraction	Appendix D	**The EAG considers the methods for data extraction to be reasonable.** The company reported that information from studies were extracted into a piloted data extraction template in Microsoft® Excel by one reviewer, and that a second, more senior, reviewer validated the accuracy of the extracted data. Any disputes were resolved through discussion between the two reviewers.
Tool for quality assessment of included study or studies	Appendix D	**The EAG considers the company's choice of quality assessment tools to be reasonable.** The ECHELON-1 RCT was assessed using the seven item checklist provided in in the NICE single technology appraisal (STA) user guide.[1] This approach is based on guidance provided by the Centre for Reviews and Disseminations for assessing the quality of studies included in SLR.[2] In addition, as part of the 2023 SLR update, ECHELON-1 was assessed using the Cochrane Risk of Bias (ROB) 2 tool for RCTs[23] along with the RATHL trial. The EAG is unsure why the Cochrane ROB2 tool was selected for the 2023 update review but considers both the NICE checklist and the Cochrane ROB2 tool to be reasonable for assessing the quality of ECHELON-1 and the RATHL trial.

Abbreviations: AVD, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; EAG, External Assessment Group; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; PET, positron emission tomography; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; ROB, risk of bias; SLR, systematic literature review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

3.2 Critique of ECHELON-1

The EAG's assessment of the design, conduct and internal validity of the ECHELON-1 trial is summarised in Table 11. The EAG broadly agrees with the company's assessment of ECHELON-1 as generally being at low risk of bias, although the EAG notes that it was an open-label study and there is thus a risk of bias in the results for some of the efficacy outcomes. Of particular note, the most mature results for progression free survival (PFS) relate to investigator-assessment (PFS-INV) rather than the independent review facility (PFS-IRF) assessment and PFS-INV from ECHELON-1 is used to inform the efficacy of A+AVD and ABVD in the analyses of cost-effectiveness.

Table 11. EAG's summary of the design, conduct and analysis of the ECHELON-1 trial

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.2.3.1 and D.1.4.3	**Appropriate** Patients were randomised 1:1 to receive either A+AVD (n=664) or ABVD (n=670), with stratification by the number of IPFP risk factors

		(0-1 vs 2-3 vs 4-7), and region (Americas vs Asia vs Europe). The company reported that the randomisation scheme was generated by Takeda and that an interactive voice/web response system was used for the randomisation.
Concealment of treatment allocation	D.1.4.3	**Appropriate** The company reported that an interactive voice/web response system was used for randomisation and that this system uses an automated randomisation and dispensation thus concealing treatment group allocation.
Eligibility criteria		**Likely to be appropriate** The key inclusion criteria for ECHELON-1 were: • Male or female patients aged ≥18 years; • Treatment-naïve patients with Ann Arbor Stage III or IV HL; • Histologically confirmed CD30+ HL (WHO classification);* • ECOG performance status ≤2; and • Radiographically documented measurable disease per the International Working Group RECIL criteria. The EAG's clinical advisors considered these to be broadly consistent with the anticipate population likely to be eligible for A+AVD in UK clinical practice.
Blinding	B.2.3.2	**ECHELON-1 was an open-label RCT** Randomised study treatment in ECHELON-1 was open-label but the company reported in the CS that both patients and investigators were blinded to aggregate efficacy data throughout the study. The EAG notes that some of the key outcome measures used from the trial are subjective and thus considers that the results may be biased as a result of the open-label nature of the trial e.g. INV-PFS and HRQL.
Baseline characteristics	B.2.3.3	**Likely to be reasonably reflective of the population eligible for A+AVD in UK clinical practice** For further discussion of the population please see Section 2.3.1.
Dropouts	B.2.4.3	**Study discontinuation appears high but discontinuations are reasonably well balanced between treatment arms and completion of study treatment was high** In the A+AVD arm, 628 patients (95%) completed study treatment per protocol and 593 patients (89%) completed the maximum number of cycles. In the ABVD arm, 634 patients (95%) completed the study treatment per protocol, and 608 patients (91%) completed the maximum number of cycles. Based on the March 2023 data cut-off, discontinuation from the study was reasonably well balanced across the two study arms with [redacted] discontinuing from follow-up in the A+AVD group and [redacted] in the ABVD treatment group.
Statistical analysis		
Sample size and power	B.2.4.2	**Appears reasonable**

		In the CS it is reported that: "*The primary endpoint of the study was modified PFS, and the study was powered on the assumption of a 2-year modified PFS rate of 81% for patients in the A+AVD treatment arm and 73% for patients in the ABVD treatment arm, assuming an emergent plateau in the PFS event rate after 2 years. A total of 260 modified PFS events provided 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 using a log-rank test. Approximately 1,240 patients were to be randomised to achieve with 95% probability 260 modified PFS events in approximately 60 months assuming 36 months of patient accrual, a 5% annual dropout rate, and 24 months of modified PFS follow-up after randomisation of the last patient*." The EAG notes that a total of 1,334 patients were randomised and the final analysis of modified PFS was performed when 263 modified PFS events occurred (data cutoff for this analysis was 20 April 2017). OS was specified as the key secondary endpoint and was tested at a 1 sided 0.025 level once the test of modified PFS was statistically significant.
Handling of missing data	B.2.4.2	**Likely to be appropriate** The company reported that data that were potentially spurious or erroneous were examined under standard data management operating procedures. Missing data were treated as missing and no data imputation was applied, unless otherwise specified.
Outcome assessment	B.2.4.1	**Appropriate** The analysis sets of relevance to the key efficacy and safety data used in the analyses of cost-effectiveness comprise the ITT population which included all patients randomised to treatment and the safety population which included all enrolled patients who received ≥1 dose of any study drug. The EAG notes that there were three formal interim analyses in the study, including one futility analysis of the CR rate and two interim analyses for OS (20 April 2017 and 1 June 2021) and the final analysis was reported using a data cutoff of 11 March 2023. The EAG notes that data collection for some outcomes had been discontinued prior to the final analysis and therefore some outcomes have data only reported using earlier data cutoffs. The EAG notes that the latest data cutoff was used for data included in the analyses of cost-effectiveness.

*Nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or CD30+ HL, not otherwise specified.

Abbreviations: A+AVD, brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CR, complete remission; CS, company submission; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; INV, investigator; IPFP, international prognostic factors project; ITT, intention-to-treat; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RCT, randomised controlled trial; RECIL, response evaluation criteria in lymphoma; UK, United Kingdom; WHO, World Health Organization.

3.3 ECHELON-1 clinical effectiveness and safety results

Results presented here focus on those informing the company's base case for the analysis of cost-effectiveness, with investigator-assessed PFS (PFS per INV) and OS from the final data-cut being the

key clinical efficacy outcomes from ECHELON-1 used in the model. In addition, EQ-5D-3L data from the final data cutoff and Grade ≥3 drug-related treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients for the A+AVD arm of ECHELON-1 (AE data for PET-adapted ABVD in the model were obtained from the RATHL trial and AE data for six-cycle ABVD were obtained from ECHELON-1) were used in the economic model. Unfortunately only data from the 20 April 2017 data cutoff were included in the CS for EQ-5D-3L but these are discussed below. Data for the relevant AEs included in the economic model using the 11 March 2023 data cutoff were provided in the company response to clarification and are discussed below.

Results for PET status after cycle 2 were also deemed of relevance by the EAG's clinical experts and listed as an outcome in the final scope issued by NICE; the EAG thus discusses these results below. Other outcomes reported in the CS are not discussed in this report, including modified PFS and the patient-reported outcomes (PROs) from the EORTC QLQ-C30, Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnea 10, and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity subscale (FACT/GOG-NTx). The results for these outcomes can be found in the CA and its appendices.

3.3.1 Progression-free survival (PFS)

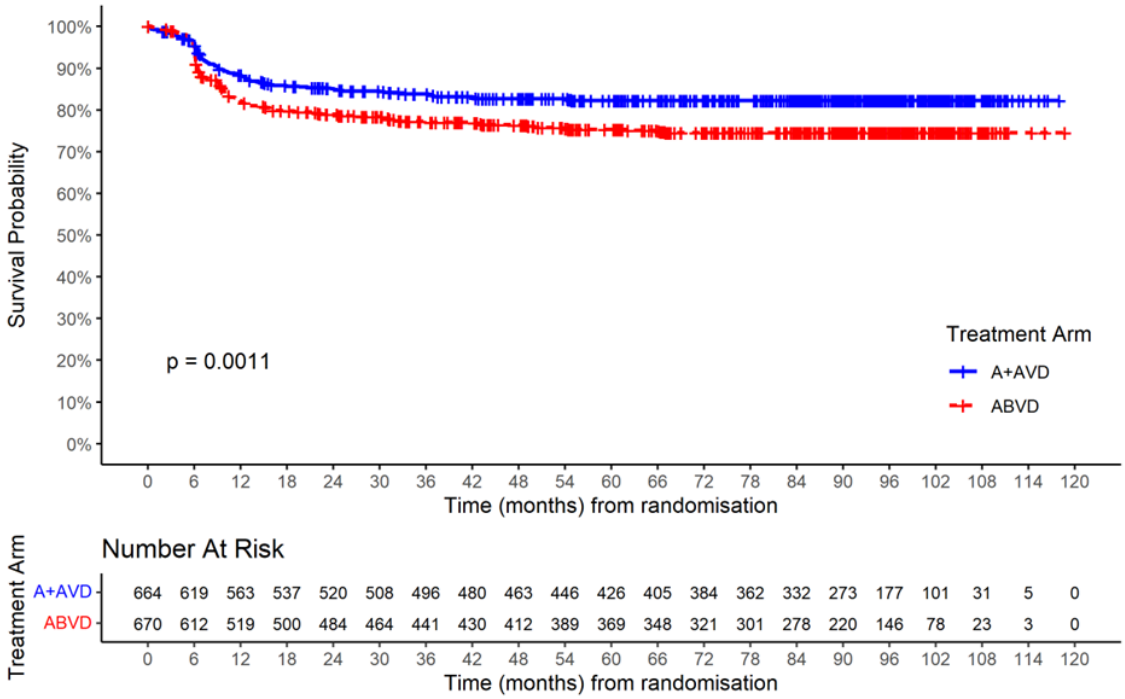
The primary endpoint in ECHELON-1 was modified PFS per IRF and this was defined as the time from the date of randomisation to the date of the first of documentation of progressive disease, death due to any cause, or for patients who were confirmed non-complete responders per IRF, receipt of subsequent anticancer therapy for HL after completion of frontline therapy. However, PFS was also included as a prespecified exploratory endpoint in ECHELON-1.[13]

Modified PFS and PFS were assessed by both the IRF and the investigator (INV) but the IRF was disbanded 5 years after the trial initiation and the latest data-cut comprises of only PFS-INV data. Therefore, data presented from the latest data cutoff of ECHELON-1 (11 March 2023) in the CS were based on the INV assessment. The company also provided the results from the analyses of modified PFS per IRF and per INV at the 20 April 2017 primary endpoint data cutoff in the CS, but as modified PFS was not deemed to be relevant by the EAG's clinical experts and it was not used in the economic model, the EAG does not discuss or present these results in this report.

3.3.1.1 PFS per INV (11 March 2023 data cut-off)

At a median follow-up of 90.0 months (95% CI: 87.3 to 90.9) in the A+AVD arm and 86.4 months (95% CI: 84.4 to 89.6) for ABVD, there were 112 PFS events (17%) in the A+AVD arm compared with 159 PFS events (24%) in the ABVD arm (Table 12). Median PFS was not estimable (NE) in either group at the 11 March 2023 data cutoff. However, analysis of PFS-INV demonstrated a 32.3% reduction in the risk of progression or death with A+AVD compared with ABVD, favouring treatment with A+AVD (HR 0.68; 95% CI: 0.53 to 0.86; p=0.001; Table 12). Kaplan–Meier plots for PFS-INV (Figure 2) suggest a plateau consistent with the company and EAG's clinical expert advice that most relapses occur in the first two years following completion of treatment and that it is consistently seen across both the A+AVD and ABVD treatment arms in ECHELON-1.

Figure 2: PFS (INV) Kaplan–Meier plots for the ITT population of ECHELON-1 using the March 2023 DCO (reproduced from company response to CQ's Figure 11)



Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; DCO, data cut-off; ITT, intent-to-treat; PFS, progression-free survival.

Table 12. ECHELON-1 PFS-INV using the 11 March 2023 data cut-off (adapted from CS Table 11 and company response to CQ's Table 10)

	A+AVD (n=664)	ABVD (n=670)
Median follow-up, months (95% CI)	90.0 (87.3 to 90.9)	86.4 (84.4 to 89.6)

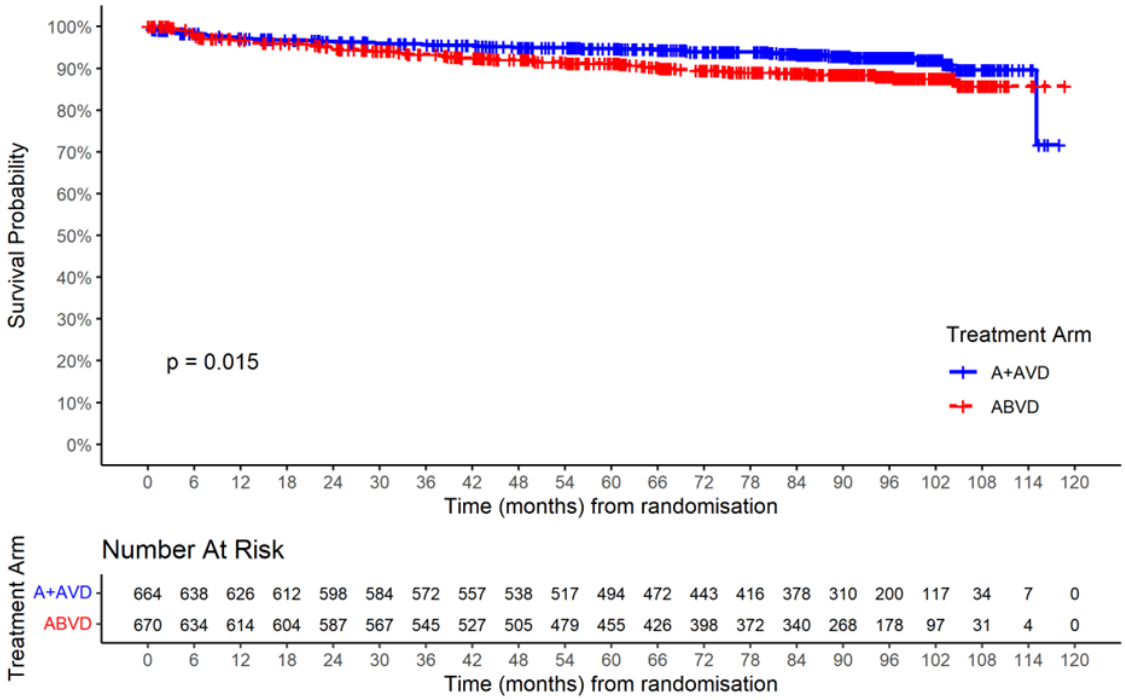
Median PFS (95% CI)	NE (NE to NE)	NE (NE to NE)
PFS range	0 to 118.0	0 to 118.7
Number of events (%)	112 (17.0)	159 (24.0)
HR (95% CI), p-value	0.677 (0.53 to 0.86), p=0.001	
Number censored (%)	552 (83.0)	511 (76.0)
Progression-free survival at timepoints*, % (95% CI), n		
12 months	88.3 (85.6 to 90.6), n=563	82.1 (78.9 to 84.8), n=519
48 months	82.7 (79.5 to 85.4), n=463	76.3 (72.8 to 79.4), n=412
84 months	82.3 (79.1 to 85.0), n=332	74.5 (70.8 to 77.7), n=278
102 months	82.3 (79.1 to 85.0), n=101	74.5 (70.8 to 77.7), n=78
108 months	[redacted]	[redacted]
114 months	[redacted]	[redacted]

*Kaplan–Meier estimates.
Data presented are based on the ITT population
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; n, number, NE, not estimable.
Source: Takeda, ECHELON-1 CSR (2024); Takeda (2023).

3.3.2 OS (11 March 2023 data cut-off)

Median follow-up for OS was 90.1 months (95% CI: 87.7 to 90.8) for A+AVD and 88.3 months (95% CI: 85.2 to 89.9) for ABVD. At the time of the final data cut-off (11 March 2023), a total of 46 deaths (7%) had occurred in the A+AVD arm and 69 deaths (10%) in the ABVD arm (Table 13). The analysis of OS showed a 38.3% reduction in the risk of death in the A+AVD arm compared with the ABVD arm and a statistically significantly difference between the two treatment arms suggesting improvement in OS with A+AVD (HR 0.617; 95% CI: 0.423 to 0.899; p=0.011). However, the EAG notes that there is a crossing of the Kaplan–Meier curves at approximately 114 months and is unclear on the rationale for this although it is also noted that there is heavy censoring from 102 months and only a small number of patients left in the analysis at 114 months(Figure 3).

Figure 3. OS Kaplan–Meier plot for ECHELON-1 ITT population using the 11 March 2023 data cut-off (reproduced from company response to CQ's, Figure 12)



Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; DCO, data cut-off; ITT, intent-to-treat; OS, overall survival.

Table 13. ECHELON-1 OS using the 11 March 2023 data cut-off (adapted from CS Table 12 and company response to CQ's Table 10)

	A+AVD (n=664)	ABVD (n=670)
Median follow-up, months (95% CI)	90.1 (87.7 to 90.8)	88.3 (85.2 to 89.9)
Median OS (95% CI)	NE (115.1 to NE)	NE (NE to NE)
OS range, months	0 to 118.0	0 to 118.7
Number of events (%)	46 (7.0)	69 (10.0)
HR (95% CI), p value	0.617 (0.42 to 0.9), p=0.011	
Number censored (%)	618 (93.0)	601 (90.0)
Survival at timepoints*, % (95% CI), n		
12 months	97.2 (95.7 to 98.3), n=626	96.7 (95.1 to 97.9), n=614
48 months	94.9 (92.9 to 96.4), n=538	92.1 (89.7 to 94.0), n=505
84 months	93.5 (91.1 to 95.2), n=378	88.8 (85.8 to 91.1), n=340
102 months	91.9 (89.0 to 94.1), n=117	87.5 (84.2 to 90.2), n=97
108 months	[redacted]	[redacted]
114 months	[redacted]	[redacted]

*Kaplan–Meier estimates.
Data presented are based on the ITT population
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin,

vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; n, number, NE, not estimable.
Source: Takeda, ECHELON-1 CSR (2024); Takeda (2023).

3.3.3 PET status after Cycle 2 (PET2) using 11 March 2023 data-cut-off

ECHELON-1 reported a higher rate of PET2 negative patients in the A+AVD arm compared with the ABVD arm but the difference between treatment groups was not statistically significant (relative risk 1.028; 95% CI: 0.99 to 1.07) (Table 14). The EAG notes from the breakdown of PET2 status by disease stage at baseline that the Stage IV disease patients had the greatest difference between treatment groups but also notes that the subgroups were not adequately powered to demonstrate statistically significant differences (Table 14).

Table 14: PET2 status by Ann Arbor stage at initial diagnosis in ECHELON-1 using 11 March 2023 data cut-off (reproduced from company response to CQ's Table 9)

n (%)	A+AVD	ABVD
ITT population	**N=664**	**N=670**
PET2 negative	588 (89)	577 (86)
PET2 positive	47 (7)	58 (9)
Missing PET at Cycle 2	29 (4)	35 (5)
PET2 negative status relative risk (95% CI)	1.028 (0.99 to 1.07)	
Stage III	**n=237**	**n=246**
PET2 negative	209 (88)	219 (89)
PET2 positive	13 (5)	15 (6)
Missing PET at Cycle 2	15 (6)	12 (5)
PET2 negative status relative risk (95% CI)	0.991 (0.93 to 1.06)	
Stage IV	**n=425**	**n=421**
PET2 negative	379 (89)	358 (85)
PET2 positive	34 (8)	42 (10)
Missing PET at Cycle 2	12 (3)	21 (5)
PET2 negative status relative risk (95% CI)	1.049 (1.00 to1.10)	

Note: subgroup numbers do not sum to ITT data presented here and in the submission dossier, as some patients had missing staging data at baseline.
PET2 positive = Deauville score >3. PET2 negative = Deauville score ≤3.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; DCO, data cut-off; PET2, positron emission tomography at end of Cycle 2.

3.3.4 Patient-reported outcomes using 20 April 2017 data cut-off

Patient-reported outcomes (PROs) were evaluated in the ITT population using the EORTC QLQ-C30, Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea 10, the EQ-5D-3L questionnaire, and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity subscale (FACT/GOG-NTx). As discussed in Section 2.3.4, the EAG notes that HRQL was assessed during post-treatment follow-up (PTFU) up to 36 months after the end of treatment by EORTC QLQ-C30 and EQ-5D-3L only and that data from only the EQ-5D-3L were included in the economic model. Unfortunately the only HRQL data presented in the CS were from the 20 April 2017 data cut-off and therefore the EAG considers the data presented below for PTFU are unlikely to directly align with the data used in the economic model (final data cut-off).

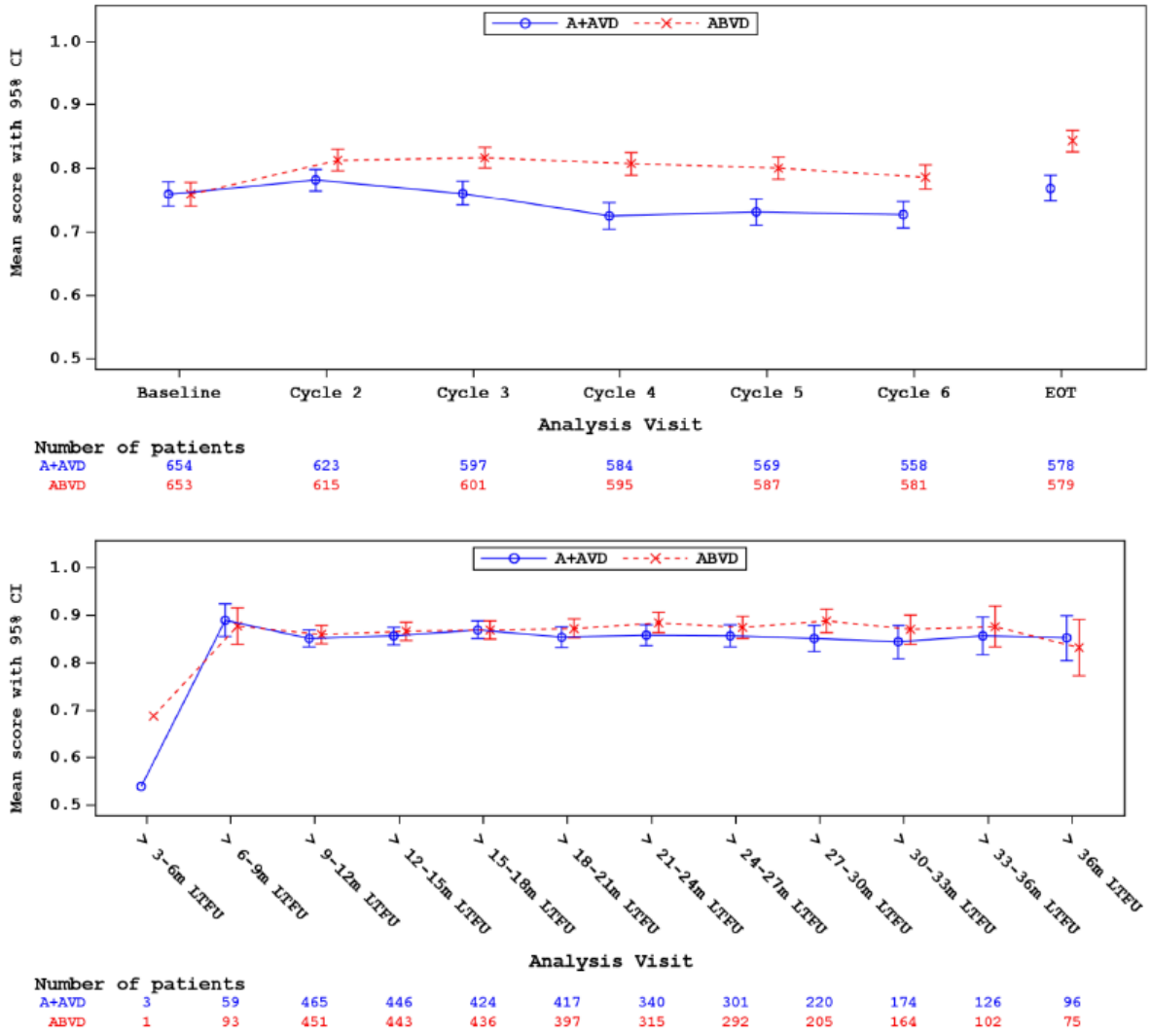
3.3.4.1 EQ-5D-3L

The company reported that the data collected for EQ-5D-3L comprised data from both the EQ-5D descriptive system and the visual analogue scale (VAS). In addition, EQ-5D time trade-off (EQ-5D TTO) indexed data were analysed using the UK-based value sets.

The mean EQ-5D-3L (UK) TTO-indexed scores over time in ECHELON-1 were higher for the ABVD arm during first-line treatment compared with the scores for A+AVD. However, the company reported that the differences were not deemed to be clinically significant when applying the minimally important difference of 0.07 established for the UK TTO score.[24]

During long-term follow-up, mean scores improved in both the A+AVD and ABVD arms and ended up at higher levels than baseline (Figure 4). The EAG also notes that the mean EQ-5D-3L UK TTO scores for A+AVD and ABVD in the PTFU period up to 36 months appear more similar compared to the on-treatment values as demonstrated by the overlapping 95% confidence intervals in the PTFU (Figure 4). The company also reported that the EQ-5D-3L index scores from 6–9 months to 36 months from end of treatment (mean: 0.88 to 0.91) are similar to population norms (mean: 0.92 across all EU5 countries and age groups, or approximately 0.89 for the UK general population aged 35 to 44 years).[25]

Figure 4. Mean EQ-5D-3L UK TTO score over time in ECHELON-1 using the 20 April 2017 data cut-off (reproduced from CS, Figure 9)



Data presented are based on the ITT population; patients on treatment were excluded.
Baseline was defined as the value collected at the time closest to, but before, the start of study drug administration. Long-term follow-up visits indexed from Study Day 1. The range of EQ-5D-3L UK TTO is 0-1; a higher score indicates a more preferred health status.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; EOT, end of treatment; European Quality of Life 5-Dimension 3-Level version; ITT, intent-to-treat; LTFU, long-term follow-up; TTO, time trade-off; UK, United Kingdom.
Source: Takeda ECHELON-1 CSR (2018).

3.3.5 Subgroups

3.3.5.1 PFS per INV using 11 March 2023 data cut-off

The results for PFS-INV across subgroups were generally consistent with the ITT population (HR 0.677; 95% CI: 0.532 to 0.863), with the majority of subgroups showing a treatment benefit with A+AVD vs ABVD (Figure 5). As discussed in Section 2.3.1, the EAG notes that the incidence of HL is bimodal and as such the EAG considers subgroup data by age of potential relevance. The results for

the subgroup analyses by age [redacted]) receive [redacted] benefit with A+AVD for INV-PFS compared with the [redacted], respectively). [redacted].

The EAG notes that the results for patients who received alternative frontline medications (AFMs) were not included in the forest plot but they were discussed narratively in the CS. The EAG has tabulated the subgroup results for patients receiving AFMs and for those with Deauville scores (DS) equal to 5 and less than 5 (Table 15). The EAG notes that the AFM and DS score subgroup results [redacted]. The EAG considers that a potential explanation for [redacted] may be because [redacted]. For A+AVD, the most common reason for switching to an AFM was [redacted] ([redacted]%), [redacted] ([redacted]%). [redacted]

In summary, the EAG notes that some of the subgroups comprise of very small patients numbers ([redacted]) and thus recommends caution in drawing any conclusions from the subgroup results.

Figure 5. Forest plot of PFS per INV for subgroups from ECHELON-1 using 11 March 2023 data cut-off (reproduced from CS, Figure 10)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; DCO, data cutoff; ECOG, Eastern Cooperative Oncology Group; INV, investigator; IPFP, international prognostic factors project; PFS, progression-free survival.

Source: Takeda ECHELON-1 CSR (2024).

Table 15. Subgroup results for PFS-INV from ECHELON-1 for patients by AFM status and by DS score using 11 March 2023 data cut-off

	A+AVD	ABVD	HR (95% CI)
Patients who received AFM	[redacted]	[redacted]	[redacted]
Patients who did not receive AFM	[redacted]	[redacted]	[redacted]
Patients with DS=5 at Cycle 2	[redacted]	[redacted]	[redacted]
Patients with DS<5 at Cycle 2	[redacted]	[redacted]	[redacted]

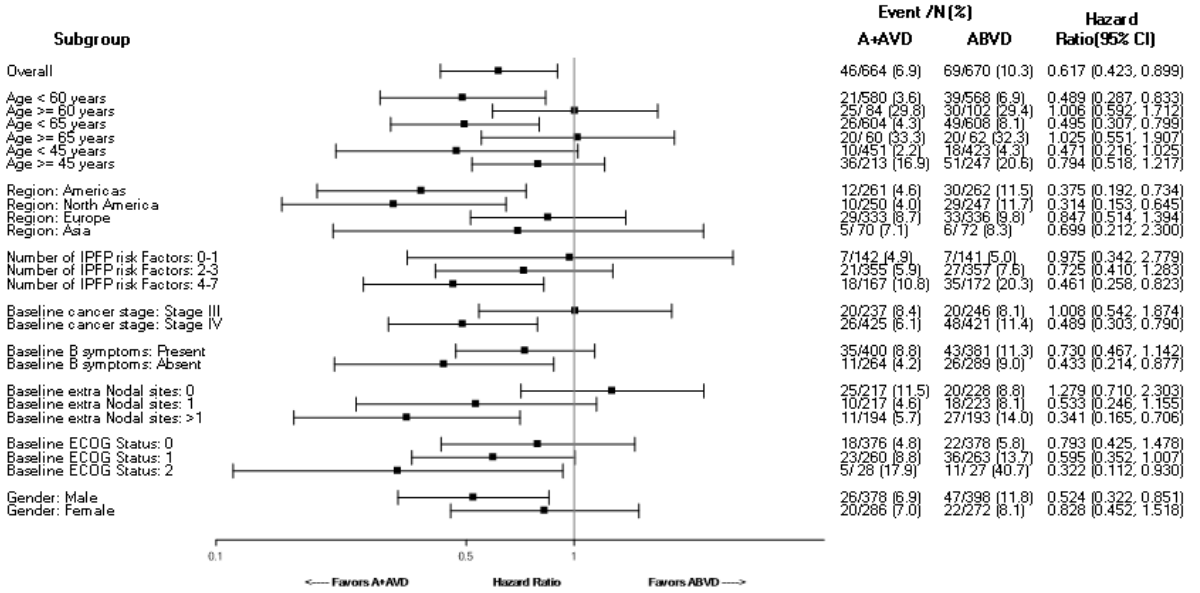
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AFM, alternative frontline medication; CI, confidence interval; DS, Deauville score; HR, hazard ratio.

3.3.5.2 OS using 11 March 2023 data cut-off

Similar to for the results for PFS-INV, for OS the results across subgroups were generally consistent with the ITT population (HR 0.617; 95% CI: 0.423 to 0.899), with the majority of subgroups showing a treatment benefit with A+AVD vs ABVD (Figure 6). The OS results for the subgroup analyses by age suggest the older age subgroups (≥45, ≥60 and ≥65 years) receive less, if any benefit, with A+AVD compared with the younger age subgroups (<45, <60 and <65 years, respectively). In particular, the EAG notes that the HRs for the ≥60 and ≥65 year subgroups favour treatment with ABVD rather than A+AVD, although the EAG also notes that these subgroups comprise small patient numbers and wide 95% confidence intervals so caution is recommended in drawing any conclusions.

Also, as for PFS-INV, the OS results for patients who received AFMs were not included in the forest plot and the EAG has tabulated these (Table 16). The EAG notes that the AFM and DS score subgroup results [redacted]. However, as noted above, the EAG notes that the reasons for the use of AFMs differ for the two treatment arms. In addition, the EAG also notes that some of the subgroups comprise of very small patients numbers ([redacted]) and thus recommends caution in drawing any conclusions from the subgroup results.

Figure 6. Forest plot of OS per INV for subgroups from ECHELON-1 using 11 March 2023 data cut-off (reproduced from CS, Figure 11)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; DCO, data cutoff; IPFP, international prognostic factors project; OS, overall survival.
Source: Takeda ECHELON-1 CSR (2024).

Table 16. Subgroup results for OS from ECHELON-1 for patients by AFM status and by DS score using 11 March 2023 data cut-off

	A+AVD	ABVD	HR (95% CI)
Patients who received AFM	[redacted]	[redacted]	[redacted]
Patients who did not receive AFM	[redacted]	[redacted]	[redacted]
Patients with DS=5 at Cycle 2	[redacted]	[redacted]	[redacted]

Patients with DS<5 at Cycle 2	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AFM, alternative frontline medication; CI, confidence interval; DS, Deauville score; HR, hazard ratio.

3.3.6 Safety

The safety data presented in the CS for ECHELON-1 were from the safety population, defined as patients who received ≥1 dose of any study drug in the frontline treatment regimen. The EAG notes that the treatment-emergent adverse events (TEAEs) from ECHELON-1 were collected from the 20 April 2017 data cut-off and additional data from the PTFU were provided from the latest data cut-off (11 March 2023). Based on clinical expert opinion and the known safety profile of brentuximab, the EAG has also provided a critique of the peripheral neuropathy adverse events in ECHELON-1 below (Section 3.3.6.4). The EAG's clinical experts also highlighted that the bleomycin component of the ABVD regimen (and also a component of escBEACOPDac) is associated with known pulmonary toxicity. The EAG thus also provides a critique of the pulmonary toxicity data from ECHELON-1 below (Section 3.3.6.3).

3.3.6.1 Summary of adverse events using 20 April 2017 data cut-off

A similar proportion of patients in both treatment arms completed all six cycles of treatment (A+AVD: n=593, 89.3%; ABVD: n=608, 90.7%) and there were a similar proportion of AEs of any grade (99% vs 98%) and drug-related TEAEs (97% vs 94%) reported for the A+AVD and ABVD treatment arms, respectively (Table 17). However, there were more Grade ≥3 and serious AEs with A+AVD compared with ABVD (Grade ≥3: 83% vs 66% and serious AEs: 43% vs 27%, respectively).

The most commonly reported drug-related treatment-emergent adverse events (TEAEs) reported for ≥20% of patients in the A+AVD treatment arm were neutropenia (55%), nausea (48%), constipation (33%), vomiting (27%), peripheral sensory neuropathy (27%), fatigue (26%), neuropathy peripheral (25%), and alopecia (24%). The most common drug-related TEAEs in the ABVD treatment arm were nausea (52%), neutropenia (41%), fatigue (27%), constipation (25%), vomiting (24%) and alopecia (20%).

Table 17. Summary of TEAEs in the safety population of ECHELON-1 using 20 April 2017 data cut-off (reproduced from CS, Table 14)

n (%)	A+AVD (n=662)	ABVD (n=659)
Any AE	653 (99.0)	646 (98.0)
Drug-related AE*	641 (97.0)	617 (94.0)
Grade ≥3 AE	[redacted]	[redacted]
Serious AE	284 (43.0)	178 (27.0)
Drug-related serious AE	240 (36.0)	125 (19.0)
AE resulting in study drug discontinuation*	88 (13.0)	105 (16.0)
AE resulting in dose modification	423 (64.0)	293 (44.0)
On-study deaths	9 (1.0)	13 (2.0)
Deaths due to treatment-related AEs	8 (1.0)	7 (1.0)

*ECHELON-1 was not locked after the original 20 Apr 2017 DCO, meaning on-treatment TEAEs were available to update as required. Subsequent to the DCO, the number and proportion of patients reporting drug-related AEs for A+AVD were revised to 646 patients (98.0%) and for ABVD to 623 patients (95.0%); likewise, AEs resulting in study drug discontinuation were observed in 87 patients (13.0%) in the A+AVD treatment arm and 104 patients (16.0%) in the ABVD arm. These are noted here for completeness
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: Takeda ECHELON-1 CSR (2018).

3.3.6.2 *Grade 3 or above treatment emergent adverse events (TEAE)* using 11 March 2023 data cut.

The company included the Grade 3 or above drug-related treatment emergent adverse events (TEAEs) that occurred in ≥5% of patients in either trial arm of ECHELON-1 (using the 11 March 2023 data cut) in the economic model and the EAG provides a summary of the data for both overall TEAEs and drug-related TEAEs in Table 18. In total, 528 patients (80%) in the A+AVD arm and 393 patients (60%) in the ABVD arm reported at least one Grade ≥3 drug-related TEAE and the most frequently reported grade 3 or above drug-related TEAE in both the A+AVD and ABVD trial arms was neutropenia (52% and 37%, respectively [Table 18]).

The company reported that peripheral neuropathy was a standardised MedDRA query (SMQ), grouping multiple peripheral neuropathy preferred terms, and that no single preferred term relating to neuropathy was reported in ≥5% of patients at the March 2023 data cut-off. However, the EAG notes that [redacted] patients ([redacted]%) in the A+AVD arm, and [redacted] patients ([redacted]%) in the ABVD arm reported one or more Grade ≥3 event under the SMQ of Peripheral Neuropathy (using MedDRA dictionary Version 22.0) by the end of treatment. Peripheral neuropathy adverse events are discussed further in Section 3.3.6.4.

Table 18. Grade ≥3 TEAEs and drug-related TEAEs that occurred in ≥5% of patients in either treatment arm for the safety population using the March 2023 data cut-off (adapted from company response to CQ's, Table 8 and CS Table 30)

Preferred term, n (%)	A+AVD (n=662)		ABVD (n=659)	
	TEAEs n (%)	Drug-related TEAEs n (%)	TEAEs n (%)	Drug-related TEAEs n (%)
Patients with at least one Grade ≥3 TEAE	[redacted]	528 (80)	[redacted]	393 (60)
Neutropenia*	[redacted]	344 (51.96)	[redacted]	242 (36.72)
Febrile neutropenia	[redacted]	120 (18.13)	[redacted]	46 (6.98)
Neutrophil count decreased	[redacted]	81 (12.24)	[redacted]	64 (9.71)
Anaemia*	[redacted]	46 (6.95)	[redacted]	18 (2.73)

* Please note that the recorded rate of anaemia and neutropenia events was updated subsequent to the 20 April 2017 data cut, and the data above therefore differ from this earlier data cut (54 patients in the A+AVD arm reported anaemia; 260 patients in the ABVD arm reported neutropenia).
Note: rows present number and proportion of patients reporting TEAEs in total/by preferred term. Event severity based on National Cancer Institute CTCAE Version 4.03. MedDRA Version 22.0 was applied. TEAEs are defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of frontline therapy.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; TEAE, treatment-emergent adverse event.

3.3.6.2.1 Impact of G-CSF primary prophylaxis on AEs for A+AVD using data from April 2018 data cut-off

As discussed in Section 2, the EAG is concerned that the usage of G-CSF in ECHELON-1 does not reflect current recommendations in UK clinical practice and considers this may have resulted in higher levels of neutrophil-related AEs with A+AVD than might be expected in UK clinical practice.

In the subgroup of A+AVD patients who received G-CSF primary prophylaxis, the incidence of neutropenia of any grade was lower compared with those who did not receive primary prophylaxis (35% vs 73%, respectively) and the incidence of febrile neutropenia at any time during treatment was also reduced (11% vs 21%, respectively; CS Figure 12). Of particular note, Grade ≥3 neutropenia was reported by 29% of patients treated with G-CSF compared with 70% who did not receive G-CSF in the A+AVD arm. The EAG therefore considers that the incidence of Grade ≥3 neutropenia in the A+AVD arm of ECHELON-1 may be higher than expected in clinical practice.

In terms of the ABVD arm of ECHELON-1, the EAG does not consider the use of the six-cycle ABVD regimen to reflect standard UK clinical practice. The EAG therefore does not consider it appropriate to draw conclusions for standard care using the safety data from ECHELON-1 alone and notes that AE data from RATHL are also used in the model (Section 4.2.8).

3.3.6.3 *Pulmonary toxicity using 20 April 2017 data cut-off*

The company reported that pulmonary toxicity events included all preferred terms in the Interstitial Lung Disease (ILD) Standardised Medical Dictionary for Regulatory Activities (MedDRA) query. The preferred terms identified were lung infiltration, pneumonitis, interstitial lung disease, acute respiratory distress syndrome (ARDS), organising pneumonia, pulmonary fibrosis, and pulmonary toxicity. In summary, the overall rate of pulmonary toxicity events was lower in the A+AVD arm (n=12; 2%) compared with in the ABVD arm (n=44; 7%) of ECHELON-1. Five (<1%) patients in the A+AVD arm and 21 (3%) patients in the ABVD arm had Grade ≥3 pulmonary toxicity. Three patients had a fatal (Grade 5) pulmonary toxicity event in the ABVD arm but no Grade 5 pulmonary toxicity events were reported in the A+AVD arm.

3.3.6.4 *Peripheral neuropathy AEs using March 2023 data cut-off*

Similar to pulmonary toxicities, the company did an analysis of all AEs falling under the umbrella term of peripheral neuropathy using a SMQ which included all relevant preferred terms reported by patients in ECHELON-1 (peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, muscular weakness, hypoesthesia, neuralgia, polyneuropathy, and autonomic neuropathy). As of March 2023, of the 443 patients (67%) in the A+AVD arm who reported peripheral neuropathy during the treatment period, 122 patients (28%) still had ongoing symptoms although [redacted] (Table 19). The EAG also notes that 68 A+AVD patients (10%) had a Grade ≥3 peripheral neuropathy TEAE and for 16 of the A+AVD patients (2%) this was ongoing at last follow-up (median follow-up of [redacted] after end of treatment).

In the ABVD arm of ECHELON, 286 patients (43%) reported peripheral neuropathy while on treatment and 58 patients (20%) had ongoing symptoms at the March 2023 data cut-off. Grade ≥3 peripheral neuropathy TEAEs occurred in [redacted] ABVD patients ([redacted]%), and 4 ABVD patients (1%) experienced ongoing Grade ≥3 peripheral neuropathy TEAEs at last follow-up (median follow-up of [redacted] after end of treatment).

In terms of the MEDRA preferred terms for the peripheral neuropathy AEs, the EAG notes that the most commonly reported Grade ≥3 peripheral neuropathy TEAE in the A+AVD treatment arm was peripheral sensory neuropathy ([redacted]% compared with [redacted]% for ABVD [Table 20]).

Table 19. Summary of peripheral neuropathy adverse events in the ECHELON-1 safety population using the March 2023 data cut-off (reproduced from company response to CQ A6)

	A+AVD (n=662)	ABVD (n=659)
Patients with treatment-emergent PN SMQ event, n (%)*	[redacted]	[redacted]
CTCAE severity of PN SMQ AEs, n (%)*	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Mean time to resolution† of resolved PN events from onset, weeks (SD)	[redacted]	[redacted]
Status of PN AEs at last follow-up, n (%)	[redacted]	[redacted]
Resolution† of all events	[redacted]	[redacted]
Resolution† or improvement in events	[redacted]	[redacted]
Improvement in events	[redacted]	[redacted]
No resolution† of improvement of any events	[redacted]	[redacted]
Ongoing events	[redacted]	[redacted]
Ongoing events ≥ Grade 3	[redacted]	[redacted]
Patients with ≥1 PN (SMQ) TEAE resulting in study drug or dose modification, n (%)‡	[redacted]	[redacted]
Dose interrupted	[redacted]	[redacted]
Dose reduced	[redacted]	[redacted]
Dose delayed	[redacted]	[redacted]
Patients with ≥1 PN (SMQ) TEAE resulting in study drug or dose discontinuation, n (%)‡	[redacted]	[redacted]

Event severity based on National Cancer Institute CTCAE Version 4.03.
*Corresponds to Table 12.aa in 2018 CSR (20 April 2017 data cut). Please note the overall rate of PN SMQ events has increased by one in the A+AVD arm due to subsequent updates after the 2018 CSR.

†Resolution defined as resolved or resolved with sequelae.

‡Corresponds to page 278 in 2018 CSR (20 April 2017 data cut). Please note the rate of dose reductions has increased by one in the A+AVD arm and discontinuations has decreased by one in the A+AVD arm and one in the ABVD arm, due to subsequent updates after the 2018 CSR.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse event; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; PN, peripheral neuropathy; SD, standard deviation; SMQ, standardised MedDRA query.

Table 20. Summary of CTCAE Grade ≥3 peripheral neuropathy TEAEs in ECHELON-1 by SMQ or preferred term using the safety population and March 2023 data cut-off (reproduced from company response to CQ's, Table 7)

	A+AVD (n=662)	ABVD (n=659)
Patients reporting PN according to standardised MedDRA query, n (%)		
Patients with ≥1 treatment-emergent Grade ≥3 PN event, n (%)	68 (10)	11 (2)
Patients reporting PN by preferred term*, n (%)		
Peripheral sensory neuropathy	32[#] (5)	3 (<1)
Neuropathy peripheral	28 (4)	6 (<1)
Peripheral motor neuropathy	13* (2)	0
Muscular weakness	2 (<1)	1 (<1)
Hypoaesthesia	1 (<1)	0
Neuralgia	1* (<1)	0
Polyneuropathy	1 (<1)	1 (<1)
Autonomic neuropathy	0	1* (<1)

* Note: some patients reported more than one PN event.

[#] Note: updating of results subsequent to the 20 April 2017 data cut means that patient numbers have changed for these preferred terms, and results may appear different to earlier data.
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; PN, peripheral neuropathy; SMQ, standardised MedDRA query.

3.4 Critique of the indirect treatment comparisons

In the economic model, the company has assumed that the efficacy of six cycles of ABVD (as per ECHELON-1) is equivalent to the PET-adapted ABVD strategy followed in the RATHL trial (ABVD RATHL strategy). The company's justification for using this assumption included evidence from a naïve (unanchored and unadjusted) comparison and from an unanchored matching-adjusted indirect comparison (MAIC), both using the six-cycle ABVD arm of ECHELON-1 and PET-adapted ABVD from the Stage III and IV subgroup of the RATHL trial. However, the EAG does not consider a naïve comparison to be appropriate due to the between study differences in baseline characteristics (e.g. age, ECOG status and disease stage), and therefore considers the use of MAICs to be potentially more appropriate for comparing data from ECHELON-1 and RATHL.

The EAG notes that unanchored MAICs, should adjust for all potential prognostic factors and treatment effect modifiers that are in imbalance between arms, as outlined in NICE decision support unit technical support document (DSU TSD) 18[26]. However, given the difficulty in confirming which factors are prognostic/effect modifying, the EAG considers it best practice to adjust for all baseline

characteristics reported in the relevant studies. The EAG notes that the MAICs presented in the CS only included adjustment for age, international prognostic score (IPS), B symptoms, and ECOG performance score (extranodal site was also considered an effect modifier, but data were not available from RATHL at the time of the CS). In response to clarification questions the company also conducted fully adjusted MAICs with adjustments considered for age, IPS, ECOG, stage, sex, B-symptoms, bulky disease and presence of extra-nodal sites.

Based on advice received from clinical experts, the EAG considers the treatment regimen used in the RATHL study to more closely reflect current clinical practice in England compared to the ABVD arm in ECHELON-1. The EAG therefore requested the company conduct a MAIC comparing A+AVD from ECHELON-1 with PET-adapted ABVD (RATHL) for the comparison of A+AVD versus ABVD. However, following review of the results of the fully adjusted MAIC comparing six-cycle ABVD from ECHELON-1 with PET-adapted ABVD from RATHL, the EAG considers the results of the MAIC likely to be unreliable and therefore the EAG does not discuss this MAIC further (results for the MAIC comparing A+AVD from ECHELON-1 with PET-adapted ABVD from RATHL are available in the company response to clarification question A3).

The results from the fully adjusted MAIC comparing six-cycle ABVD from ECHELON-1 with PET-adapted ABVD from RATHL are discussed below.

3.4.1 Results from the MAIC comparing six-cycle ABVD from ECHELON-1 with PET-adapted ABVD from RATHL

Firstly, the EAG considers it important to highlight that the assumption of proportional hazards was not considered to hold following the company's assessments for the fully adjusted MAICs of six-cycle ABVD from ECHELON-1 versus PET-adapted ABVD from RATHL. The EAG also notes that digitised published data from RATHL was used in the MAICs and that the MAICs are unanchored and thus they are potentially subject to bias relating to any unmeasured or otherwise unaccounted for confounding factors. The EAG therefore agrees with the company that the results from any of the unanchored MAICs should be interpreted with caution.

In the fully adjusted MAIC comparing six-cycle ABVD from ECHELON-1 with PET-adapted ABVD from RATHL, after weighting for all baseline characteristics both PFS and OS outcomes were slightly improved in the six-cycle ABVD arm of ECHELON-1 compared with the unweighted six-cycle ABVD arm outcomes. For PFS, the relative efficacy of six-cycle ABVD (ECHELON-1) compared to PET-

adapted ABVD (RATHL) was associated with a HR of 0.89 (95% CI: 0.70 to 1.13; p=0.342) in the fully adjusted MAIC. For OS, the relative efficacy of six-cycle ABVD compared to PET-adapted ABVD (RATHL) was associated with a HR of 0.59 (95% CI: 0.40 to 0.85, p=0.005) in the fully adjusted MAIC, suggesting a statistically significant benefit with six-cycle ABVD compared to PET-adapted ABVD (RATHL).

The EAG is concerned that the results of the MAIC appear to contradict the findings in the RATHL trial of noninferiority for PFS and no significant difference in OS for de-escalated ABVD/AVD compared with six-cycle ABVD. In addition, the EAG notes that the six-cycle ABVD data includes patients who are PET2 positive (9%) and who may be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac. The also EAG notes that the majority of the PET2 positive patients in the ABVD arm of ECHELON-1 have remained on six-cycle ABVD as only [redacted]% of ABVD patients (full trial ITT population) switched to an alternative frontline medication (AFM). The EAG is therefore concerned about the face validity and generalisability of the findings from the fully adjusted MAIC comparing six-cycle ABVD with PET-adapted ABVD (RATHL approach) and does not consider it reasonable to draw conclusions relating to the efficacy of PET-adapted ABVD in UK clinical practice from the MAICs of six-cycle ABVD in ECHELON-1 versus PET-adapted ABVD in RATHL.

3.4.2 Safety data from ECHELON-1 compared with RATHL

For ABVD-based treatment, although the company assumed equivalent efficacy in the economic model, they noted differences in tolerability between the six-cycle and PET-adapted ABVD treatment regimens. Therefore, the base case analysis included data on Grade ≥3 treatment related AEs occurring in ≥5% of patients from both the six-cycle ABVD arm of ECHELON-1, and the PET-adapted ABVD regimen from the RATHL trial to reflect the AEs of PET-adapted ABVD.

The AE data from RATHL were weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3–6), and 16.3% escBEACOPP (cycles 3–6) and the overall ABVD AE data used in the model were then further weighted to reflect the assumed use of ABVD-based treatment in UK clinical practice (10% six-cycle ABVD from ECHELON-1 and 90% PET-adapted ABVD regimen from the RATHL). The incidence of AEs from ECHELON-1 and RATHL trials of relevance to the model are presented in Table 21, with the adverse events included in the economic model discussed further in Section 4.2.8.

The EAG notes that there are large discrepancies in the Grade ≥3 AE incidences reported for ABVD in ECHELON-1 compared to those reported for PET-adapted ABVD from RATHL. In particular, there

were 0 patients with Grade ≥3 anaemia or neutrophil count decreased in RATHL compared to 2.73% and 9.71% of patients with these AEs in the ABVD arm of ECHELON-1. A further important potential discrepancy between the AE data from the two studies is that the data reported from ECHELON-1 comprise treatment-related AEs, whereas for the data from RATHL appears likely to be TEAEs rather than only those deemed to be treatment-related (data from RATHL are reported as Grade 3 or 4 AEs among patients with negative PET findings who started their assigned treatment)[8]. The EAG therefore considers the AE data likely to be confounded.

For A+AVD, the use of drug-related AE data rather than TEAE data is likely to underestimate the AEs with A+AVD but then as noted in Section 3.3.6.2.1, the EAG considers the use of G-CSF in ECHELON-1 not to be reflective of clinical practice and to potentially lead to an over-estimate in some of the AEs for A+AVD. The EAG therefore does not consider it possible to predict the resulting direction of any bias. Similarly for ABVD, the EAG considers it difficult to predict the direction of any resulting bias relating to the AE data, as the escBEACOPP regimen used in RATHL doesn't align with the escBEACOPDac regimen used in UK clinical practice.

Finally, the EAG notes that likely due to the timing of the ECHELON-1 and RATHL studies, different versions of the National Cancer Institute CTCAE were used for recording AEs (Version 4.03 in ECHELON-1 and Version 3.0 in RATHL). This adds further concerns regarding the comparability of the AE data from the two studies. Despite the differences highlighted above, the EAG considers the AE data used in the model likely to be the most suitable data currently available, but the EAG also recommends caution in drawing any definitive conclusions on the safety of A+AVD versus PET-adapted ABVD due to the issues highlighted above.

Table 21. Grade ≥3 AEs in ≥5% of patients (reproduced from Table 30 in the CS and Table 20 in the company response to CQ's)

	ECHELON-1 (March 2023 data cut-off)		PET-adapted ABVD (RATHL)			
	A+AVD	ABVD (6 cycles)	ABVD (cycles 1–2)	AVD (cycles 3–6)	escBEACOPP (cycles 3–6)	Weighted PET-adapted ABVD*
N	662	659	1203	457	78	1598
Anaemia, n (%)	[redacted]	[redacted]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Febrile neutropenia, n (%)	[redacted]	[redacted]	24 (2%)	10 (2.19%)	52 (66.67%)	41 (2.56%)

Neutropenia, n (%)	[redacted]	[redacted]	694 (57.69%)	269 (58.86%)	20 (25.64%)	922 (57.71%)
Neutrophil count decreased, n (%)	[redacted]	[redacted]	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3–6), and 16.3% escBEACOPP (cycles 3–6).
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; N, number; TEAE, treatment-emergent adverse events.

3.5 Conclusions of the clinical effectiveness section

The EAG considers the key evidence submitted by the company in support of the clinical efficacy and safety of brentuximab vedotin (ADCETRIS®; Takeda) with doxorubicin, dacarbazine and vinblastine (A+AVD) in the treatment of [redacted] to be the ECHELON-1 RCT of A+AVD (n=664) versus ABVD (n=670). The EAG notes that the company also included a comparison with PET-adapted ABVD (the key comparator of relevance to UK clinical practice) from the RATHL trial using unanchored MAICs. The RATHL trial randomised PET2 negative ABVD patients to either continue treatment with ABVD or to de-escalate treatment to AVD. RATHL also included follow-up of PET2 positive patients and these were all escalated to receive a BEACOPP treatment regimen.

The EAG broadly agrees with the company's assessment of ECHELON-1 as generally being at low risk of bias, but notes that it was an open-label study and there is thus a risk of bias in the results for some of the efficacy outcomes. Of particular note, the most mature results for progression free survival (PFS) relate to investigator-assessment (PFS-INV) rather than the independent review facility (PFS-IRF) assessment and PFS-INV from ECHELON-1 is used to inform the efficacy of A+AVD and ABVD in the analyses of cost-effectiveness. In addition, the EAG notes that the data cut-off used for the efficacy and safety analyses reported in the CS were not consistently based on the final data cut-off (11 March 2023), although the company reported that the final data cut-off was used for all data that were subsequently used in the economic model (including OS, PFS-INV and Grade 3 or above drug-related TEAEs occurring in ≥5% of patients in either trial arm).

The EAG considers the population addressed in the CS to be reasonable but notes that the company's proposed positioning of A+AVD is for the treatment of previously untreated patients with CD30+ Stage III or IV HL who would otherwise be suitable for treatment with ABVD and that this is a subgroup of the population with previously untreated patients with CD30+ Stage III or IV HL.

In terms of the intervention, the EAG notes that only 13% of patients in the A+AVD treatment arm of ECHELON-1 received G-CSF primary prophylaxis but in the summary of product characteristics (SmPC) for brentuximab, primary prophylaxis with growth factor support (G-CSF) beginning with the first dose, is recommended for all adult patients with previously untreated HL receiving combination therapy; i.e. A+AVD. The EAG therefore considers that most patients in UK clinical practice would be expected to receive prophylactic G-CSF and is concerned that the use of G-CSF in ECHELON-1 does not reflect current recommendations for its use alongside A+AVD from Cycle 1. However, the EAG also notes that 81% of patients in the A+AVD arm received G-CSF during ECHELON-1. The EAG considers the potential discrepancy in G-CSF usage may impact on both the efficacy and safety results of A+AVD in ECHELON-1 due to potentially more AEs in the trial and the impact this may have on receiving the full A+AVD treatment regimen.

The EAG's main concern with the clinical data is that the comparator in the ECHELON-1 trial is six-cycle ABVD, whereas current recommended standard care in UK clinical practice is PET-adapted ABVD. In PET-adapted ABVD patients who are PET2 negative would be de-escalated to AVD and those who are PET2 positive would be escalated to receive escBEACOPDac. The EAG is concerned that there is a lack of robust clinical effectiveness data to support the company's assumption of clinical equivalence between six-cycle ABVD and the PET-adapted RATHL approach. The EAG notes that the company provided an unanchored MAIC comparing the efficacy of the ABVD arm from ECHELON-1 with PET-adapted ABVD (RATHL approach) using the RATHL study in the CS but the EAG is concerned about the face validity and generalisability of the findings from the MAIC analysis. This is because the results of the MAIC suggested a statistically significant benefit for OS with six-cycle ABVD compared to PET-adapted ABVD (RATHL) and the HR for INV-PFS also favoured treatment with six-cycle ABVD (although it did not reach statistical significance). The EAG notes that the six-cycle ABVD data includes patients who are PET2 positive and who may be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac. The EAG thus considers the results of the MAIC to contradict the findings in the RATHL trial of noninferiority for PFS and no significant difference in OS for de-escalated ABVD/AVD compared with six-cycle ABVD.

In response to clarification questions the company conducted an unanchored MAIC to provide a comparison of A+AVD (from ECHELON-1) with PET-adapted ABVD (RATHL approach) from the stage III and IV subgroup of the RATHL study but the EAG considers the results from this MAIC are likely to also be unreliable similar to for the MAIC of ABVD arm from ECHELON-1 versus PET-adapted ABVD from RATHL. In addition, the EAG notes that there is evidence to suggest the assumption of

proportional hazards is violated. The EAG therefore agrees with the company that the most robust source of evidence for the comparison of A+AVD with ABVD is currently the ECHELON-1 trial, but the EAG is also concerned that the ABVD arm of ECHELON-1 comprises of six-cycle ABVD rather than the PET-adapted ABVD which is used in UK clinical practice.

In terms of the results from ECHELON-1, the median follow-up for OS and PFS was 90.1 and 90.0 months, respectively. The analysis of OS from ECHELON-1 showed a 38.3% reduction in the risk of death in the A+AVD arm compared with the ABVD arm and a statistically significantly difference between the two treatment arms suggesting improvement in OS with A+AVD (HR 0.617; 95% CI: 0.423 to 0.899; p=0.011). However, the EAG notes that there is a crossing of the Kaplan–Meier curves at approximately 114 months and is unclear on the rationale for this although it is also noted that there is heavy censoring from 102 months and only a small number of patients left in the analysis at 114 months. The analysis of PFS-INV from ECHELON-1 demonstrated a 32.3% reduction in the risk of progression or death with A+AVD compared with ABVD, favouring treatment with A+AVD (HR 0.68; 95% CI: 0.53 to 0.86; p=0.001).

In ECHELON-1, more patients in the A+AVD arm reported at least one Grade ≥3 drug-related TEAE compared with in the ABVD arm (80% versus 60% of patients, respectively) suggesting A+AVD is associated with a worse safety profile compared to ABVD. Also peripheral neuropathy is an AE known to be associated with brentuximab, and the EAG notes that 68 A+AVD patients (10%) had a Grade ≥3 peripheral neuropathy TEAE, and 16 of the A+AVD patients (2%) had an ongoing Grade ≥3 peripheral neuropathy TEAE at last follow-up (median follow-up of [redacted] weeks after end of treatment). In contrast, only 11 ABVD patients (2%) experienced Grade ≥3 peripheral neuropathy TEAEs, and 4 ABVD patients (1%) experienced ongoing Grade ≥3 peripheral neuropathy TEAEs at last follow-up (median follow-up of [redacted] weeks after end of treatment).

The EAG therefore considers that life-long peripheral neuropathy AEs should be accounted for in the economic model (Section 4.2.8).

The EAG considers there to be multiple issues with the suitability of the AE data used to inform ABVD in the economic model, including that the data reported from ECHELON-1 comprise treatment-related AEs, whereas for the data from RATHL it appears likely to be all TEAEs rather than only those deemed to be treatment-related (data from RATHL are reported as Grade 3 or 4 AEs among patients with negative PET findings who started their assigned treatment). In addition, the

EAG considers the use of G-CSF in ECHELON-1 likely not to be reflective of clinical practice and to potentially lead to an over-estimate in some of the AEs for A+AVD. Nevertheless, the EAG considers the AE data used in the model likely to be the most suitable data currently available, but the EAG also recommends caution in drawing any definitive conclusions on the safety of A+AVD versus PET-adapted ABVD.

In summary, the EAG considers the clinical efficacy of A+AVD versus PET-adapted ABVD to be uncertain and is concerned that the clinical efficacy data used in the cost effectiveness analyses may not accurately reflect outcomes in UK clinical practice. However, the EAG agrees with the company that the best available efficacy evidence for the comparison of A+AVD with ABVD in the economic model is currently the ECHELON-1 trial.

4 Cost effectiveness

Table 22 below presents the company's updated (i.e., post clarification) incremental cost-effectiveness base case results. The costs presented in this document are inclusive of a [redacted] patient access scheme (PAS) discount for brentuximab vedotin, base cases and scenario analyses that included the PAS for relevant treatments are provided in the confidential appendix.

The company's base case analysis compared brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine (A+AVD) to doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) for the treatment of previously untreated late-stage classical Hodgkin's lymphoma.

Table 22. Company's base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
A+AVD	[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

4.1 EAG comment on the company's review of cost effectiveness evidence

The company conducted two systematic literature reviews (SLRs) to identify evidence to inform the cost-effectiveness model, as follows:

- SLR to identify existing economic evaluations relevant to first-line treatment of patients with advanced HL (searches were initially run in August 2022, and were updated in January 2024); and
- SLR to identify health-related quality of life (HRQoL), health care resource use and cost evidence relevant to patients with HL (searches for this SLR were initially run in July 2016 and were updated in May 2018, June 2022 and December 2023).

The SLRs included searches of an appropriate selection of data sources, including electronic literature databases, namely, Embase, MEDLINE, MEDLINE In-Process, EconLit, the National Health Service Electronic Evaluations Database (NHS EED) and the International Network of Agencies for Health Technology Assessment (INAHTA) database. Hand-searching was also conducted of

conference proceedings, health technology assessment (HTA) bodies and reference lists of included publications.

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Tables 47- 55, Section 1.2, Appendix G	Tables 60-77, Section 1.2, Appendix H	Tables 60-77, Section 1.2, Appendix H	**Appropriate**
Inclusion/ exclusion criteria	Table 56, Section 1.3.1, Appendix G	Table 78, Section 1.3.1, Appendix H	Table 81, Section 1.3.1, Appendix I	**Appropriate**
Screening	Section 1.3, Appendix G	Section 1.3, Appendix H	Section 1.3, Appendix I	**Appropriate**
Data extraction	Section 1.3.2, Appendix G	Section 1.3.2, Appendix H	Section 1.3.2, Appendix I	**Appropriate**
Quality assessment of included studies	Section 1.3.2, Appendix G	Section 1.3.2, Appendix H	Section 1.3.2, Appendix I	**Appropriate**

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life.

In total, including both the original search and subsequent update, the SLR of economic evaluations identified a total of 493 records. Twenty-two of these were selected for full text screening, of which 11 were selected for final inclusion. A summary of the identified publications is given in Table 57, Section 1.4.2, Appendix G. In general, a comprehensive range of prior economic evaluations were identified, six of which included A+AVD as a comparator. However, one of the evaluations took a UK perspective. Only one previous HTA was identified (a Canadian appraisal for brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine for previously untreated patients with stage IV HL), which is to be expected, since the current standard of care in this indication has broadly included combinations of the same generic chemotherapy options for several decades.[27]

The SLR of HRQoL, costs and resource use identified a total of 12,569 records across the original search and subsequent updates. Of these, 307 were selected for full text screening, of which 47 were selected for final inclusion (28 for HRQoL evidence and 19 for cost or resource use evidence). A summary of the identified publications relevant to HRQoL is given in Table 79, Section 1.4.2, Appendix H, and a summary of the publications relevant to cost and resource use is given in Table 82, Section 1.4.2, Appendix I.

In general, a limited selection of evidence was identified, with no usable HRQoL, cost or resource use evidence specific to the UK being identified. Only two studies were identified that included EQ-5D

data, neither of which were appropriate for parametrising HRQoL in the economic model. One study, Brandt *et al.* 2010, reported only utility values for patients receiving conventional or high-dose chemotherapy, while the other, Ramchandren *et al.* 2019, only explicitly presented EQ-VAS results.[28, 29] Therefore, in the absence of appropriate model inputs in existing literature, the company used the British Society for Haematology (BSH) and the European Society for Medical Oncology (ESMO) guidelines, supplemented by input from UK clinicians, to parametrise costs and resource use in the model. Further details of the approach used to model HRQoL are given in Section 4.2.9, and details of the approach to modelling costs and resource use is given in Section 4.2.10.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 23 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.1.

Table 23. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All major health outcomes for untreated late-stage HL have been included in the economic model.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis has been provided by the company with fully incremental analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (100 years of age).
Synthesis of evidence on health effects	Based on systematic review	The company has performed an appropriate systematic review.
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 outcomes have been expressed in terms of QALYs, with health state utility values being informed by EQ-5D values.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D values were obtained from late-stage HL patients from the ECHELON-1 trial, that was also

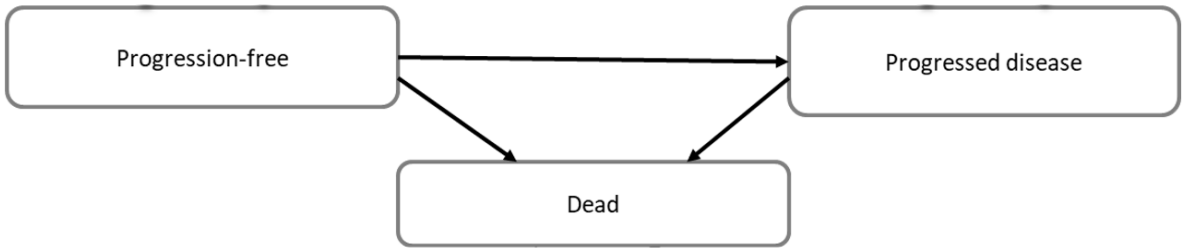
		used to inform treatment effects in the model.[30]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The source considered for HRQoL can be considered relevant to the UK.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
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	All relevant costs appear to be included appropriately.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: EAG, External Assessment Group; HL, Hodgkin's lymphoma; HRQoL, health related quality of life; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year; UK, United Kingdom.

4.2.2 Modelling approach and model structure

The company developed a *de novo* partition survival model comprised of three mutually exclusive health states; progression-free (PF), progressed disease (PD) and dead (Figure 7).

Figure 7. Model structure (reproduced from Figure 13 in the CS)



Health state occupancy was directly informed using the extrapolated overall survival (OS) and progression-free survival (PFS) curves. The area under the PFS curve was used to calculate the proportion of patients considered PF and the difference between the OS and PFS curves was used to derive the proportion of PD patients.

As the company's clinical experts expected that a high proportion of patients might be considered "cured" post-treatment, with the data from ECHELON-1 trial appearing to support this assumption, the company included a cure timepoint in the model for both A+AVD and ABVD treated patients. The

company's clinical experts outlined that 24 months after treatment was a reasonable cure timepoint, suggesting that this timepoint also agreed with the ECHELON-1 PFS data and the British Society for Haematology (BSH) guidelines that state patients are usually followed up for two years after first-line treatment. [6]

The company's clinical experts additionally added that the majority of patient relapses will occur within two years from treatment discontinuation and a minority of patients will relapse after five years. One expert from the advisory board considered that the treatment pathway is generally completed after seven years, including patients who experience disease progression and required multiple lines of therapy. When considering the clinical trial data, the company suggested that a 24-month cure point may be conservative as there is a plateau in the ECHELON-1 PFS as early as 12 months. The company therefore assumed a two-year cure time point in their base case, with additional scenario analysis conducted using two and five years timepoints.

After the cure timepoint, PF patients were considered cured and assumed to not incur any additional health care resources costs. This assumption was based on company's clinical expert advisory board who stated that if a patient had not relapsed within 24 months post-treatment discontinuation, then patients would be considered cured and would be discharged with no further follow up. Cured patients were additionally assumed to experience general population health related quality of life (HRQoL) utilities. This was also the opinion of the company's clinical expert advisory board, with the company justifying this assumption using with HRQoL data collected in the ECHELON-1 trial, which is discussed in further in Section 4.2.9.

4.2.2.1 EAG critique

The EAG considers that the company's model broadly captures the key changes in health outcomes associated with late-stage HL but notes that the model consists of three health states, with relapsed and refractory PD patients being modelled within a single health state. Comparatively, of the relevant publications captured in the company's SLR that used a model, the majority were five health state models, with relapsed and refractory patients being considered separately.

When requested to justify their approach given the loss of precision from the model structure simplification, the company responded that the evaluations captured in the SLR were informed using data with a much shorter follow-up than compared to the ECHELON-1 trial (a mean of 24.9 months vs 89.3 months respectively). In the evaluations highlighted, OS was estimated via a surrogacy

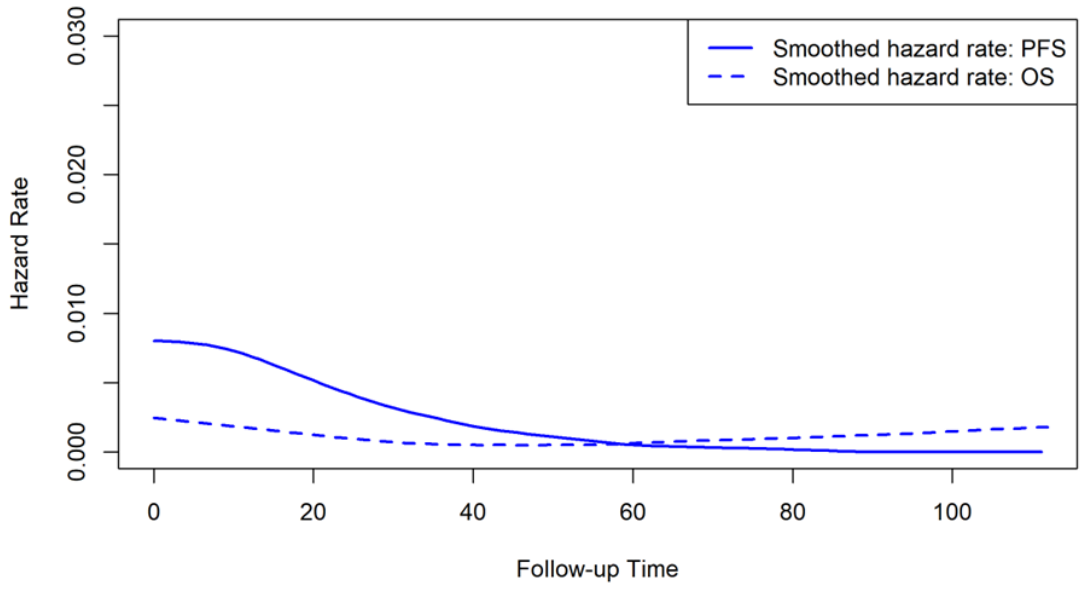
relationship between intermediate events and mortality and relied on external data across several studies to inform post-progression survival. Therefore, in the absence of more mature data, an approach using additional health states may be more appropriate. The company maintained that characterising relapsed and refractory disease in a single progressed disease health state was appropriate for decision-making given the maturity of the ECHELON-1 data, which they considered to sufficiently captures all outcomes relating to the progressed disease health state. The company additionally suggested that due to the small incremental difference in PD events between A+AVD and ABVD treated patients, incorporating an additional post-progression health state would likely not lead to materially changes in cost-effectiveness estimates and may introduce unnecessary uncertainty given the additional modelling assumptions required, which the EAG considers reasonable.

With respect to the cure fraction and timepoint considered in the model. The EAG's clinical experts agreed that due to the high proportion of cured patients following treatment, a cure fraction was appropriate. One of the EAG's clinical experts agreed with the company's assumption that patients who are non-relapse or refractory two years after treatment discontinuation can be consider cured and will require no additional follow-up or health care resources related to the primary HL. Another expert stated that while the majority of relapse events occur within the first two years, it would be unusual to discharge a patient after two years and a five-year follow-up is more common. Patients would usually have three instances of follow-up per year for the first two years and thereafter be seen annually for up to five years after which time they would be discharged.

Given the discrepancy in opinion between the clinical experts, the company was requested to provide PFS hazard rates. The EAG considers that a plateauing of the hazards would provide an estimate for when the cure timepoint occurs, assuming progression would be less of a competing risk factor to mortality in the calculation of PFS hazards. The company provided the hazards as requested, with Figure 8, Figure 9 and Figure 10 presenting the smoothed PFS and OS hazards for A+AVD, ABVD and both treatments combined. From the figures, the EAG considers that the ABVD hazards support a two-year cure timepoint given the flattening of the curve around 24-months following a peak. The A+AVD hazards conversely do not peak but steadily decline over time, suggesting that A+AVD may be working to delay patient progression, with an eventually plateauing of the curve around sixty months. The company conducted a scenario using instead a cure timepoint of 36 months and 60 months which showed little impact to the ICER. Given that in the combined treatment hazard plots the plateau is seen at approximately 25 to 30 months and that the cure

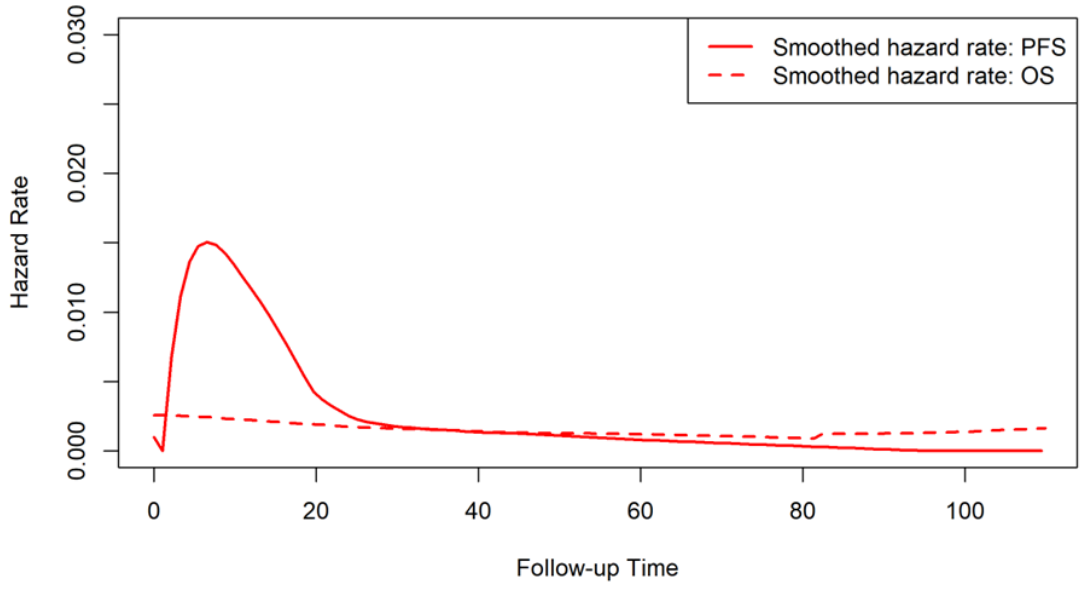
timepoint has little bearing on the ICER, the EAG considers that the two-year cure time point assumption is appropriate.

Figure 8. A+AVD (ITT population) smoothed hazard curves (reproduced from Figure 24 in the CQ response)



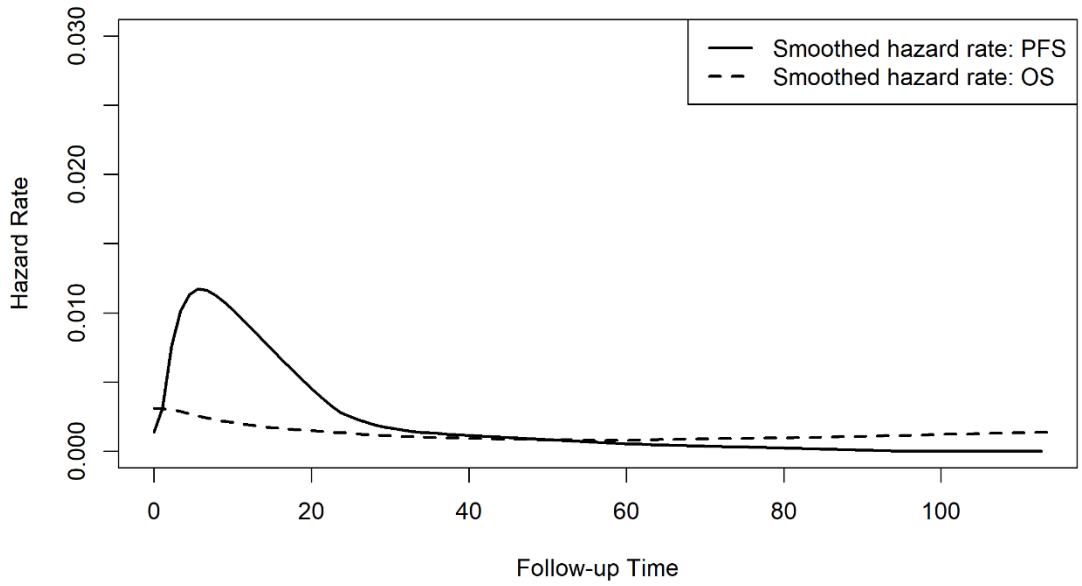
Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression-free survival

Figure 9. ABVD (ITT population) smoothed hazard plots (reproduced from Figure 25 in the CQ response



Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression-free survival

Figure 10. Combined treatments (ITT population) smoothed hazard plots (reproduced from Figure 23 in the CQ response)



Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression-free survival

4.2.3 Population

The population considered in the model reflected that of the ECHELON-1 trial, the characteristics of which are presented in Table 24.

Table 24. Patient baseline characteristics (reproduced from Table 21 in the CS)

Population characteristics	Value (SD, 95% CI)	
	ECHELON-1	RATHL
Age (years)	39.53 (0.44, 38.68 to 40.39)	[redacted]
Proportion male	58.17% (0.01, 55.51 to 60.81%)	[redacted]
Body weight (kg)	75.06 (0.53, 74.03 to 76.09)	NA
BSA (m^2)	1.88 (0.01, 1.87 to 1.89)	NA

Abbreviations: BSA, body surface area; CI, confidence interval; kg, kilogram; NA, not available; SD, standard deviation.

4.2.3.1 EAG critique

When asked to describe the previously untreated late-stage classical HL population the EAG's clinical experts stated that the disease effects the population bimodally, with 20–24 year and 75–79-year-olds being most likely to have the condition.

The EAG was therefore concerned that the company's mean age-based approach may be overly simplistic, and does not appropriately capture the expected differences in the two discrete populations. The EAG requested the company to provide a scenario that accounted for the bimodal population by providing a weighted ICER based on the proportion of <60 and ≥60-year-old patients in the ECHELON-1 trial. The company agreed with the EAG that the incidence of late-stage HL is bi-modal, however, they did not believe it appropriate to consider the patient populations separately, given a potential negative impact on health inequities, that the subgroup analysis breaks randomisation and that there were considerably less ≥60-year-old patients in the study. The EAG considers that by providing a weighted ICER, the populations are not considered separately and so there is no negative impact to health inequities.

The company conducted the scenario as requested: first fitting dependent and independent parametric curves (parametric, mixed cure models [MCM] and splines) to the <60 years and ≥60 years subgroup data from ECHELON-1. Patient characteristics were updated, in accordance with the subgroups, with the company highlighting that 1,148 patients were considered <60 years old and only 186 patients ≥60. Proportional hazard and tests for best fit were conducted, the results of which are provided in the appendix of this report. Extrapolating the OS Kaplan Meier (KM) data using a one-knot spline model and PFS using a MCM, which the company considered the most appropriate, resulted in the ICER increasing to [redacted] from [redacted] when weighted by the number of patients in each subgroup (86.1% <60 years old and 13.9% aged ≥60). Given that the late-stage HL patient population is bi-modal population, that there are differences in the subgroup treatment effects but accounting for these differences has no inference to if the ICER lies above or below a £30,000 cost effectiveness threshold, the EAG considers that the weighting of the ICER according to age is appropriate and is included in the EAG's base case assumptions.

4.2.4 Intervention and comparators

Mirroring the ECHELON-1 clinical trial, the intervention considered in the model was A+AVD, with ABVD being the comparator. In contrast to the six-cycle ABVD treatment approach used in the trial, the company's clinical experts both stated that the more appropriate comparator would be a PET-adapted treatment approach given its recommendation within BSH guidelines and its routine use in clinical practice.[6] The company therefore aimed to model separate proportions of ABVD patients that would receive either the PET-adapted or six-cycle approach. The company's clinical experts

outlined that 90% of patients would likely be treated with the PET-adapted approach and 10% the six-cycle approach in clinical practice and so these proportions were assumed in the model.

To investigate the difference in treatment efficacies between the ABVD treatment approaches, the company conducted a naïve comparison between the ECHELON-1 ABVD trial arm and the PET adapted arm from RATHL as presented in Figure 11 and Figure 12 (discussed in detail in Section 3.4).[8] The company concluded that given the similarity in outcomes, it was appropriate to assume PET-adapted and six-cycle ABVD as having equal treatment effects in the model.

Figure 11. PFS Kaplan–Meier overlay between ABVD – ECHELON-1 and RATHL (reproduced from Figure 14 in the CS)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PFS, progression-free survival; RATHL, Response-Adjusted Therapy for Advanced Hodgkin Lymphoma

Figure 12. OS Kaplan–Meier overlay between ABVD – ECHELON-1 ITT and RATHL (reproduced from Figure 15 in the CS)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival; RATHL, Response-Adjusted Therapy for Advanced Hodgkin Lymphoma

4.2.4.1 EAG critique

The EAG's clinical experts agreed that the PET-adapted ABVD was the more appropriate comparator due to its routine use in clinical practice following the RATHL trial and thereafter its recommendation withing BSH guidelines. The EAG notes that their clinical experts could not consider under what circumstances a six-cycle approach may be preferred to PET-adapted, given the utility of escalating and de-escalating treatment in reaction to a positive or negative PET scan.

In addition to the PET-adapted approach being more appropriate, it may also be considered more effective than the six-cycle approach in PET2 positive patients. While the RATHL study concluded that de-escalated ABVD (AVD) was non-inferior to six-cycle ABVD, the EAG's clinical experts considered that escalated ABVD may be more effective in PET2 positive patients compared to remaining on six-cycle ABVD. Thus, the treatment effect of ABVD may be underestimated in the model when considering the proportion of ABVD patients who are PET positive (9% of ABVD patients in ECHELON-1).

For these reasons the company was requested to perform a fully adjusted MAIC comparing A+AVD from ECHELON-1 to PET-adapted ABVD from RATHL. As described in Section 3.4, the company conducted the MAIC as requested, however, the results were considered to be unreliable.. The EAG thus considers that the MAIC does not provide generalisable PET-adapted ABVD treatment effects and so the results and outcomes were not evaluated further. Model outcomes and results using the MAIC treatment effects are reported in the company's response to the EAG's clarification questions.

The EAG therefore considers that the ABVD treatment effectiveness uncertainty stemming from the difference in approaches has not been addressed. The modelled ABVD treatment effect is therefore highly uncertaint and potentially underestimated given treatment effects are derived from the six-cycle used in the ECHELON-1 trial compared to the PET-adapted approach used in clinical practice.

4.2.5 Perspective, time horizon and discounting

The model cycle length was seven days with a half cycle correction applied. A lifetime horizon was used (up to age 100) allowing for the model to continue for 60 years given a patient starting age of 39.5 years, aligning with the ECHELON-1 study mean age. The perspective of the analysis was based

on the UK NHS and PSS, with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case. [31]

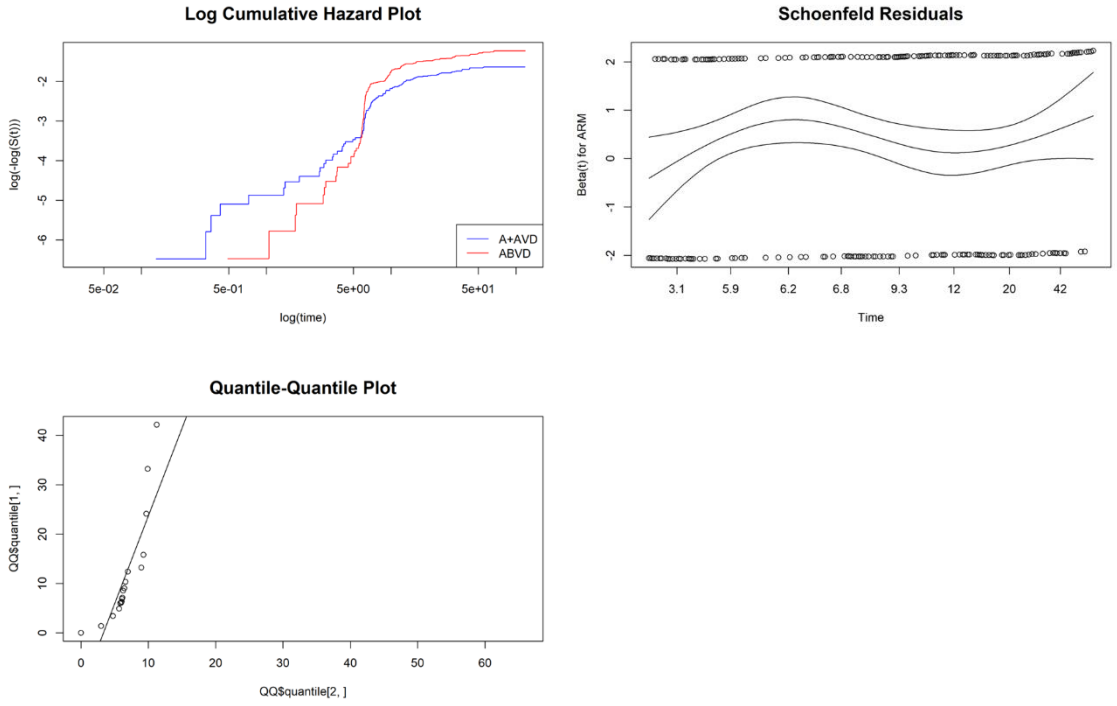
4.2.6 Treatment effectiveness

A+AVD and ABVD treatment effects were informed using the ITT patient data from the ECHELON-1 trial. Patient observations were taken from the final data-cut (11 March 2023), which provided a median follow-up time of 89.2 and 89.3 months for PFS and OS respectively. Tests for proportional hazards extrapolation model for best fit were conducted for PFS and OS and are considered below.

4.2.6.1 Progression free survival

The company tested proportional hazards and accelerated failure time assumptions for investigator-assessed PFS, as presented in Figure 13.

Figure 13. PFS proportional hazards and accelerated failure time tests (reproduced from Figure 19 in the CS)

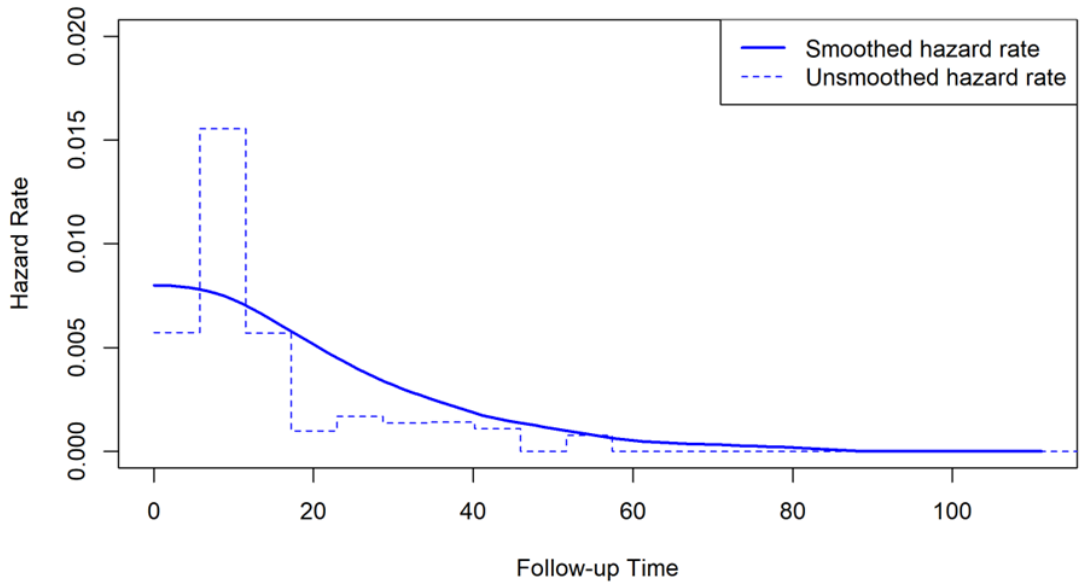


Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

The Schoenfeld residuals and Grambsch-Therneau tests resulted in a p-value of 0.68, suggesting that the proportional hazards assumptions may not be violated; however, the log-cumulative hazard

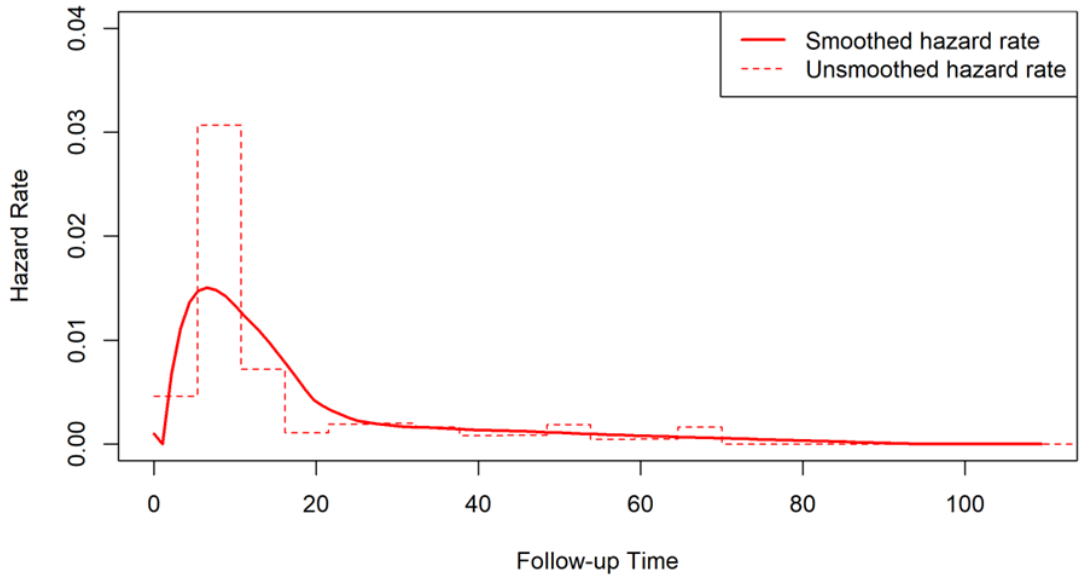
plots showed a clear crossing of curves, leading the company to conclude that proportional hazard assumptions had been violated. The company additionally noted that observed hazard plots (Figure 14 and Figure 15) were different in shape, further supporting the company's proportional hazards conclusion. As such the company aimed to fit independent extrapolation models to each treatment arm.

Figure 14. Observed hazards | A+AVD | PFS per INV (reproduced from Figure 20 in the CS)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

Figure 15. Observed hazards | ABVD | PFS per INV (reproduced from Figure 21 in the CS)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Given the appropriateness in assuming a patient cure fraction from the clinical trial results, literature and clinical expert opinions, mixed cure models (MCMs) were explored and applied to the PFS KM data in the company's base case. One-knot spline models were explored by the company as scenario analyses after considering that a flexible cure model was appropriate, as the conditions postulated in Palmer *et al.* had been sufficiently satisfied (Table 22 in the CS). [32]

Figure 16 and Table 25 present the A+AVD MCMs (excluding adjusted background mortality) and their AIC and BIC values. Similarly, Figure 17 and Table 26 present the extrapolated ABVD MCMs (excluding adjusted background mortality) and their respective AIC and BIC values.

Figure 16. A+AVD PFS independent MCMs (reproduced from Figure 22 in the CS)

Notes: extrapolations exclude adjusted background mortality
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival.

Table 25. A+AVD PFS independent MCM AIC and BIC values (reproduced from Table 23 in the CS)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1380	5	1389	2
MCM: Weibull	1378	4	1392	4
MCM: Lognormal	1386	7	1400	7
MCM: Loglogistic	**1372**	**1**	**1385**	**1**
MCM: Gompertz	1382	6	1396	6
MCM: Generalised Gamma	1377	2	1395	5
MCM: Gamma	1377	2	1390	3

Notes: bold represents the base case
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; ITT, intention-to-treat; MCM, mixture cure model; PFS, progression-free survival

Figure 17. ABVD PFS independent MCMs (reproduced from Figure 23 in the CS)

Notes: extrapolations exclude adjusted background mortality
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 26. ABVD PFS independent MCM AIC and BIC values (reproduced from Table 24 in the CS)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1860	6	1869	5
MCM: Weibull	1856	5	1869	5
MCM: Lognormal	1811	3	1825	2
MCM: Loglogistic	**1802**	**1**	**1816**	**1**
MCM: Gompertz	1861	7	1874	7
MCM: Generalised Gamma	1810	2	1828	3
MCM: Gamma	1846	4	1860	4

Notes: bold represents the base case
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; ITT, intention-to-treat; MCM, mixture cure model; PFS, progression-free survival.

Of the models and extrapolations presented to the company's clinical and health economic advisors, all unanimously agreed that the MCMs provided the best approach given a proportion of patients can be considered cured post treatment discontinuation. Given the similarities between extrapolations, the advisors considered that all independent MCMs explored were plausible; however, the log-logistic was the most appropriate for the base case with the model also resulting in the lowest AIC and BIC values. The company's advisors additionally considered that the spline models were supportive of the MCMs, given their close alignment, but reiterated that MCMs were the most relevant to the decision problem. Following these opinions, the loglogistic MCM model was selected to extrapolate A+AVD and ABVD PFS in the company's base case.

Table 27 presents the predicted cure fractions for each MCM for A+AVD and ABVD. As shown, the predicted cure fractions are similar across all extrapolations for each treatment arm, highlighting the stability of the cure fraction independent of the parametric model considered. Furthermore, the company highlights that the predicted cure rates for ABVD align with those seen in the literature (70-80%) and the company's clinical expert opinions.

Table 27. PFS cure fractions (reproduced from Table 25 in the CS)

	A+AVD	ABVD
MCM: Exponential	[redacted]	[redacted]
MCM: Weibull	[redacted]	[redacted]
MCM: Lognormal	[redacted]	[redacted]
MCM: Loglogistic	[redacted]	[redacted]
MCM: Gompertz	[redacted]	[redacted]
MCM: Generalised Gamma	[redacted]	[redacted]
MCM: Gamma	[redacted]	[redacted]

Notes: bold represents the base case

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; PFS, progression-free survival.

Figure 18 presents the company's base case PFS extrapolations, now including background mortality with standardised mortality ratios applied (described further in Section 4.2.7), and Table 28 the observed vs predicted outcomes.

Figure 18. Company base case PFS curve preference, adjusted to include background mortality (reproduced from Figure 24 in the CS).

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 28. Observed vs predicted PFS (reproduced from Table 26 in the CS)

	ECHELON-1		Predicted		RATHL
	A+AVD	**ABVD**	**A+AVD**	**ABVD**	**ABVD**
Median	NR	NR	[redacted]	[redacted]	NR
Mean	NA	NA	[redacted]	[redacted]	NA
% progression-free at					
6 months	[redacted]	[redacted]	[redacted]	[redacted]	97.7%
1 year	[redacted]	[redacted]	[redacted]	[redacted]	89.0%
2 years	[redacted]	[redacted]	[redacted]	[redacted]	81.9%
3 years	[redacted]	[redacted]	[redacted]	[redacted]	79.6%
4 years	[redacted]	[redacted]	[redacted]	[redacted]	77.6%
5 years	[redacted]	[redacted]	[redacted]	[redacted]	75.4%
6 years	[redacted]	[redacted]	[redacted]	[redacted]	74.0%
7 years	[redacted]	[redacted]	[redacted]	[redacted]	73.1%
8 years	[redacted]	[redacted]	[redacted]	[redacted]	71.8%
10 years	[redacted]	[redacted]	[redacted]	[redacted]	70.5%
20 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
30 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
40 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
50 years	[redacted]	[redacted]	[redacted]	[redacted]	NR
60 years	[redacted]	[redacted]	[redacted]	[redacted]	NR

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival; vs., versus.

4.2.6.1.1 EAG critique

The EAG considers that the methodologies employed to evaluate the proportional hazard assumptions are appropriate as is the company's conclusion that proportional hazards do not hold following the crossing of log cumulative hazard plots in Figure 13.

Given that a proportion of patients can be considered cured after treatment, with this proportion noted to be between 70-80% from the ECHELON-1 and RATHL trials and available literature, the EAG considers the company's use of a MCM to extrapolate PFS in the base case is appropriate. Similarly, the EAG considers that the log-logistic MCM is also the most appropriate between the models

assessed, resulting in the lowest AIC and BIC scores and providing a deterministic and probabilistic cure fractions range in line with the literature and clinical expert opinions.

While the company suggests that modelled PFS closely reflects the observed outcomes from the ECHELON-1 and RATHL for both A+AVD and ABVD treated patients (Table 28) the EAG strongly considers that no robust conclusions can be drawn from the naïve comparisons between the ECHELON-1 trial and RATHL, and by extension the model, due to the difference in patient characteristics and treatments, contributing to a difference in treatment effects.

Given the bimodal patient population as discussed in Section 4.2.3, in order to calculate an age weighted ICER the company fit separate survival models to the <60 and ≥60-year-old PFS KM data. Due to the large number of extrapolation and model fits, only the EAG preferred extrapolations have been provided in each relevant subsection with individual extrapolations and model fit statistics by progression status, treatment arm and age subgroup provided in the appendix (Appendix 8.2). As described in Section 4.2.3, the subgroup outcomes of those aged <60 years and aged ≥60 years were weighted by 86.1% and 13.9%, respectively, aligning with proportional age of patients in ECHELON-1, which the EAG notes was similar to the age distribution in RATHL.

Of the MCMs fit to the PFS KM data for the A+AVD <60-year-old subgroup, the loglogistic was the best fitting curve in terms of AIC and BIC score with all extrapolations being a good visual fit to the data and little long-term variation between the curves. With respect to the ABVD <60-year-old subgroup, the loglogistic was also the best fitting curve statistically and visually with little difference between extrapolations. A loglogistic MCM was therefore assumed in the EAG base case.

When fitting MCMs to the A+AVD ≥60 years old PFS KM data, all curves provided a similar visual fit with the exponential curve providing the best fit in terms of AIC and BIC score. For the ≥60 years old ABVD patients, all extrapolations provided similar visual fits with the generalised gamma model providing the lowest AIC and BIC score. These MCMs were therefore applied in the EAG base case.

Figure 19 presents the subgroup PFS KM data and the EAGs preferred MCM extrapolations, alongside Table 29 which provides the model fits.

Figure 19. PFS age subgroup survival modelling using MCMs

Table 29. PFS MCM curve fit statistics

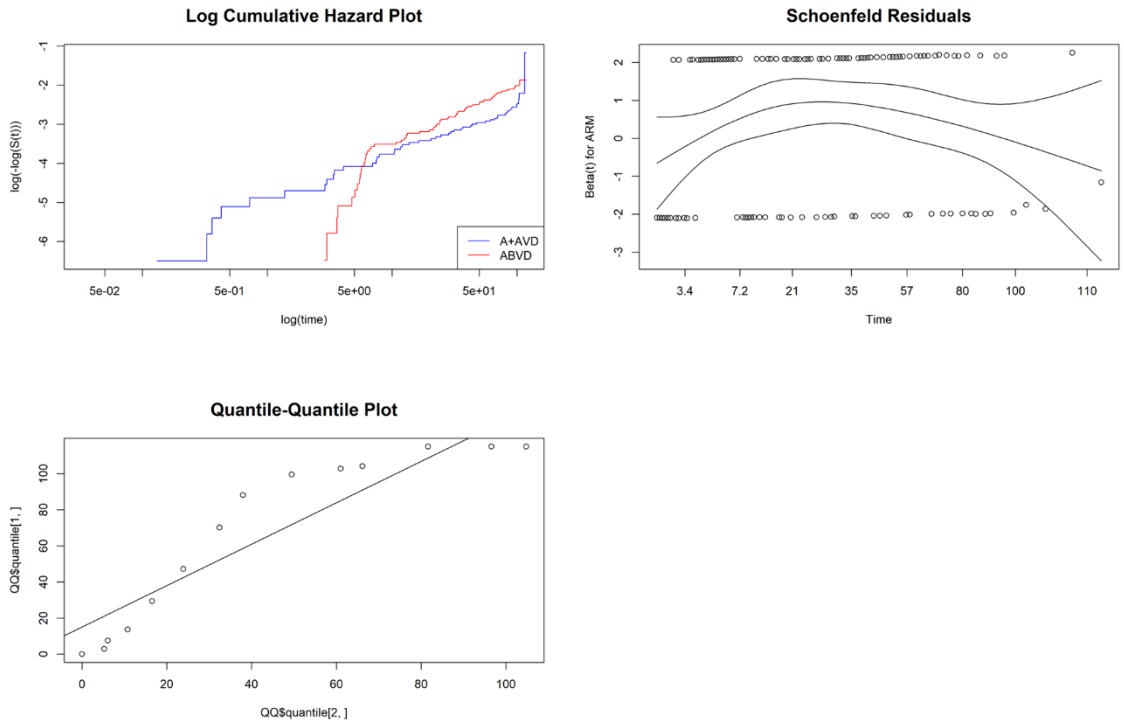
	A+AVD				ABVD			
	AIC	Rank (AIC)	BIC	Rank (BIC)	AIC	Rank (AIC)	BIC	Rank (BIC)
<60-years old								
MCM: Exponential	1094	7	1103	4	1439	6	1448	6
MCM: Weibull	1087	4	1101	3	1433	5	1446	5
MCM: Lognormal	1091	5	1104	4	1399	2	1412	2
MCM: Loglogistic	**1080**	**1**	**1093**	**1**	**1386**	**1**	**1399**	1
MCM: Gompertz	1094	6	1107	7	1441	7	1454	7
MCM: Generalised Gamma	1086	3	1103	4	1401	3	1418	3
MCM: Gamma	1085	2	1098	2	1422	4	1435	4
≥60 years old								
MCM: Exponential	**278**	**1**	**283**	**1**	412	4	417	4
MCM: Weibull	279	4	286	3	414	7	422	7
MCM: Lognormal	280	6	287	6	404	2	412	2
MCM: Loglogistic	278	1	285	2	406	3	414	3
MCM: Gompertz	278	1	286	3	413	5	421	5
MCM: Generalised Gamma	281	7	290	7	**392**	**1**	**403**	**1**
MCM: Gamma	279	5	287	5	413	5	421	5

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; ITT, intention-to-treat; MCM, mixture cure model; PFS, progression-free survival.

4.2.6.2 Overall survival

Proportional hazards and accelerate failure time assumptions were assessed between A+AVD and ABVD OS KM curves. Plots are presented in Figure 20.

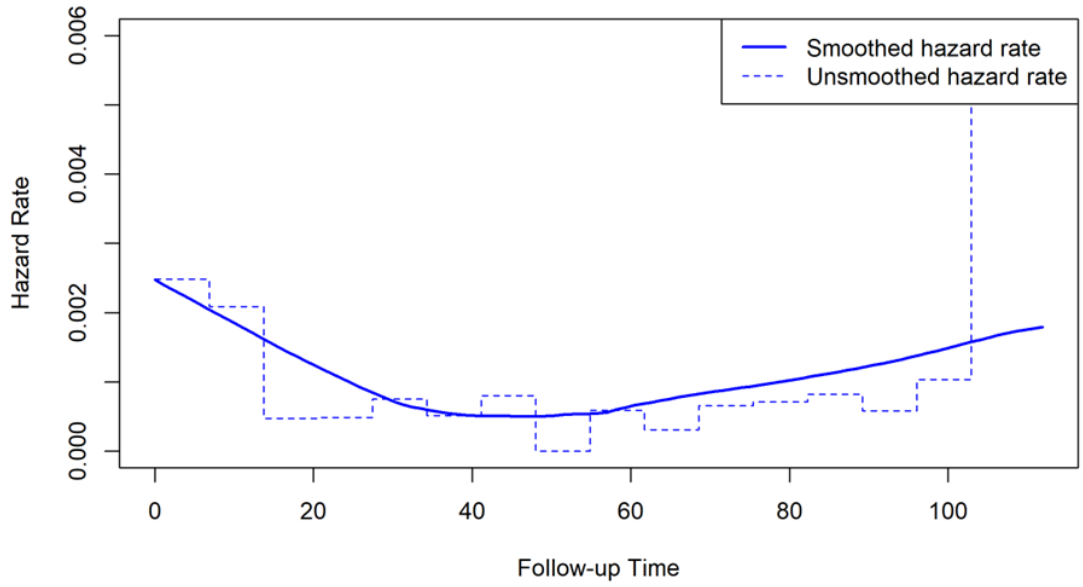
Figure 20. OS proportional hazards and accelerated failure time testing (reproduced from Figure 25 in the CS)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival.

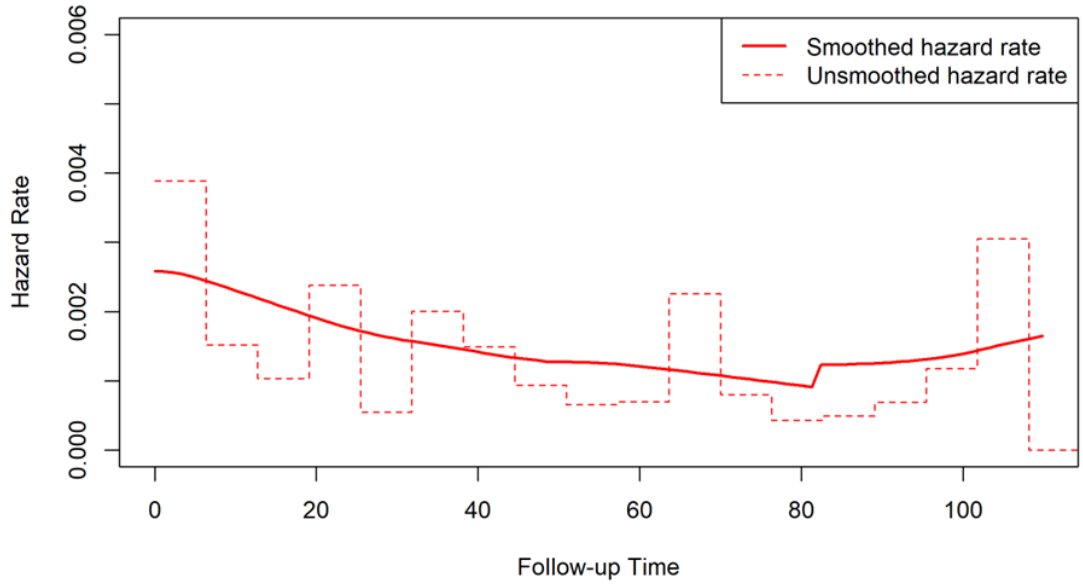
Similar to PFS, the Schoenfeld residuals and Grambsch-Therneau tests indicated that the proportional hazards assumption may not be violated (p=0.7216); however, the log-cumulative hazard plots showed clear crossing of the curves leading to the proportion hazard assumption being concluded as violated. The company noted that as the log-cumulative hazard plots were not straight lines, a more flexible parametric modelling method should be explored and that the clear turning point within the hazard plots further support this claim (Figure 21 and Figure 22). As such, the company chose to extrapolate the OS data using independent one-knot spline models in their preferred base case, with independent standard parametric models and independent MCMs explored in scenario analyses.

Figure 21. OS observed hazards | A+AVD (reproduced from Figure 26 in the CS)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; OS, overall survival.

Figure 22. OS observed hazards | ABVD (reproduced from Figure 27 in the CS)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; OS, overall survival.

Given the use of a MCM model to extrapolate PFS, and the arguments for its appropriateness being equally relevant for OS, the company justified the difference in approach by stating that although

the MCMs provided a good fit to the observed data in the deterministic analysis, the extrapolations explored in the probabilistic analysis estimated cure rates and outcomes that were clinically implausible and did not align with the observed data from ECHELON-1, the company's clinical experts opinions or the literature. The company added that the implausible cure fractions were the result of the wide confidence intervals stemming from the low number of patient deaths observed in ECHELON-1. As such, the company preferred the use of one-knot spline models as it allowed for the change in hazards for cured patients to be captured without directly making assumptions around the proportion of cure vs non-cured patients.

Figure 23 and Table 30 present the A+AVD one-knot splines models (excluding adjusted background mortality) and their AIC and BIC values. Similarly, Figure 24 Table 31 present the extrapolated ABVD one-knot splines models (excluding adjusted background mortality) and their respective AIC and BIC values.

Figure 23. OS independent one-knot splines | A+AVD (reproduced from Figure 28 in the CS)

Notes: excluding adjusted background mortality
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival.

Table 30. OS independent one-knot splines AIC and BIC values | A+AVD (reproduced from Table 27 in the CS)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	726	2	739	2
One-knot hazards	**726**	**1**	**739**	**1**
One-knot normal	726	3	739	3

Notes: bold represents the base case
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival

Figure 24. OS independent one-knot splines | ABVD (reproduced from Figure 29 in the CS)

Notes: excluding adjusted background mortality
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; OS, overall survival.

Table 31. OS independent one-knot splines AIC and BIC values | ABVD (reproduced from Table 28 in the CS)

	AIC	Rank (AIC)	BIC	Rank (BIC)
One-knot odds	1034	2	1048	2
One-knot hazards	**1034**	**3**	**1048**	**3**
One-knot normal	1033	1	1046	1

Notes: bold represents the base case
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival.

As presented, there is little difference in statistical fit between the models with differences of one or less AIC or BIC values between the A+AVD extrapolations and a difference of two or less between ABVD AIC and BIC values. The company's clinical experts stated that OS hazard profiles would not differ based on treatment and it was therefore considered appropriate to utilise the same splines model for both treatments. As the one-knot hazard extrapolations predicted the lowest proportion

of patients surviving in both treatment arms and was therefore the most conservative, it was selected to inform the company's base case.

Table 32 presents observed vs predicted OS outcomes when applying the one-knot spline model to the ECHELON-1 OS data, including comparative RATHL values while also including adjustments to background mortality (described further in Section 4.2.7). The company notes that the predicted outcomes closely align to the ABVD PET-adapted outcomes observed in RATHL, with a used example being the [redacted] difference between modelled and RATHL ABVD OS at 10 years ([redacted] and 85.7% respectively).

Table 32. Observed vs. predicted OS outcomes | one-knot splines (hazards) including adjusted background mortality for A+AVD and ABVD

	ECHELON-1		Predicted		RATHL
	A+AVD	ABVD (6-cycles)	A+AVD	ABVD	ABVD (PET-adapted)
Medians	NR	NR	[redacted]	[redacted]	NR
Means	NA	NA	[redacted]	[redacted]	NA
% surviving at					
1 year	[redacted]	[redacted]	[redacted]	[redacted]	99.2%
2 years	[redacted]	[redacted]	[redacted]	[redacted]	98.2%
3 years	[redacted]	[redacted]	[redacted]	[redacted]	96.5%
4 years	[redacted]	[redacted]	[redacted]	[redacted]	94.4%
5 years	[redacted]	[redacted]	[redacted]	[redacted]	92.2%
6 years	[redacted]	[redacted]	[redacted]	[redacted]	91.3%
7 years	[redacted]	[redacted]	[redacted]	[redacted]	90.3%
8 years	[redacted]	[redacted]	[redacted]	[redacted]	88.7%
9 years	[redacted]	[redacted]	[redacted]	[redacted]	87.0%
10 years	NR	NR	[redacted]	[redacted]	85.7%
20 years	NR	NR	[redacted]	[redacted]	NR
30 years	NR	NR	[redacted]	[redacted]	NR
40 years	NR	NR	[redacted]	[redacted]	NR
50 years	NR	NR	[redacted]	[redacted]	NR
60 years	NR	NR	[redacted]	[redacted]	NR

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; NR, not reported; OS, overall survival; vs., versus.

Lastly, the company's clinical and health economic advisors believed that the MCMs provided the best approach given patient cure is well established in clinical practice and reflected in the trial data. They acknowledged that the MCMs and one-knot splines provided similar long-term predictions

when compared deterministically and agreed that predicted cure rates below 70% (considered possible by the company under probabilistic conditions) did not align with the literature nor UK clinician expectations. As such, the company concluded that one-knot spline models should be preferred to extrapolate OS given the implausible cure fractions possible under probabilistic conditions.

4.2.6.2.1 EAG critique

The EAG considers the methodologies employed by the company to evaluate proportional hazards are appropriate as is the company's conclusion that proportional hazards do not hold between the trial arms.

With respect to the extrapolations, the EAG is concerned with company's use of a one-knot spline over MCMs, as were used to model PFS survival; noting that the characteristics of the data which made modelling PFS with a MCM an appropriate choice similarly apply to OS. The EAG's concern stems from the cure fraction not being estimated by the spline model but instead the spline being modelled around the company assumed cure fraction leading to inherent bias and potential overfitting of the model to the KM data. As such, the EAG considers that a MCM may be more appropriate, noting that the company's clinical experts also suggested the use of MCMs.

The EAG notes the company's concern that under probabilistic conditions the MCM extrapolations lead to clinically implausible estimated cure rates, with the company suggesting that the root cause of the improbable probabilistic cure fractions may be the large confidence intervals, stemming from a small number of observations. The EAG, however, considers that this should be true for both trial arms and so should not lead to bias in one treatment over another. The company disagreed with the EAG's opinion, stating that there was a difference in the deaths between the A+AVD (n=46; 6.9%) and ABVD (n=69; 10.3%) arms in ECHELON-1.

The EAG requested the company to provide further justification for preferring to extrapolate OS with a one-knot spline model in their preferred base case. The company responded that both independent MCMs and one-knot splines predicted highly congruent extrapolations when fitted to the OS data from ECHELON-1, therefore, one-knot splines were considered plausible candidates. MCMs were initially considered appropriate to extrapolate OS for the same reasons that extrapolating PFS with a MCM was appropriate; however as previously mentioned by the company, the cure fractions generated for A+AVD, which are presented in Table 44, lacked face validity.

Table 33. Predicted cure rates from independent MCMs (reproduced from Table 13 in the CQ response)

	A+AVD cure fraction (95% confidence intervals)	ABVD-based treatment cure fraction (95% confidence intervals)
MCM: Exponential	[redacted]	[redacted]
MCM: Weibull	[redacted]	[redacted]
MCM: Lognormal	[redacted]	[redacted]
MCM: Loglogistic	[redacted]	[redacted]
MCM: Gompertz	[redacted]	[redacted]
MCM: Generalised Gamma	[redacted]	[redacted]
MCM: Gamma	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MCM, mixture cure model; NE, not estimable; OS, overall survival

The company stated that the Gompertz and exponential MCMs were the only distributions that predicted A+AVD cure fractions that aligned with the literature and clinical expectations (70–80% of patients achieving cure). However, the company noted that the Gompertz MCM produced implausible probabilistic cure fractions within the confidence intervals and while the exponential MCM confidence intervals were narrower than the Gompertz, modelling the treatment arms independently led to the ABVD cure fraction exceeding that of A+AVD treated patients which the company considered was not clinically plausible.

The EAG considers that the company's arguments to dismiss the use of the exponential MCM model lack evidence. As presented in Table 33, the exponential MCM cure fraction means and upper and lower confidence intervals for both A+AVD and ABVD align with the literature and clinical expectations. While the company considers that it is not clinically plausible for the ABVD cure fraction to exceed that of A+ABD treated patients, the EAG notes that the deterministic A+AVD mean cure fraction is greater than that of ABVD and that the variance introduced under probabilistic conditions reflects the uncertainty of treatment effects measured in the ECHELON-1 trial and is therefore supported by clinical evidence.

Figure 25 and Figure 26 present the MCM fits to the A+AVD and ABVD KM data. The exponential curve resulted in the lowest BIC and third lowest AIC values when fit to the ABVD OS KM data (Table 35); however, the exponential was one of the worst fitting curves for A+AVD OS (Table 34). When considering the clinical opinion that 70–80% of patients will achieve cure, the exponential and Gompertz curves were seen to have the greatest face validity.

The EAG notes that the tail of the A+AVD OS KM curve appears inconsistent with the previously maintained decline in survival. In Figure 19, between months 115 to 116, [redacted] of the [redacted] at risk population died leading to a decrease in the proportion of non-censored surviving patients from [redacted] to [redacted]. The poor model fits may therefore be an artifact caused by the small number of at-risk patients at these time points.

Given that spline models do not inherently calculate cure fractions but instead require additional assumptions and data transformations to fit the extrapolation to an assumed cure fraction, leading to increased model complexity and potential over-fitting of curves; the EAG considers that modelling OS survival using a MCM is more appropriate. The EAG reflects that the arguments for using a MCM may be seen as further supported by the maturity of the data and that a cure fraction is well established in the literature, with ECHELON-1 similarly appearing to support a cure fraction.

In light of the exponential curve being a poor statistical fit to A+AVD OS, given it provides the most clinically plausible extrapolation in addition to probabilistically robust cure fractions, the EAG considers that extrapolating A+AVD and ABVD OS using an exponential MCM is appropriate.

Figure 25. OS independent MCMs | A+ABD (reproduced from Figure 37 in the CS Appendix)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Figure 26. OS independent MCMs | ABVD (reproduced from Figure 39 in the CS Appendix)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 34. OS independent MCMs AIC and BIC values | A+AVD (reproduced from Table 95 in the Appendix)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	736	6	745	5
MCM: Weibull	726	2	739	2
MCM: Lognormal	726	4	740	4
MCM: Loglogistic	726	3	739	3
MCM: Gompertz	737	7	751	7
MCM: Generalised gamma	727	5	745	6
MCM: Gamma	725	1	739	1

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Table 35. OS independent MCMs AIC and BIC values | ABVD (reproduced from Table 95 in the Appendix)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1035	3	1044	1
MCM: Weibull	1037	6	1051	6
MCM: Lognormal	1033	2	1046	2
MCM: Loglogistic	1036	4	1050	4
MCM: Gompertz	1037	5	1050	5
MCM: Generalised gamma	1032	1	1050	3
MCM: Gamma	1037	7	1051	7

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

As discussed in Section 4.2.3, in addition to MCM the EAG considers that the age bimodal population should be accounted for in the model. As such, separate survival curves were fit to the <60 and ≥60-year-old OS data. Due to the large number of extrapolation and model fits, only the EAG preferred extrapolations have been provided with all extrapolations and model fit statistics added to the appendix.

Of the MCMs fit to the <60-year-old A+AVD OS KM data, the lognormal resulted in the lowest AIC and BIC rankings, with all extrapolations being an appropriate visual fit. With respect to the cure fractions calculated in the model, only the Gompertz and exponential curves provided stable cure fractions under probabilistic conditions. Therefore, given that the exponential curve had the equal lowest BIC score and was within four points of the lowest AIC score, it was assumed in the EAG base case.

When extrapolating the <60-year-old ABVD OS data using a MCM, all extrapolations provided a good visual fit to the KM data with little variation between the curves. As the exponential curve provided the best statistical fit in terms of BIC and AIC and a robust probabilistic cure fraction, it was assumed in the EAG base case.

Fitting MCMs to the ≥60 years old A+AVD OS KM data provided highly uncertain extrapolations with no curve being a good visual fit to the KM data. The KM data described a downward trajectory with no plateau emerging from the extrapolations. Given that the EAG's clinical experts consider that a cure fraction in treated patients is well founded, with a stable cure fraction in the KM data being established in all other age subgroups in the ECHELON-1 trial, the EAG preferred to extrapolate ≥60 years old A+AVD OS using the lognormal distribution which provided the most optimistic long term patient survival. The EAG notes that, while the lognormal has face validity deterministically, cure fractions calculated under probabilistic conditions were implausibly low or implausibly high as presented in Figure 27.

Figure 27. Probabilistic ≥60-year-old A+AVD lognormal MCM cure fractions

The EAG notes that the covariance of the theta parameter, corresponding to the proportion of patients cured, was orders of magnitude larger than all other covariates across all MCM distributions for the ≥60-year-old A+AVD OS data, leading to the cure fractions to be implausible under probabilistic conditions. As a pragmatic approach, in the EAG's probabilistic sensitivity analyses the theta covariate was kept constant at its deterministic value, while all other covariates varied probabilistically. This allowed for ≥60 years old A+AVD OS to be varied probabilistically around a stable and appropriate cure fraction.

Finally, the ≥60 years old ABVD OS MCM curves showed a slight spread in extrapolations with a satisfactory visual fit to the KM data. The exponential curve provided the best statistical fit with all curves achieving similar AIC and BIC scores. The exponential curve was therefore used in the EAG base case. Figure 28 presents the subgroup OS KM data and the EAGs preferred MCM survival extrapolations, alongside Table 36 which provides the model fits.

Figure 28. OS age subgroup survival modelling using MCMs

Table 36. OS MCM curve fit statistics

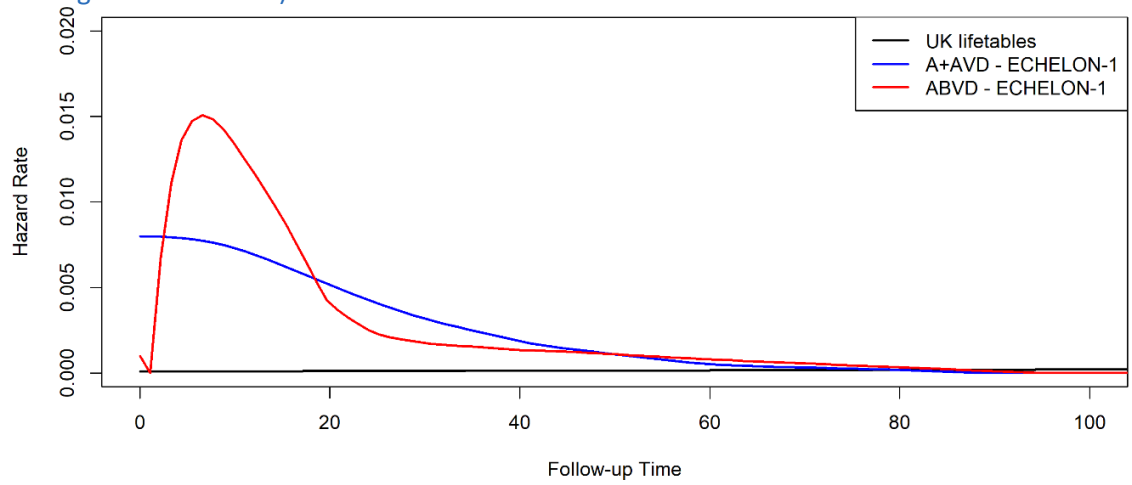
	A+AVD				ABVD			
	AIC	Rank (AIC)	BIC	Rank (BIC)	AIC	Rank (AIC)	BIC	Rank (BIC)
<60 years								
MCM: Exponential	**363**	**6**	**372**	**1**	**621**	**1**	**630**	**1**
MCM: Weibull	359	1	372	1	623	6	636	3
MCM: Lognormal	359	1	372	1	621	1	634	2
MCM: Loglogistic	359	1	372	5	623	4	636	3
MCM: Gompertz	364	7	377	6	623	5	636	3
MCM: Generalised Gamma	361	5	378	7	621	1	638	7
MCM: Gamma	359	1	372	1	623	7	636	3
≥60 years								
MCM: Exponential	323	5	328	3	**382**	**1**	**387**	**1**
MCM: Weibull	320	1	327	1	384	5	392	6
MCM: Lognormal	**323**	**5**	**330**	**5**	382	1	390	2
MCM: Loglogistic	321	3	328	3	383	4	391	3
MCM: Gompertz	325	7	332	7	384	5	392	4
MCM: Generalised Gamma	321	3	331	6	383	3	393	6
MCM: Gamma	320	1	327	1	384	5	392	5

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; ITT, intention-to-treat; MCM, mixture cure model; PFS, progression-free survival.

4.2.7 *Mortality*

In the ECHELON-1 study, the majority of mortality events occurred within the first 24 months from treatment discontinuation ([redacted] of PFS events) after which time the number of events was low and stable, with the company suggesting that survival may be predicted using UK life tables. The company's clinical experts added that as PFS was used to define cure, the observed hazards from the general population (using life tables) can be compared to A+AVD and ABVD PFS (from ECHELON-1) to support this assumption. Figure 29 presents the hazards of progression or death from ECHELON-1. The trial hazards decrease over time, aligning with UK lifetable mortality, with the curves eventually converging. Given the alignment over time, the company applied ECHELON-1 mortality as a cap to general population mortality to ensure modelled patients do not have a lower risk of death compared to the general population. General population background mortality estimates were informed using the UK lifetables from the Office of National Statistics 2020-2022.[33]

Figure 29. Comparison of observed hazards for PFS in ECHELON-1 with UK lifetables (reproduced from Figure 17 in the CS)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PFS, progression-free survival.

Background mortality was further adapted to account for the difference in long term treatment effects. The company stated that current treatments for untreated late-stage HL are associated with burdensome adverse effects; specifically calling to attention pulmonary toxicity associated with bleomycin-containing regimes. In addition to the treatment related adverse events, second malignancies, and exposure to additional toxicities with subsequent treatments were also considered to contribute to an elevated mortality risk compared to general population estimates. To reflect this increase, the company applied standardised mortality ratios (SMRs) to mortality rates.

The company stated that the use of SMRs was appropriate given their use in previous relevant appraisals as presented in Table 37. In the absences of A+AVD and ABVD specific values the company relied on feedback from their clinical experts to inform the SMRs. The company's clinical experts stated that the risk of death after the cure time point was between 5% and 10% higher than the general population, while also considering SMRs used in previous relevant NICE appraisals. The experts added that excess mortality in frontline HL was expected to be lower than in the frontline lymphomas considered in TA641 and TA874 as long-time survivorship is comparatively more of a widely recognised goal in HL.[34, 35] Similarly, SMRs should be lower in frontline treatments compared relapsed lymphomas as treatment toxicities will accumulate across additional lines of therapy. To reflect an increase in the risk of mortality compared to the general population, the company assumed an SMR of 1.1 for ABVD and 1.05 for A+AVD given ABVD is a bleomycin containing treated and therefore is associated with elevated risk of pulmonary toxicity in addition to being associated with increased second malignancies, disease progression and subsequent treatment toxicity. As the SMRs assumed were based on opinion, due to the lack robust available evidence from the literature, the company conducted a scenario analysis using an SMR of 1.1 for A+AVD treated patients and 1.15 for ABVD treated patients.

Table 37. Comparison of background mortality approach across NICE lymphoma appraisals (reproduced from Table 19 in the CS)

NICE appraisal	Disease setting	Base case	Scenario
TA874[35]	Untreated DLBCL	Unadjusted background mortality from UK lifetables i.e. an SMR of 1.00	Equivalent to an SMR of 1.10
TA641[34]	Untreated sALCL	Adjusted background mortality from UK lifetables and equivalent to an SMR of 1.05	Equivalent to SMRs of 1.075 and 1.10
TA872[36]	Later line DLBCL	Unadjusted background mortality from UK lifetables i.e. an SMR of 1.00	SMR of 1.09
TA677[37]	Later line MCL	Adjusted background mortality from UK lifetables and equivalent to an SMR of 1.09	NA
TA567[38]	Later line DLBCL	Unadjusted background mortality from UK lifetables i.e. an SMR of 1.00 from 2 years.	Applied up to 5 years.

Abbreviations: DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; NA, not applicable; NICE, National Institute for Health and Care Excellence; sALCL, systemic anaplastic large cell lymphoma; SMR, standardised mortality rate.

4.2.7.1 EAG critique

The EAG considers that the use of an SMR to adjust background mortality is appropriate given the long-term mortality implications of second malignancies, treatment toxicities and long-term adverse events. However, while SMRs have been used to adjust baseline mortality in comparable STAs, the same SMR was applied to both the comparator and the intervention independent of the disease setting in all NICE TAs highlighted by the company compared to the different SMRs applied in the company base case.

As previously stated, the company justified the application of a greater SMR to ABVD treated patients by highlighting that bleomycin is associated with pulmonary toxicity, ABVD patients experience greater second malignancies, and are more likely to progress and experience subsequent treatment toxicities. Conversely the EAG notes that the incidence of second malignancies between treatments were broadly aligned in the ECHELON-1 trial with (Table 38) and while pulmonary toxicity is considered an outcome of interest for bleomycin-based treatments, A+AVD was associated with a greater adverse event disutility, as further discussed in Section 4.2.8.

Table 38. QALY decrement due to second malignancies

Regimen	Treatment	Proportion with second malignancies
A+AVD	A+AVD	4.98%
ABVD	Six-cycle ABVD	5.92%
	PET-adapted ABVD	4.58%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; PET, positron emission tomography.

As such, due to the lack of robust evidence to support any difference in mortality rates between treatments, the EAG considers that use of differing SMRs is inappropriate and the same SMR should be applied to each treatment arm. This assumption is included in the EAG base case.

With respect to the value of the SMR, the EAG considered that more robust evidence may be available to inform the SMRs, rather than opinion. The EAG requested the company to explore a range of alternative SMRs values sourced from a review of the literature. The company complied with the EAG's request and conducted a rapid targeted literature review. The literature review was conducted using PubMed on 13 May 2024 using the search string *"Hodgkin" AND "lymphoma" AND ("excess mortality" OR "standardized mortality rate" OR "standardised mortality rate" OR "SMR")*,

with year of publication restricted to the past 10 years to limit the publications to more current treatment practices and outcomes. Of the 21 publications identified, four were deemed relevant to the evaluation and explored further and are summarised Table 39.

Table 39. SMRs from the company's rapid targeted SLR.

Publication	Population and disease setting	SMR	Company comments
Glimelius *et al*. 2015[39]	1,947 Swedish HL patients diagnosed between 1992-2009, aged 18-59 years old.	1.01 for relapse free patients at five years and 1.05 at 15 years.	Relative survival was not provided by HL stage or by age.
Núñez-García *et al*. 2023[40]	338 HL Spanish patients with up to 45 years of follow-up.	The overall SMR was 3.57. The SMR of those diagnosed after 2000 was 2.73 when excluding HL as the cause of death.	Survival outcomes were considered implausible when compared to the UK HL population. PFS and OS curves differed substantially to those observed in the ECHELON-1 and RATHL study. The SMRs are inconsistent with the clinical opinion that mortality in HL patients, compared to general population, has improved over time.
Dores *et al*. 2016[41]	20,007 US patients aged 20 to 74 years old with HL diagnosed between 2001 and 2009.	2.4 for advanced HL when excluding cancer related mortalities.	No distinction was made between relapsed or cured/relapse free patients. Reduced side effects have occurred in recent years due to the changing of treatment practices (RATHL) and minimising exposure to more toxic chemotherapy treatments.
Perez-Callejo *et al*. 2018[42]	595 Spanish patients diagnosed with HL between 1966 and 2014.	Excluding the primary tumour as the cause of death, the SMR obtained was 2,266.	A higher SMR was calculated for those diagnosed before 2000 compared to those after 2000 which lacks face validity. The majority of the patient cohort were Stage I or II (64%).

Abbreviations: HL, Hodgkin's lymphoma; SMR, standardised mortality multiplier.

The company considered that only the study by Glimelius *et al.* 2015 was relevant to the decision problem as it was the only publication to provide an SMR for PF patients, which the company considered the most relevant to inform the SMR.[39] The EAG notes that the SMR identified by Glimelius *et al.* 2015 supports the SMR previously assumed by the company and measured a 1.05 rate of mortality for HL patients after 15 years compared to the Swedish general population. The EAG's clinical experts similarly stated that the mortality of cured patients could be considered broadly comparable to general population estimates, with an SMR of 1.05 being reasonable. An SMR of 1.05 has therefore been assumed in the EAG base case.

4.2.8 Adverse events

In the economic model, Grade ≥3 treatment related adverse events occurring in ≥5% of patients from ECHELON-1 were included for A+AVD based treatments. For ABVD-based treatment, although the company assumed equivalent efficacy, there are differences in tolerability between the six-cycles and PET-adapted approaches. Therefore, the base case analysis includes Grade ≥3 treatment related AEs occurring in ≥5% of patients from ECHELON-1 for six cycles of ABVD, and Grade ≥3 AEs occurring in ≥5% of patients from the RATHL trial to reflect PET-adapted ABVD. The AEs from RATHL were weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3–6), and 16.3% escBEACOPP (cycles 3–6), and the final AE input data for the model were weighted to reflect use of ABVD-based treatment in UK clinical practice (10% six-cycle ABVD and 90% PET-adapted ABVD). Adverse events incidence in the ECHELON-1 and RATHL trials are presented in Table 40 with the AEs included in the economic model given in Table 41.

Table 40. Grade ≥3 treatment related AEs in ≥5% of patients (reproduced from Table 30 in the CS and Table 20 from the company response to CQ's)

	ECHELON-1 (March 2023 data cut-ff)		PET-adapted ABVD (RATHL)			
	A+AVD	ABVD (6 cycles)	ABVD (cycles 1–2)	AVD (cycles 3–6)	escBEACOPP (cycles 3–6)	Weighted PET-adapted ABVD*
N	662	659	1203	457	78	1598
Anaemia, n (%)	[redacted]	[redacted]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Febrile neutropenia, n (%)	[redacted]	[redacted]	24 (2%)	10 (2.19%)	52 (66.67%)	41 (2.56%)
Neutropenia, n (%)	[redacted]	[redacted]	694 (57.69%)	269 (58.86%)	20 (25.64%)	922 (57.71%)

Neutrophil count decreased, n (%)	[redacted]	[redacted]	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*weighted based on 100% ABVD (cycles 1–2), 83.7% AVD (cycles 3–6), and 16.3% escBEACOPP (cycles 3–6).
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; N, number; TEAE, treatment-emergent adverse events.

Table 41. AEs and incidence included in the economic model (reproduced from Table 31 in the CS)

Event	A+AVD	ABVD-based treatment*
Anaemia, n (%)	46 (6.95%)	2 (0.12%)
Febrile neutropenia, n (%)	120 (18.13%)	41 (2.75%)
Neutropenia, n (%)	344 (51.96%)	855 (56.82%)
Neutrophil count decreased, n (%)	81 (12.24%)	6 (0.43%)

*Weighted based on 10% ABVD (six cycles) and 90% ABVD (PET-adapted).
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine.

4.2.8.1 EAG critique

The EAG considers that the company's inclusion criteria for adverse events in the economic model (i.e. grade 3+, and occurring in at least 5% of patients in one arm of ECHELON-1 or RATHL) is broadly appropriate; however, the EAG notes that peripheral neuropathy is an adverse event of particular interest, and that a large proportion of patients receiving A+AVD experienced grade ≥3 peripheral neuropathy (10.3%) compared to patients receiving ABVD (1.7%) in ECHELON-1. The EAG's clinical expert advisors also suggested that peripheral neuropathy can have substantial and long-lasting effects on patient quality of life.

At clarification, the company was asked to justify the exclusion of peripheral neuropathy in the model. The company replied that peripheral neuropathy was a standardised MedDRA query, grouping multiple peripheral neuropathy preferred terms, and that no single preferred term relating to neuropathy was reported in ≥5% of patients at the March 2023 data cut-off.

In response to the clarification questions, the company provided a scenario including peripheral neuropathy in the model. This scenario led to an increase in the [redacted]. In the company's scenario the EAG noted that an average time to peripheral neuropathy resolution between the treatment arms was assumed but notes that the time to resolution in the A+AVD arm was [redacted] than in the ABVD arm, with mean time to resolution being [redacted] weeks and [redacted] weeks for A+AVD and ABVD patients respectively. Given the difference the EAG conducted a

scenario using the treatment specific mean times to resolution which led to a small increase in the ICER.

Furthermore, the EAG noted that 16 (2.4%) and 4 (0.6%) of A+AVD and ABVD patients had unresolved grade ≥3 peripheral neuropathy at last follow up of ECHELON-1. Median follow up after end of treatment for A+AVD patients was [redacted] and [redacted] for ABVD patients. Given the length of the study and the opinion of the EAG's clinical experts, it may be likely that patients with unresolved symptoms will suffer lifelong peripheral neuropathy which the EAG considers should be captured in the model. Therefore, the EAG conducted a scenario assuming that 2.4% of A+AVD and 0.6% of ABVD patients experienced lifelong peripheral neuropathy making sure to reflect the difference in the 10.3% and 1.7% of A+AVD and ABVD patients already accounted for in the previous scenarios. The scenario also led to an increase in the ICER as more A+AVD patients experienced unresolved peripheral neuropathy compared to ABVD patients.

For completeness, the EAG considered conducting a scenario to account for incidence of pulmonary toxicity given its relevance to bleomycin containing regimens. The EAG notes, however, that pulmonary toxicity, similar to peripheral neuropathy, is treated with dose modification or discontinuation with symptoms diminishing with reduced treatment and no long-term pulmonary toxicity reported in the clinical study report. Additionally, only 1% of ABVD patients were recorded with treatment emergent grade ≥3 or above pulmonary toxicity. If instead considering the wider interstitial lung disease related group of adverse events (lung infiltration, pneumonitis, interstitial lung disease, organising pneumonia, pulmonary fibrosis and pulmonary toxicity), the proportion of ABVD patients increase to 3%. As such, the EAG did not include a scenario. The EAG notes that for measures of dyspnoea there was little difference between treatments, with A+AVD patients reporting slightly worse shortness of breath (Figure 30).

Figure 30. Mean FACIT-Dyspnoea 10 subscale scores over time (reproduced from Figure 25 in the company submission appendix)

Note: the higher the score, the worse the dyspnoea

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; EOT, end of treatment; ITT, intent-to-treat.

4.2.9 Health-related quality of life

The economic model developed by the company accounted for HRQoL by deriving utility values from EQ-5D-3L data collected during the ECHELON-1 trial. This approach was chosen since the data were directly relevant to the patient group of interest and no appropriate alternative values were identified from existing literature (further details of the SLR for HRQoL model inputs conducted by the company are given in Section 4.1).

Utility values were derived using a mixed effects repeated measures linear regression model fitted to the available EQ-5D-3L data. This regression model was used to inform health state utility values (HSUVs) for the progression-free and progressed disease health states, distinguishing between patients on and off treatment in the progression-free health state. These utilities were applied to all patients, with the exception of patients who reached the cure timepoint in the progression-free health state, to whom general population utility values derived from Hernández-Alava et al. were applied.[43]

In the company's preferred base case, adverse event disutilities were derived using the linear regression model, although a scenario was also provided in which adverse event disutility was calculated using the existing literature. Further details are given in the following sections.

4.2.9.1 EQ-5D-3L data from ECHELON-1

HRQoL inputs were informed by EQ-5D-3L data collected from patients in the ECHELON-1 trial, based on the 1st June 2021. For each patient, EQ-5D-3L data were collected at the following points:

- At screening;
- Day 1 of each treatment cycle;
- 30 days after the last dose of frontline therapy;
- Every three months during post-treatment follow-up, until three years after the last dose of frontline therapy or development of progressive disease (whichever occurs first).

The UK-specific EQ-5D-3L tariff developed by Dolan *et al.*[44] was used to map individual patients' responses to EQ-5D-3L index scores. Patient EQ-5D-3L data were included in the linear regression model analysis if the following criteria were met:

- A baseline utility value was recorded;
- At least one post-baseline assessment was recorded;
- At least one pre-progression assessment was recorded.

Three patients were also excluded due to inappropriate disease stage or missing information on disease stage.

Overall, 16,557 post-baseline records were available from the 1,268 patients. 16,040 of these records were relevant to the progression-free health state, while 517 records (from over 158 patients) were relevant to the progressed disease health state. The mean utility calculated at baseline was 0.764.

4.2.9.1.1 EAG critique

The EAG agrees with the company's approach to evaluating HRQoL by using the EQ-5D-3L data from ECHELON-1 in the absence of alternative appropriate EQ-5D-3L data from existing literature (more details are given in Section 4.1). The EAG notes that there was limited EQ-5D-3L data collected from relapsed and refractory patients in ECHELON-1 trial (517 records, compared to the 16,040 records collected for the progression-free health state) due to the small number of progressed patients. It is also likely that most of these records correspond to patients soon after disease progression, potentially even before receiving subsequent treatment, contributing to a much higher level of uncertainty in the utility value for the progressed disease health state.

4.2.9.2 *Linear regression models for health state utility values*

A mixed effects repeated measures linear regression model was fit to the EQ-5D-3L data identified from ECHELON-1, with the covariates listed in Table 42. Appropriate covariates were selected by identifying factors which were potentially predictive of HRQoL outcomes, based on review of previous NICE appraisals in classical Hodgkin lymphoma (TA874, TA641, TA478, TA524, and TA577) and feedback from clinicians.[34, 45-47] A correlation analysis was performed, and clinical input sought, to subsequently refine the choice of covariates to avoid collinearity.

Of the identified factors, treatment arm was excluded as a covariate due to anticipated correlation with presence of adverse events (AEs), while Eastern Cooperative Oncology Group (ECOG) performance status, disease stage and presence of B symptoms were excluded based on correlation with International Prognostic Score (IPS).

Table 42. Covariates included in linear regression model for utility values

Covariate	Continuous/categorical	Values
On treatment vs off treatment	Categorical	0 (off treatment) 1 (on treatment)
Age (years)	Continuous	18-83 years
Sex	Categorical	0 (female) 1 (male)
Baseline utility score	Continuous	Not specified
Receipt of primary prophylaxis with G-CSF	Categorical	0 (no) 1 (yes)
IPS risk factor	Categorical	0 1 2 3 4 5 6 7
Presence of grade 3+ AEs	Categorical	0 (no) 1 (yes)
Progression status	Categorical	0 (progression-free) 1 (progressive)

Abbreviations: AE, adverse event; G-CSF, granulocyte colony stimulating factor; IPS, International Prognostic Score.

The company initially fitted a 'saturated' model including all covariates in Table 42, with fixed effect terms for all covariates, and an additional random effect term for patient ID to account for repeated

measurements from the same patient. A summary of the fitted coefficients for the saturated model are given in Table 43.

Table 43. Coefficients in saturated regression model

Coefficient*	Estimate	SE	t-value	p-value
Intercept	0.7399	0.0251	29.4938	<0.0001
Treatment status	−0.0805	0.0028	−29.1613	<0.0001
Age (years)	−0.0028	0.0003	−10.3958	<0.0001
Sex	0.0087	0.0089	0.9817	0.3264
Baseline utility score	0.2846	0.0172	16.5523	<0.0001
Receipt of G-CSF	−0.0107	0.0138	−0.7781	0.4367
IPS risk factor = 1	0.0051	0.0222	0.2298	0.8183
IPS risk factor = 2	0.0065	0.0219	0.2987	0.7652
IPS risk factor = 3	0.0089	0.0222	0.4025	0.6874
IPS risk factor = 4	0.0164	0.0235	0.6980	0.4853
IPS risk factor = 5	0.0407	0.0264	1.5417	0.1234
IPS risk factor = 6	0.0826	0.0405	2.0397	0.0416
IPS risk factor = 7	0.0165	0.0687	0.2398	0.8105
Grade 3+ AEs	−0.0268	0.0044	−6.1037	<0.0001
Progression status	−0.0698	0.0089	−7.8853	<0.0001

*Variables which are statistically significant at the 5% level are denoted in bold text.

Abbreviations: AE, adverse event; G-CSF, granulocyte colony stimulating factor; IPS, International Prognostic Score; SE, standard error.

To calculate the health state utility values, a weighted average was taken over sex, receipt of primary prophylaxis with granulocyte colony stimulating factor (G-CSF), and IPS risk factor values, which were assumed to remain constant in line with the values at baseline in ECHELON-1. Baseline utility score was also aligned with ECHELON-1.[22] The values used are presented in Table 44.

Table 44. Baseline characteristics informing HRQoL

Variable	Baseline value (95% CI)
Gender (% male)	58.17% (55.51-60.81%)
Baseline utility score	0.76 (0.60-0.90)
Receipt of G-CSF	9.45% (7.68–11.37%)
IPS risk factor 0	4.2% (3.65–4.71%)
IPS risk factor 1	17.02% (17.11–16.94%)
IPS risk factor 2	27.59% (28.49–26.69%)
IPS risk factor 3	25.79% (26.53–25.03%)
IPS risk factor 4	15.52% (15.5–15.54%)

IPS risk factor 5	7.87% (7.4–8.29%)
IPS risk factor 6	1.65% (1.19–2.11%)
IPS risk factor 7	0.37% (0.14–0.67%)

Abbreviations: CI, confidence interval; G-CSF, granulocyte colony stimulating factor; HRQoL, health-related quality of life; IPS, International Prognostic Score.

Utility values for each health state, not taking into account adverse events, were then calculated for each cycle using the mean patient age for that cycle and the relevant progression and treatment status. The predicted health state utility values for the mean patient age at baseline (i.e. 39.53 years) are given in Table 45.

Table 45. Predicted health state utility values at baseline, saturated model

Health state	Mean utility at baseline
Progression-free, on treatment	0.781
Progression-free, off treatment	0.861
Progressed disease	0.791

Abbreviations: AE, adverse event; SE, standard error.

To examine whether the non-statistically significant terms had a substantial effect on the ICER, the company also fitted a 'reduced' model, which reduced the number of covariates included through stepwise selection, for use as a scenario. Starting from the saturated model, the least statistically significant variable was removed, and the model was refitted with the remaining variables. This process was repeated iteratively until all included variables were statistically significant at the 5% level. The variables remaining in the final model were treatment status, age, baseline utility, grade 3+ AEs, and progression status. Details of the fitted coefficients are given in Table 46, and the resulting health state utility values for the mean patient age at baseline are given in Table 47.

Table 46. Coefficients in reduced regression model

Coefficient*	Estimate	SE	t-value	p-value
Intercept	0.7527	0.0170	44.2875	<0.0001
Treatment status	−0.0803	0.0028	−29.1176	<0.0001
Age (years)	−0.0026	0.0003	−10.1001	<0.0001
Baseline utility value	0.2775	0.0167	16.5743	<0.0001
Grade 3+ AEs	−0.0269	0.0044	−6.1158	<0.0001
Progression status	−0.0691	0.0088	−7.8043	<0.0001

Abbreviations: AE, adverse event; SE, standard error.

Table 47. Predicted health state utility values at baseline, saturated model

Health state	Mean utility at baseline
Progression-free, on treatment	0.780
Progression-free, off treatment	0.861
Progressed disease	0.792

4.2.9.2.1 EAG critique

The EAG had a number of concerns with the methodology used to determine the health state utility values, outlined in the sections below.

4.2.9.2.1.1 Face validity of utility values

The EAG notes that the utility values used in the company base case potentially lack face validity, since the calculated utility value for a patient in the progression-free, on treatment health state (0.78 at baseline) is consistently lower than the utility value for a patient in the progressed disease health state (0.792 at base line) with the same age and baseline utility. The converse would be expected to be true, since the progressed disease health state includes patients receiving later lines of treatment, as well as patients with considerably more severe disease. The unexpectedly high utility value for the progressed disease state compared to being progression free and on treatment might be explained by the lack of an on or off treatment covariate when calculating the progressed disease utility in the linear regression model.

During clarification, the EAG requested that the company fitted an alternative linear regression model accounting for patients' treatment status in the progressed disease health state as well as the progression-free health state. In the company's response, they clarified that the treatment status covariate in the regression model was indeed specific to 'on' versus 'off' frontline treatment and not subsequent treatment. The company added that due to the expected challenges in running the regression analysis with the post-progression data availability (missing values and inconsistency across reporting) the requested scenario analysis was not conducted.

The EAG notes that since A+AVD shows a lower rate of disease progression than ABVD, a high utility value for the progressed disease state would reduce the calculated incremental QALYs for A+AVD compared to ABVD. Similarly, the duration of time over which a progressed disease, on treatment disutility would be applied is relatively short leading to the impact to the total ABVD and incremental

QALYs to be minimal. Therefore, the use of this health state utility value could be considered conservative.

4.2.9.2.1.2 Linear regression approach

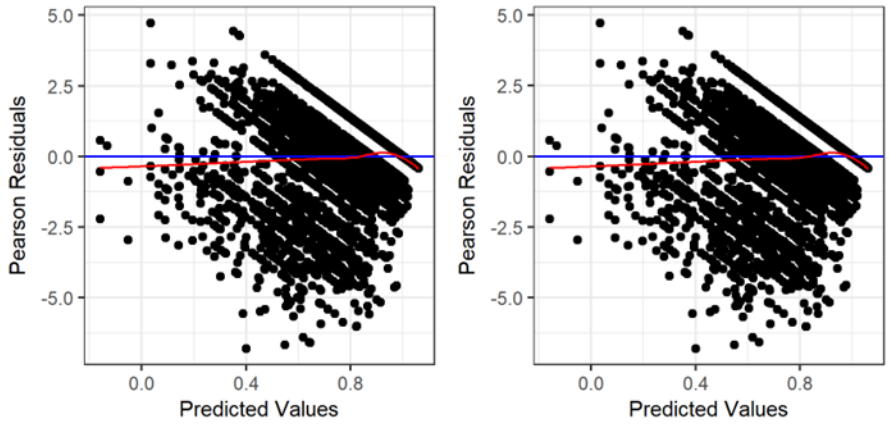
The EAG noted that the company submission did not include any documentation of the goodness of fit of the fitted linear regression models described in Section 4.2.9.2. In particular, no goodness of fit statistics (for example, R^2, Akaike information criterion [AIC] or Bayesian information criterion [BIC]) or diagnostic plots (for example, residuals plots) were provided. The EAG requested that evidence of goodness of fit and residual plots be provided during clarification, which the company shared and are presented in Table 48 and Figure 31. The saturated model provided the lowest AIC and BIC score suggesting a better statistical fit, with the residual plots showing that the points in both the saturated and reduced model are randomly distributed around the zero-line, suggesting a liner model is appropriate.

Table 48. Comparative utility regression goodness-of-fit statistics (reproduced from Table 19 in the CQ response)

Model	AIC	BIC	logLik	deviance	Chi-sq	Df	Pr(>Chi-sq)
Reduced	-13576	-13514	6796.1	-13592	-	-	-
Saturated	-13570	-13439	6802.3	-13604	12.317	9	0.196

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; Chi-sq, Chi-squared; Df, degrees of freedom

Figure 31. Residual plots (L: Saturated model; R: Reduced model)



Finally, although the stepwise selection methodology used to develop the reduced linear regression model was broadly acceptable in the EAG's opinion, it is preferable to use the saturated model since it accounted for all factors which are expected to affect HRQoL. The EAG also notes that there is very

little difference in the calculated utility values from the saturated and reduced models, leading to a minimal difference in ICER. Therefore, the EAG agrees with the company's preference for using the saturated model to inform HRQoL in the economic model.

4.2.9.3 Disutilities due to adverse events

To account for AEs in the economic model, the calculated utility value in the first cycle was adjusted by the coefficient for grade ≥3 AEs, multiplied by the proportion of patients expected to experience a grade ≥3 AE, and the expected duration. This essentially corresponds to a one-off disutility applied to cover all AEs using the linear regression model.

The duration of individual adverse events was derived by taking the mean of the relevant AEs used in TA641[34] (for brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma), and TA874[35] (for polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma). The durations used in TA641 were derived from the ECHELON-2 trial for brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma, and the durations used in TA874[35] were sourced from TA306[48], which were in turn derived from the PIX301 trial for pixantrone in patients with relapsed or refractory aggressive non-Hodgkin lymphoma. Further details are provided in Table 49. An overall mean duration for all adverse events was derived by taking the average of the individual durations, weighted by the incidence of each category of adverse event. Overall, calculating adverse event utilities using the linear regression model gave a QALY decrement of -0.0007 for patients receiving A+AVD, and -0.0005 for patients receiving ABVD.

Table 49. Incidence and duration of grade 3+ adverse events

Adverse event	Incidence for patients receiving A+AVD	Incidence for patients receiving ABVD	Duration (days)
Anaemia	6.95%	0.12%	11.60 (mean of 7.2 days as reported in TA641, and 16 days as reported in TA874)[34, 35]
Febrile neutropenia	18.13%	2.75%	6.40 (mean of 6.8 days as reported in TA641, and 6.0 days as reported in TA874) [34, 35]
Neutropenia	51.96%	56.80%	13.05 (mean of 11.1 days as reported in TA641, and 15.0 days

			as reported in TA874) [34, 35]
Neutrophil count decreased	12.24%	0.43%	7.50 (mean of 0 days as reported in TA641, and 15 days as reported in TA874) [34, 35]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine

The model also included a scenario in which the one-off QALY decrement accounting for adverse events was calculated using disutilities sourced from the literature, instead of the fitted coefficient from the linear regression model. Individual disutilities were sourced from TA641 and TA874, and the mean value across the two appraisals was used in the model. [34, 35] Details of the values used in the model are given in Table 50.

Table 50. Adverse event disutilities sourced from existing literature

Adverse event	Utility decrement
Anaemia	-0.17 (mean of -0.09 as reported in TA641, and -0.25 as reported in TA874) [34, 35]
Febrile neutropenia	-0.12 (mean of -0.09 as reported in TA641, and -0.15 as reported in TA874) [34, 35]
Neutropenia	-0.09 (based on TA641)[34]
Neutrophil count decreased	-0.05 (mean of 0 as reported in TA641, and -0.09 as reported in TA874) [34, 35]

For each adverse event, the QALY decrement applied in the model was calculated by multiplying the utility decrement sourced from the literature by the duration of the AE and the expected incidence (as detailed in Table 49). The individual decrements for each adverse event were then summed over all adverse events to give a one-off QALY decrement for application in the first model cycle. The calculated QALY decrements in this scenario were -0.0025 for patients receiving A+AVD, and -0.0016 for patients receiving ABVD.

4.2.9.3.1 EAG critique

The EAG notes that the one-off QALY decrement for adverse events is considerably larger when calculated using disutilities from existing literature, compared to the company's preferred base case, in which the coefficient from the fitted linear regression model is used as a disutility. The EAG considers that the approach in which disutilities are sourced from existing literature is more appropriate, since this allows decrements of adverse events to be applied individually to each

corresponding disutility, rather than applying a weighted average duration of disutilities. This approach also allows an additional QALY decrement for peripheral neuropathy to be incorporated the exclusion of which from the company base case is discussed in Section 4.2.8.

When asked to discuss the face validity of the adverse event disutility calculated using the linear regression model, given the calculated disutility using the literature-based approach, the company acknowledged that the utility decrements derived from the saturated utility regression model were lower than those reported in TA641 and TA874. However, these estimates were based on EQ-5D-3L data reported by patients in ECHELON-1, for the population and interventions of interest, thereby aligning with the NICE manual and DSU guidance (TSD 6) and the source of efficacy inputs in the CEM. The company maintained that the utility decrements estimated using the utility regression were valid despite being lower than the literature values.

To support their response, the company sought feedback from a UK clinical expert who indicated that febrile neutropenia was likely to have the greatest impact on HRQoL as a treatment related adverse event. To explore this, a scenario was conducted which derived disutility for febrile neutropenia based on the ratio of neutropenia to febrile neutropenia observed in TA874; this equates to a utility decrement of −0.04 for febrile neutropenia (−0.03 from the utility regression x [−0.15/−0.09 from TA874] = −0.04). This scenario increased the ICER from [redacted] to [redacted].

The EAG notes that from literature sourced adverse event disutilities, peripheral neuropathy is likely to have the greatest impact on patient HRQoL and has the following additional concerns around the methodology employed by the company:

- Taking the average durations and disutilities for AEs across two prior NICE appraisals does not necessarily result in clinically meaningful results; in particular, the company has assumed a duration and disutility of 0 for neutrophil count decreased, as this is not included in TA641.
- The disutilities for anaemia, febrile neutropenia sourced from TA874 appears to be incorrect; the source given in TA874 is a previous appraisal (TA306). However, the values used in TA874 do not align with the values used in TA306.

The EAG proposes an alternative approach to sourcing disutilities and durations; the EAG's preferred disutilities and durations, along with sources, are given in Table 51 and are assumed in the EAG base case.

Table 51. EAG preferred disutilities and durations for adverse events

Adverse event	Disutility	Source	Duration	Source
Anaemia	-0.069	Doyle *et al.* 2008[49]	7.2 days	ECHELON-2[34]
Febrile neutropenia	-0.115	Lloyd *et al.* 2006[50]	6.8 days	ECHELON-2[34]
Neutropenia	-0.048	Nafees *et al.* 2008 [51]	11.1 days	ECHELON-2[34]
Neutrophil count decreased	Assumed same as neutropenia		Assumed same as neutropenia	
Peripheral neuropathy	-0.33	Swinburn *et al.* 2015[52]	40.5 weeks (A+AVD), 27.3 weeks (ABVD)	Mean time to resolution of peripheral neuropathy events, ECHELON-1[53]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine.

As discussed in Section 4.2.8, the EAG considers that peripheral neuropathy, resolvable and lifelong, should be accounted for in the model. In the EAG's scenario accounting for patients with grade ≥3 lifelong peripheral neuropathy, in contrast to applying the disutility as a one-off cost to the first cycle of the model, a weekly peripheral neuropathy disutility was calculated and applied for 2.4% and 0.6% of A+AVD and ABVD patients.

4.2.9.4 Disutilities due to second malignancies

The model included a scenario accounting for HRQoL impact of second malignancies, which was not included in the company's base case for the following reasons;

- The difference in incidence of second malignancies between patients receiving A+AVD and patients receiving ABVD is very small (0.4% difference between A+AVD and PET-adjusted ABVD); therefore, the inclusion of disutilities for second malignancies has a minimal impact on the ICER.
- The disutility used to quantify the resulting QALY decrement is highly uncertain.
- The duration of the effect on HRQoL is highly uncertain.

The EAG agrees with the company's exclusion of second malignancies from the base case. Thus, second malignancies are not considered further in this assessment.

4.2.10 Resource use and costs

The economic model presented by the company included the following categories of costs:

- Acquisition costs for first line and subsequent treatments, as well as concomitant medications;
- Administration costs for first line and subsequent treatments;
- Monitoring and follow-up resource use costs; and
- Adverse event costs.

The model also included a scenario accounting for costs associated with second malignancies; this was not included in the model base case.

In general, all drug costs were obtained in 2024, and resource use costs were identified from the 2021/22 NHS reference costs and Personal Social Services Research Unit (PSSRU) unit costs.[54, 55] Further details of the implementation of these costs are given in the following subsections.

Please note, a confidential patient access scheme (PAS) discount is available for brentuximab vedotin. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 8.3 for details on the source of the confidential price for brentuximab vedotin.

The EAG broadly agrees with the methodology used for calculating costs and resource use in the economic model and found that this was explained clearly in the company submission; however, several issues were noted, which are described in further detail in the relevant sections below.

4.2.10.1 First line treatment acquisition costs

The A+AVD regimen comprises brentuximab vedotin, doxorubicin, vinblastine and dacarbazine, as stated in the SmPC. The comparator is represented as a combination of the six-cycle ABVD regimen and the PET-adapted ABVD regimen. In the ABVD regimen, patients receive six cycles of bleomycin, doxorubicin, vinblastine and dacarbazine. In the PET-adapted ABVD regimen, patients receive two cycles of the ABVD regimen, after which they receive a PET scan. Thereafter, patients who are PET2-negative (i.e. patients with Deauville score 1-3) are de-escalated to treatment with AVD (doxorubicin, vinblastine and dacarbazine) for four cycles, while patients who are PET2-postive (i.e.

patients with Deauville score 4-5) are escalated to treatment with escBEACOPDac (prednisolone, doxorubicin, cyclophosphamide, etoposide, dacarbazine, vincristine and bleomycin) for four cycles. The dosing regimen for the six-cycle ABVD regimen aligns with the ECHELON-1 protocol and NHS protocols, while the PET-adapted ABVD regimen aligns with NHS protocols.[56-69] As described in Section 4.2.4, the company assumed that 10% of the patient cohort is treated with the six-cycle ABVD regimen, with the remaining 90% being treated with the PET-adapted ABVD regimen.

Full details of the dosages used in the economic model are given in Table 52.

Table 52. Intervention and comparator dosages

Regimen	Treatment	Dosage	Administrations/cycle	Cycle length	Maximum cycles
A+AVD	Brentuximab vedotin	1.2 mg/kg	IV infusion, days 1 and 15	28 days	6
	Doxorubicin	25 mg/m^2			
	Vinblastine	6 mg/m^2			
	Dacarbazine	375 mg/m^2			
ABVD (PET-adapted and six-cycle ABVD regimens)	Bleomycin	10 U/m^2	IV infusion, days 1 and 15	28 days	2 (PET-adapted ABVD) or 6 (six-cycle ABVD)
	Doxorubicin	25 mg/m^2			
	Vinblastine	6 mg/m^2			
	Dacarbazine	375 mg/m^2			
AVD (de-escalation stage of PET-adapted ABVD regimen)	Doxorubicin	25 mg/m^2	IV infusion, days 1 and 15	28 days	4
	Vinblastine	6 mg/m^2			
	Dacarbazine	375 mg/m			
escBEACOPDac (escalated stage of PET-adapted ABVD regimen)	Prednisolone	40 mg/m^2	Oral administration, days 1-14	28 days	4
	Doxorubicin	35 mg/m^2	IV infusion, day 1		
	Cyclophosphamide	1,250 mg/m^2	IV infusion, day 1		
	Etoposide	1,200 mg/m^2	IV infusion, days 1-3		
	Dacarbazine	250 mg/m^2	IV infusion, days 2-3		
	Vincristine	1.4 mg/m^2	IV infusion, day 8		
	Bleomycin	10 U/m^2	IV infusion, day 8		

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; AVD, doxorubicin, vinblastine and dacarbazine; escBEACOPDac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and dacarbazine; IV, intravenous; kg, kilograms; m, metres; mg, milligrams; PET, positron emission tomography.

Brentuximab vedotin has a list price of £2,500 per 50 mg vial; however, a simple PAS discount is available for brentuximab vedotin, resulting in a price of [redacted].

[redacted] Costs for other treatment components for the intervention and comparator were obtained from eMIT where possible, and BNF otherwise; in both cases, costs were sourced in 2024.[70, 71] Further details of the cost inputs for each treatment are given in Table 53.

Table 53. Intervention and comparator pack prices

Treatment	Strength per unit	Units per pack	Price per pack
Brentuximab vedotin	50 mg	1	£2,500 (list price) [redacted](with PAS)
Doxorubicin	200 mg	1	£17.18
Vinblastine	10 mg	1	£17.00
Dacarbazine	500 mg 1000 mg	1 1	£37.50 £70.00
Bleomycin	15,000 mg	1	£19.06
Etoposide	100 mg	1	£11.50
Cyclophosphamide	500 mg 1000 mg	1 1	£8.61 £12.96
Vincristine	1 mg 2 mg	5 5	£25.38 £33.89
Prednisolone	5 mg 10 mg 20 mg 25 mg 30 mg	28 28 28 56 28	£0.83 £9.70 £19.46 £42.41 £29.12

Abbreviations: mg, milligrams; PAS, patient access scheme.

When calculating the cost per administration, the model assumed no vial sharing. A 'method of moments' approach was used to calculate a weighted average of the cost per administration over the patient cohort. Body weight and body surface area (BSA) were assumed to follow a log-normal distribution, with mean and standard deviation aligned with the patient characteristics in the ECHELON-1 trial; patients had a mean body weight of 75.06 kg (SD = 0.53 kg), and a BSA of 1.88 m^2 (SD = 0.01 m^2).[56] For each possible combination of vial sizes per administration, the total cost was weighted by the proportion of patients expected to fall into the corresponding range for body weight or BSA as appropriate.

In order to account for early discontinuation of treatment due to toxicity, it was assumed that the number of cycles of treatment patients received with A+AVD, and the six-cycle ABVD regimen, aligns with the duration of treatment observed in ECHELON-1. It was also assumed that all patients

receiving the PET-adapted ABVD regimen receive the full two cycles of treatment with ABVD. The duration of escalated or de-escalated treatment was calculated by assuming that the overall duration of treatment is the same as the duration of treatment for the AVD component in the ABVD arm of ECHELON-1.

The model also accounted for dose modifications (for example, dose reductions to manage peripheral neuropathy) by applying a relative dose intensity (RDI) for each treatment. For patients receiving A+AVD, the mean RDI observed in ECHELON-1 in the A+AVD arm was used. For patients receiving ABVD in either regimen, or receiving AVD in the PET-adapted ABVD regimen, the mean RDI observed in ECHELON-1 in the ABVD arm was used. For patients receiving escBEACOPDac, the median RDI reported in the GHSG HD18 trial, which compared standard and PET-adapted BEACOPP-based treatment regimens, was used.[9]

Details of the duration of treatment and RDI are given in Table 54.

Table 54. Intervention and comparator duration of treatment and RDI

Regimen	Treatment	Mean number of cycles (95% CI)	RDI (95% CI)
A+AVD	Brentuximab vedotin	5.50 (5.41 to 5.59)	94.01% (93.06 to 94.89%)
	Doxorubicin	5.60 (5.50 to 5.70)	99.11% (98.66 to 99.47%)
	Vinblastine	5.60 (5.51 to 5.69)	96.56% (95.73 to 97.30%)
	Dacarbazine	5.60 (5.52 to 5.69)	99.12% (98.77 to 99.41%)
ABVD (six-cycle ABVD regimen)	Bleomycin	5.40 (5.31 to 5.50)	93.51% (92.20 to 94.71%)
	Doxorubicin	5.70 (5.63 to 5.77)	99.54% (99.17 to 99.80%)
	Vinblastine	5.70 (5.63 to 5.77)	96.91% (96.13 to 97.61%)
	Dacarbazine	5.70 (5.63 to 5.77)	98.93% (98.42 to 99.34%)
ABVD (PET-adapted ABVD regimen)	Bleomycin	2.00 (1.93 to 2.00)	93.51% (92.20 to 94.71%)
	Doxorubicin	2.00 (1.91 to 2.00)	99.54% (99.17 to 99.80%)
	Vinblastine	2.00 (1.92 to 2.00)	96.91% (96.13 to 97.61%)
	Dacarbazine	2.00 (1.93 to 2.00)	98.93% (98.42 to 99.34%)
AVD (de-escalation stage of PET-adapted ABVD regimen)	Doxorubicin	3.70 (3.61 to 3.80)	99.54% (99.17 to 99.80%)
	Vinblastine	3.70 (3.62 to 3.78)	96.91% (96.13 to 97.61%)
	Dacarbazine	3.70 (3.63 to 3.77)	98.93% (98.42 to 99.34%)
escBEACOPDac (escalated stage of PET-adapted ABVD regimen)	Prednisolone	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)
	Doxorubicin	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)
	Cyclophosphamide	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)
	Etoposide	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)
	Dacarbazine	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)

	Vincristine	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)
	Bleomycin	3.70 (3.61 to 3.80)	97.00% (96.45 to 97.50%)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; AVD, doxorubicin, vinblastine and dacarbazine; escBEACOPDac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and dacarbazine; CI, confidence interval; PET, positron emission tomography; RDI, relative dose intensity.

The overall calculated mean cost for each course of treatment, taking into account the distribution of patient body weight or BSA as appropriate, early discontinuation and dose modification, is given in Table 55.

Table 55. Intervention and comparator mean total treatment cost

Regimen Treatment		Total regimen cost	Cost used for intervention/comparator
A+AVD		£61,793 (list price) [redacted](with PAS)	
ABVD	Six-cycle ABVD	£1,530	£1,478
	PET-adapted ABVD	£1,472	

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; PAS, patient access scheme; PET, positron emission tomography.

4.2.10.2 Treatment administration costs

Administration costs for the intervention and comparator were informed by appropriate NHS reference costs: £256.95 (SB13Z) for the first administration per cycle and £326.46 for subsequent administrations (SB15Z). [54] For escBEACOPDac, an additional administration cost of £13.75, corresponding to the cost for 15 minutes of pharmacist time was applied to account for dispensing an oral therapy (i.e. prednisolone), sourced from PSSRU unit costs.[55] Further details of the administration costs applied are given in Table 56.

Table 56. Intervention and comparator administration costs

Treatment	Description of administration costs	Total administration cost per cycle
A+AVD	• 1 complex IV administration per cycle • 1 subsequent administration per cycle	£583.42
ABVD	• 1 complex IV administration per cycle	£583.42

	• 1 subsequent administration per cycle	
AVD	• 1 complex IV administration per cycle • 1 subsequent administration per cycle	£583.42
escBEACOPDac	• 1 oral administration per cycle • 1 complex IV administration per cycle • 3 subsequent administrations per cycle	£597.17

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; AVD, doxorubicin, vinblastine and dacarbazine; escBEACOPDac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and dacarbazine; IV, intravenous.

4.2.10.3 Concomitant medication costs

The economic model included costs for concomitant medications, encompassing primary prophylaxis with granulocyte colony stimulating factor (G-CSF), anti-emetics, anti-infectives, and pain management. The concomitant medications included were selected on the basis of clinical input, and high proportions of patients receiving the medication of interest in ECHELON-1.

The proportions of patients receiving each concomitant medication were largely based on ECHELON-1, with the exception of primary prophylaxis with G-CSF, since clinical opinion indicated that this was not representative of how G-CSF would be used in clinical practice. In line with the summary of product characteristics (SmPC), all patients receiving A+AVD or escBEACOPDac would be expected to receive primary prophylaxis with G-CSF, whereas patients receiving ABVD or AVD would not be expected to receive G-CSF.[72] In the absence of any available data to inform concomitant medications received alongside PET-adapted ABVD, it was assumed that the proportion of patients receiving each concomitant medication in ECHELON-1 would be representative of both ABVD regimens. Further details are given in Table 57.

Table 57. Proportion of patients receiving concomitant medications

Treatment category	Treatment	Proportion receiving treatment, A+AVD	Proportion receiving treatment, ABVD
G-CSF	Filgrastim (10 admins/cycle)	100%	0%

	Filgrastim 5 admins/cycle)	0%	100% for patients receiving escBEACOPDac, 0% otherwise
Anti-emetics	Dexamethasone	100%	100%
	Ondansetron	100%	100%
	Aprepitant	100%	100%
Anti-infectives	Acyclovir	22.4%	15.3%
	Levofloxacin	19.8%	15.9%
Pain management	Oxycodone	14.4%	9.7%
	Tramadol	14.4%	9.3%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; escBEACOPDac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and dacarbazine; G-CSF: granulocyte colony stimulating factor.

Costs for concomitant G-CSF were applied to patients receiving active first line treatment; for patients in the ABVD arm, it was assumed that 10% receive concomitant G-CSF relevant to the six-cycle ABVD regimen, while the remaining 90% receive concomitant medications in line with the PET-adapted ABVD regimen. Dosing regimens for concomitant G-CSF were informed by NHS protocols for treatment with ABVD.[57, 60, 61, 65, 66] All other concomitant medication use for ABVD was in line with ECHELON-1. Costs were obtained from eMIT, where possible, and BNF otherwise.[70, 71] Administration costs for concomitant medications were not included in the model. Further details are given in Table 58.

Table 58. Dosing and costs for concomitant medications

Treatment category	Treatment	Dose per admin	Admins per cycle	Strength per unit	Units per pack	Price per pack	Total cost per cycle
G-CSF	Filgrastim (10 admins/cycle)	0.38 mg	10	0.6 mg	0.5	£52.70	£659.29
	Filgrastim 5 admins/cycle)	0.38 mg	5	0.6 mg	0.5	£52.70	£329.65
Anti-emetics	Dexamethasone (day 1)	8 mg	2	8 mg	50	£68.06	£2.72
	Dexamethasone (days 2-3)	4 mg	4	4mg	50	£35.95	£2.88
	Ondansetron	8 mg	8	8 mg	10	£0.54	£0.11
	Aprepitant (day 1)	125 mg	2	125 mg	5	£10.81	£4.32
	Aprepitant (day 2-3)	80 mg	2	80 mg	2	£4.12	£8.25
	Acyclovir	1000 mg	5	200 mg	25	£0.78	£0.78

Anti-infectives	Levofloxacin	500 mg	7	500 mg	5	£1.46	£2.05
Pain management	Oxycodone	20 mg	7	20 mg	56	£13.53	£.69
	Tramadol	100 mg	7	50 mg	30	£0.59	£0.28

Abbreviations: G-CSF: granulocyte colony stimulating factor; mg, milligrams.

The overall concomitant medication costs for each cycle are given in Table 59, as well as the overall cost, assuming treatment durations as specified in Table 54.

Table 59. Total concomitant medication costs for intervention and comparator

Regimen	Treatment	Cost per cycle
A+AVD	A+AVD	£678.44
ABVD	ABVD	£18.92
	AVD	£18.92
	escBEACOPDac	£348.56

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; escBEACOPDac, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and dacarbazine.

4.2.10.4 Monitoring and follow-up costs

In the economic model, costs for monitoring and follow-up were included, with differential resource use for the following health states:

- Pre-progression, 0-6 months after starting treatment;
- Pre-progression, from 6 months after starting treatment to the cure timepoint;
- Progressed disease;
- Cured.

Based on input from UK clinicians, the point at which progression-free patients were considered to be functionally cured, and incur no further follow-up, was assumed to be two years after treatment; however, a scenario with a cure point of five years was also explored.

Monitoring and follow-up resource use for the pre-progression health states were informed by BSH and ESMO guidelines, as well as input from UK clinicians.[6, 7, 73] Resource use for the progressed disease health state was informed by the previous NICE appraisals for brentuximab vedotin monotherapy for HL in the relapsed/refractory context (TA446), which used estimates of resource use for patients with relapsed or refractory HL obtained through interviews of clinical experts.[74]

These estimates were also subsequently used in the NICE appraisal for nivolumab for HL in the relapsed/refractory context (TA462).[75]

It was also assumed that resource use would be the same, regardless of whether patients receive A+AVD or ABVD; this assumption was validated by UK clinicians.[7] Details of the health state resource use for each health state is given in Table 60.

Table 60. Resource use per year by health state

Resource	Pre-progression, 0-6 months	Pre-progression, 6 months-cure	Progressed disease	Cure
Full blood count	4	2	10.4	0
Blood chemistry	4	2	10.4	0
Consultation	4	2	10.4	0
CT scan	1	0	1.5	0
PET scan	2	0	1.5	0

Abbreviations: CT, computed tomography; PET, positron emission tomography.

The costs for resource use have been identified using appropriate NHS reference costs.[54] Details are given in Table 61.

Table 61. Monitoring and follow-up costs by resource

Resource	Cost	Source
Full blood count	£2.96	NHS reference costs 2021/22; Haematology; DAPS05[54]
Blood chemistry	£1.55	NHS reference costs 2021/22; Clinical biochemistry; DAPS04[54]
Consultation	£209.41	NHS reference costs 2021/22; Clinical haematology; WF01A 303; non-admitted face to face attendance, follow-up[54]
CT scan	£146.34	NHS reference costs 2021/22; Outpatient; RD26Z; CT scan (three areas, with contrast)[54]
PET scan	£702.78	NHS reference costs 2021/22; Outpatient; RN02A; PET-CT scan (two or three areas)[54]

Abbreviations: CT, computed tomography; NHS: National Health Service; PET, positron emission tomography.

A summary of the overall monitoring and follow-up costs per year for each health state is given in Table 62.

Table 62. Total monitoring and follow-up costs per year for each health state

Health state	Total monitoring/follow-up cost per year
Pre-progression, 0-6 months	£2,407.57
Pre-progression, 6 months - cure	£427.83
Progressed disease	£3,498.42

4.2.10.5 Adverse event costs

The economic model included a one-off cost at baseline accounting for AEs. The only adverse events assumed to incur costs were anaemia, febrile neutropenia, neutropenia, and neutrophil count decreased, based on criteria of grade 3+ AEs occurring in at least 5% of patients in one arm of ECHELON-1.

The frequency of these adverse events was assumed to align with the ECHELON-1 trial; the frequency of adverse events for patients receiving PET-adapted ABVD was sourced from the RATHL study and weighted by 90%, and the frequency of adverse events for patients receiving six-cycle ABVD was per ECHELON-1 and weighted by 10%.. Further details are given Table 49.

The adverse event costs were informed using NHS reference costs, with the exception of anaemia, which was costed using a combination of an NHS reference for the transfusion procedure itself, and an additional cost for two standard red cell components sourced from the NHS Blood and Transplant Price List 2023/24.[54, 76] Further details of the adverse events costs are given in Table 63.

Table 63. Adverse event costs

Adverse event	Cost per event	Source
Anaemia	£649.49 *Comprising:* *£333.13 (transplant procedure)* *2 x £158.15 (two standard red blood cell components)*	NHS Blood and Transplant List 2023/24, and NHS reference costs 2021/22; Outpatient procedure; SA44A 303; Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over
Febrile neutropenia	£646.71	NHS reference costs 2021/22; Non-elective short stay; SA35B; Agranulocytosis with CC Score 9-12
Neutropenia	£387.69	NHS reference costs 2021/22; Non-elective short stay; SA35C; Agranulocytosis with CC Score 5-8
Neutrophil count decreased	Assumed same as neutropenia	

Abbreviations: CC, complication and comorbidity; NHS, National Health Service

4.2.10.5.1 EAG critique

Similar to the calculation of disutilities arising from adverse events (Section 4.2.9.3), the EAG notes that costs for peripheral neuropathy were not included in the economic model. Since the incidence of peripheral neuropathy was higher for patients receiving A+AVD compared to ABVD, and patients with peripheral neuropathy may require long-term treatment, the EAG considers that it would be appropriate to include the costs for peripheral neuropathy.

In response, the company justified the assumption of no cost associated with peripheral neuropathy as this aligned with the Committee's decision in TA641, which stated in the FAD that *"excluding costs for grades 3 and 4 peripheral neuropathy is appropriate"*.[43] To further support their response, the company elicited feedback from a UK clinical expert who confirmed that peripheral neuropathy in previously untreated HL would be managed in via dose modifications or discontinuation. Dose modifications observed in ECHELON-1 are already reflected in the base case CEM through the application of relative dose intensity and mean treatment duration for A+AVD and ABVD and so no additional costing assumptions are required. The EAG acknowledges that peripheral neuropathy would be treated with dose modification or treatment discontinuation but caveats that by the end of the study a proportion of A+AVD and ABVD patients had unresolved treatment related grade ≥3 PN at last follow up. It is therefore likely that dose modification will not resolve all treatment related peripheral neuropathy and that patients may require lifelong symptom management. As such, adverse event costs for both A+ABD and ABVD are likely underestimated in the model, with A+AVD costs being [redacted] so given [redacted] A+AVD patients were recorded with unresolved peripheral neuropathy at the last study follow up.

4.2.10.6 Subsequent treatment costs

The economic model included a single, one-off cost covering acquisition and administration of subsequent treatments, as well as stem cell transplants and radiation therapy, which was applied to all patients upon progression. In the company's preferred base case, it was assumed that the subsequent treatments received, and the proportion of patients expected to receive each treatment, aligned with observed subsequent treatments in the ECHELON-1 trial. However, a scenario was also provided in which the proportion of patients receiving each treatment has been

determined based on input from UK clinicians in an advisory board conducted in December 2023.[12] Details of the parameters used in the base case and scenario are given in Table 64; it should be noted that the sum over all proportions exceeds 100% since multiple lines of treatment are accounted for. Likewise, the proportion of patients expected to receive multiagent chemotherapy exceeds 100% in both arms for the estimates based on clinical opinion, since some patients are expected to receive multiple lines of chemotherapy.

Table 64. Proportion of patients receiving subsequent therapies

Treatment	Proportion receiving treatment, A+AVD (ECHELON-1)	Proportion receiving treatment, ABVD (ECHELON-1)	Proportion receiving treatment, A+AVD (clinical opinion)	Proportion receiving treatment, ABVD (clinical opinion)
ASCT	31.25%	33.96%	57.9%	60.08%
Pembrolizumab	1.55%	3.65%	65.85%	52.04%
Nivolumab	13.16%	14.59%	8.05%	8.24%
Brentuximab vedotin monotherapy	8.09%	44.03%	23.53%	47.88%
alloSCT or donor lymphocyte infusion	7.72%	14.47%	3.13%	3.82%
Multiagent chemotherapy	78.68%	87.42%	106.59%	108.26%
Radiation	8.58%	9.1%	0%	0%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; alloSCT: allogenic stem cell transplant; ASCT: autologous stem cell transplant.

Drug acquisition costs were sourced from eMIT, where possible, and BNF otherwise; the list price was used for all treatments, with the exception of brentuximab vedotin monotherapy, for which the PAS was applied.[70, 71] Multiagent chemotherapy was costed based on the gemcitabine, cisplatin and dexamethasone (GDP) regimen, which was considered most representative of later lines of treatment for advanced HL, based on clinician feedback.

In general, dosages were aligned with the relevant SmPC for each treatment, with the exception of GDP, in which dosages aligned with those used in a previous NICE appraisal (TA462).[75] Duration of treatment for brentuximab vedotin and nivolumab was sourced from the relevant NICE appraisal in relapsed or refractory HL (TA446 and TA462 respectively).[74, 75] The duration of treatment for GDP was also aligned with TA462. In the absence of other appropriate evidence, the company assumed that the duration of treatment for pembrolizumab was equal to the duration of treatment for nivolumab. For all treatments, an RDI of 100% and no vial sharing were implicitly assumed.

Administration costs for subsequent treatments were based on appropriate NHS reference costs. [54] No administration cost was assumed for dexamethasone, which is an oral treatment.

Further details of the acquisition and administration costs for pharmacological treatments are given in Table 65.

Table 65. Subsequent treatments: acquisition costs for pharmacological treatments

Treatment	Dose per admin	Administrations per cycle	Treatment duration	Strength per unit	Units per pack	Price per pack	Administration costs	Total costs
Pembrolizumab	200 mg	1	13 cycles	100 mg	1	£2,630	£207.59 (SB12Z)	£71,079
Nivolumab	3 mg/kg	1	13 cycles	40 mg	1	£439	£207.59 (SB12Z)	£36,941
Brentuximab vedotin	1.2 mg/kg	2	9.24 cycles	50 mg	1	£2,500 (list price) [redacted] (with PAS)	£207.89, first admin/cycle (SB12Z) £326.46, subsequent admins (SB15Z)	[redacted]
GDP: gemcitabine	1000 mg/m^2	2	2 cycles	1000 mg	1	£10.90	£440.71, first admin/cycle (SB14Z) £326.46, subsequent admins (SB15Z) Assumed no admin cost for dexamethasone	£1,658
GDP: cisplatin	75 mg	1		50 mg 10 mg	1 1	£5.58 £2.42		
GDP: dexamethasone	40 mg	4		2 mg	50	£2.62		

Abbreviations: GDP, gemcitabine, dexamethasone and cisplatin; kg, kilograms; m, metres; mg, milligrams; PAS, patient access scheme.

The costs for subsequent autologous stem cell transplant (ASCT) and allogeneic stem cell transplant (alloSCT) included the cost for the procedure itself, as well as bone marrow harvest for ASCT, peripheral blood stem cell harvest for alloSCT, and long-term follow-up for all transplants. The costs for harvesting and transplants were based on appropriate NHS reference costs. Long-term follow-up costs were sourced from a previous NICE appraisal for polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma (TA874), inflated from 2019/20 to 2020/21 using the NHS Cost Inflation Index (NHSCII) prices index. [35, 55]

The costs for radiotherapy were calculated based on dosages informed by British Society for Haematology (BSH) guidelines, with costs per administration based on appropriate NHS reference costs (SC45Z and SC22Z).[6, 54]

Further details of the costs for subsequent stem cell transplants and radiotherapy are given in Table 66.

Table 66. Subsequent treatments: costs for procedures

Procedure	Component	Number of procedures required	Cost per procedure	Cost source	Total cost
ASCT	Transplant	1	£19,136	NHS Reference Costs 2021/22. SB26A. Peripheral blood stem cell transplant, autologous, 19 years and older (elective)[54]	£32,786
	Bone marrow harvest	1	£5,808	NHS Reference Costs 2021/22. SA18Z. Bone marrow harvest (elective)[54]	
	Long-term follow-up	1	£7,842	TA874, inflated from 2019/20 to 2020/21 using NHSCII[35, 55]	
AlloSCT	Transplant	1	£51,390	NHS Reference Costs 2021/22. SA40Z. Peripheral blood stem cell transplant, allogeneic (donor type not specified) (elective)[54]	£98,412
	Peripheral blood stem cell harvest	1	£5,375	NHS Reference Costs 2021/22. SA18Z. Bone marrow harvest (elective)[54]	
	Long-term follow-up	1	£41,648	TA874, inflated from 2019/20 to 2020/21[35, 55]	

Radiotherapy	Preparation with image and dosimetry	1	£575.00	NHS reference costs 2021/22; Outpatient; SC45Z[54]	£4,079
	Delivery of radiotherapy	20	£175.19	NHS reference costs 2021/22; Outpatient; SC22Z[54]	

Abbreviations: alloSCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant.

The total calculated subsequent treatment costs per patient for both the company's preferred base case and the scenario using proportions of patients receiving subsequent treatment elicited from clinicians are given in Table 67.

Table 67. Total costs for subsequent treatment

Treatment	Subsequent treatment based on ECHELON-1	Subsequent treatment based on clinical opinion
A+AVD	[redacted]	[redacted]
ABVD	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine.

4.2.10.6.1 EAG critique

Based on feedback from clinical experts, the EAG considers that the proportions of patients receiving each subsequent treatment based on clinical input, rather than ECHELON-1, are more likely to be representative of clinical practice. In particular, the EAG's clinical expert commented that the proportion of patients receiving ASCT, multiagent chemotherapy, pembrolizumab and brentuximab vedotin monotherapy in ECHELON-1 were lower than expected in ECHELON-1.

The EAG's clinical experts also stated that the expected proportion of patients receiving radiotherapy would be higher than the 0% expressed by the company's clinical experts. At clarification the EAG asked the company what information was informing this opinion with the company responding that clinical expert view from the advisory board engagements was that radiation is rarely used in the relapsed/refractory HL setting in the UK.

To support their response, the company reached out to an additional UK clinical expert who confirmed that radiation is used "*highly infrequently*". They indicated that they may use radiation as a supportive bridge to ASCT if their multi-agent chemotherapy response is verging on satisfactory;

however, this is rare and may only be relevant for 5–10% of patients. Adding that the UK is a lower user of radiation compared to other markets, which may explain the differential between the two sources given ECHELON-1 is a global trial. The EAG conducted a scenario using the company's clinical experts preferred subsequent treatment proportions combined with the assumption that 5% of patients in each treatment arm would require radiation as a subsequent treatment. The scenario had a negligible impact on the ICER but is included in the EAG base case assumptions.

The EAG notes that the company has assumed that the duration of treatment for pembrolizumab was the same as the duration of treatment for nivolumab (13 21-day cycles). As no justification for this assumption was given by the company the EAG requested a scenario using the duration of treatment from the KEYNOTE-087 trial (14.8 months).[77] The company responded that assuming equal subsequent treatment durations was a simplification based on their similar mechanism of action and that KEYNOTE-087 reported a similar median durations of treatment for pembrolizumab (14.8 months) vs CheckMate205 for nivolumab (14.3 months).[57, 58] For completeness the company conducted a scenario in which patients receive 200mg every 3 weeks for 14.8 months as per KEYNOTE-087.[57] This is converted into the 3-week treatment cycle length specific to pembrolizumab treatment in the relapsed or refractory Hodgkin's lymphoma setting, which equates to 21.45 3-week cycles. Using the duration of subsequent pembrolizumab from the KEYNOTE-087 trial marginally reduced the ICER, with the updated subsequent treatment duration assumed in the company base case.

The EAG noted that the model used a treatment duration of 9.24 cycles for brentuximab vedotin monotherapy, based on the NICE submission for brentuximab vedotin monotherapy as a treatment for relapsed or refractory classical Hodgkin lymphoma (TA466). However, the treatment duration stated in TA446 is 9.7 cycles.[74] At clarification the company responded that the 13-cycle assumption was based on the second set of Committee papers in TA462 which indicated that a median of 13 doses of nivolumab were received when combining CheckMate 039 and CheckMate 205. [60] In line with the EAG's request, a scenario was conducted assuming that the duration of subsequent nivolumab treatment was 14.3 months, to align with the median duration of treatment observed in CheckMate 205. The assumption had a minimal impact on the ICER and was incorporated into the company's base case assumptions

Similarly, the EAG identified that the model assumed a dosage of 3mg/kg for each administration of nivolumab; however, the SmPC for nivolumab states that an appropriate dosage for classical

Hodgkin lymphoma is 240 mg every two weeks.[78] The company responded that 3mg/kg per administration was used as it equates to 225.19 mg every two weeks. For completeness the company conducted a scenario using 240mg every two weeks directly which led to no change in the ICER.

Furthermore, the EAG considered that assuming a dose of 1.2 mg/kg in the model for brentuximab vedotin monotherapy as a subsequent treatment was inappropriate as the SmPC for brentuximab vedotin states that a dosage of 1.8 mg/kg should be used in the relapsed/refractory setting. The company in response stated that a dose of 1.2 mg/kg instead of 1.8 mg/kg was assumed to ensure the correct subsequent brentuximab vedotin cost was applied in the model, given the cycle length is 4 weeks rather than 3 weeks. Additionally, the model was used to calculate the number of cycles required to ensure the cost of subsequent brentuximab vedotin was equal to the acquisition cost from NICE TA446 ([redacted]). To align with the approach conducted for other subsequent therapies the company conducted a scenario dosing brentuximab vedotin as 1.8 mg/kg once per 3-week treatment cycle. The scenario resulted in a lower cost for brentuximab as a subsequent treatment ([redacted]) compared to that from TA446. The company considered that the estimate from TA446 was likely to be more accurate as it accounts for the distribution of weight using method of moments while the submission bases the cost of subsequent treatments on the average weight and BSA, as such the true cost of brentuximab vedotin as a subsequent treatment may be underestimated. However, the assumption was included into the company base case. The EAG considers that that the cost of brentuximab vedotin should be considered independently of NICE TA446 and that the average weight and BSA are taken from ECHELON-1 and so are directly relevant to this evaluation. As such, the EAG considers the inclusion of the modelling assumption into the company base case as appropriate.

Finally, the costs for ASCT and alloSCT included a component for long-term follow-up, obtained from TA874 and inflated using the NHSCII prices index from 2019/20 to 2020/21; however, the EAG considers it would be more appropriate to inflate the NHSCII prices to 2021/22, to align with other costs in the model. Following a request from the EAG the company use the provisional inflation indices from PSSRU 2022 to inflate the costs for long-term follow-up for ASCT and alloSCT to 2021/22 values which led to a small change in the ICER with the updated cost being incorporated into the company base case.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 68 presents the cost-effectiveness results of the company's base case deterministic and probabilistic analyses. A probabilistic sensitivity analysis (PSA) was conducted to assess the joint parameter uncertainty around base case results using a Monte Carlo simulation that derived probabilistic results from 1,000 generated simulations. When compared deterministically to doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), doxorubicin, vinblastine and dacarbazine (A+AVD) generated an additional [redacted] QALYs at an additional cost of [redacted], resulting in an ICER of [redacted] per QALY. Under probabilistic conditions, the ICER was calculated at [redacted] per QALY, reflecting a close alignment between the deterministic and probabilistic results.

Table 68. Company's base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
A+AVD	[redacted]	[redacted]	[redacted]	–	–	–	–
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
A+AVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

The company's PSA scatterplot is presented in Figure 32 and cost effectiveness acceptability curve (CEAC) in Figure 33. Based on the analyses, the probability that A+AVD is cost-effective versus ABVD at a £20,000 and £30,000 willingness to pay (WTP) threshold is [redacted] and [redacted], respectively, using the company's base case assumptions.

Figure 32. Company's PSA scatterplot, reproduced from the company's model

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine

Figure 33. Company's cost-effectiveness acceptability curve, reproduced from the company's model

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CEAC, cost-effectiveness acceptability curve

5.2 Company's sensitivity analyses

The company conducted one-way sensitivity analyses (OWSA) to assess the sensitivity of the model to individual parameter uncertainty. The company provided a tornado diagram displaying the most influential parameters on the ICER. This diagram is reproduced below based on the company's updated model.

Figure 34. OWSA tornado plot. Reproduced from the company's updated model

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICER, incremental cost-effectiveness ratio

5.3 Company's scenario analyses

The company undertook a range of scenario analyses to explore the impact of alternative assumptions for key model parameters. Results of the scenarios are presented below in Table 69. The results are based on the deterministic version of the model which the EAG considers is reasonable given the similarity in the company's deterministic and probabilistic base case results. As presented, the ICER ranged from [redacted] (Baseline characteristics: RATHL study) to [redacted] (OS: independent MCMs exponential for A+AVD and ABVD).

Table 69.Company base case scenario analysis

Scenario	ICER	Change from base case	% change from base case
Updated base case	[redacted]	-	-
Time horizon: 50-years	[redacted]	[redacted]	1.68%
Time horizon: 70-years	[redacted]	[redacted]	-0.06%
Exclude half-cycle correction	[redacted]	[redacted]	0.04%
Discount rates: 0%	[redacted]	[redacted]	-56.31%
Discount rates: 1.5%	[redacted]	[redacted]	-35.60%
Baseline characteristics: RATHL study (ITT)	[redacted]	[redacted]	-7.68%
PFS: KM and adjusted background mortality	[redacted]	[redacted]	2.95%
PFS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	3.23%
PFS: independent MCMs Weibull for A+AVD and ABVD	[redacted]	[redacted]	3.07%
PFS: independent MCMs log-normal for A+AVD and ABVD	[redacted]	[redacted]	0.49%
PFS: independent MCMs log-logistic for A+AVD and ABVD	[redacted]	[redacted]	0.00%
PFS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	4.08%
PFS: independent MCMs generalised gamma for A+AVD and ABVD	[redacted]	[redacted]	2.61%
PFS: independent MCMs gamma for A+AVD and ABVD	[redacted]	[redacted]	2.28%
PFS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	3.36%
PFS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	-2.07%
PFS: independent one-knot splines (hazard) for A+AVD and ABVD	[redacted]	[redacted]	-0.17%
PFS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	-0.43%
OS: KM and adjusted background mortality	[redacted]	[redacted]	9.10%

OS: independent MCMs exponential for A+AVD and ABVD	[redacted]	[redacted]	9.78%
OS: independent MCMs Gompertz for A+AVD and ABVD	[redacted]	[redacted]	6.28%
OS: independent standard Gompertz for A+AVD and ABVD	[redacted]	[redacted]	9.18%
OS: independent one-knot splines (odds) for A+AVD and ABVD	[redacted]	[redacted]	0.54%
OS: independent one-knot splines (normal) for A+AVD and ABVD	[redacted]	[redacted]	0.49%
PET-adapted ABVD: 100% of ABVD-based comparator	[redacted]	[redacted]	-0.13%
PET-adapted ABVD: 95% of ABVD-based comparator	[redacted]	[redacted]	-0.07%
SMR 1.10 for A+AVD and 1.15 for ABVD	[redacted]	[redacted]	0.99%
Cure timepoint: 36-months	[redacted]	[redacted]	-0.38%
Cure timepoint: 60-months	[redacted]	[redacted]	0.07%
AE disutilities: literature	[redacted]	[redacted]	1.79%
AE disutilities: excluded	[redacted]	[redacted]	-0.17%
Second malignancies: included	[redacted]	[redacted]	0.24%
Subsequent therapy distribution: UK clinical opinion	[redacted]	[redacted]	0.89%
RDI: excluded	[redacted]	[redacted]	5.57%
Primary prophylaxis with G-CSF as per ECHELON-1	[redacted]	[redacted]	-9.11%

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ITT, intention-to-treat; LYs, life years; MCM, mixture cure models; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity; SMR, standardised mortality rate; TEAE, treatment-related adverse event

5.4 Model validation and face validity check

An internal Takeda health economic expert not involved in the development of the model conducted a model quality check. The check was based on a standardised checklist based on Drummond *et al.* 1996, Phillips *et al.* 2004, and the NICE health technology evaluations manual suggested checklist.[79-81]

Three further health economists reviewed the model independently using a checklist and a targeted sheet-by-sheet approach. The aim of the reviewers was to assess the accuracy and transparency of the model calculations and functionality. The checklist used to review the model covered tests included in the Philips and TECH-VER checklists. [81, 82]

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External Assessment Group (EAG) identified a number of lower treatment costs compared to those included in the model (Table 70). The model has therefore been updated to reflect these corrections, resulting in the company corrected base case presented in Table 71.

Table 70. Update to treatment costs

Name	Dose per unit	Cost	Cost source, provided by company in appendix K	Alternative source and pricing
Doxorubicin	200 mg/100ml	£17.18	eMIT[70]	eMIT - £15.98 (DHA209)
Dacarbazine	500mg 1000mg	£37.50 £70.00	BNF[71]	eMIT 500 mg - £27.15 (DHA156) 1000 mg - £57.20 (DHA157)
Etoposide	100 mg/5ml 500 mg/25ml	£11.50 £60.70	BNF[71]	eMIT 100mg - £4.57 (DHA320) 500mg - £13.40

Abbreviations; BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool.

Table 71. Company's corrected base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case							
A+AVD	[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corrected company base case							
A+AVD	[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

6.2 EAG scenario analysis

[redacted]

Table 72 presents the results of the EAG's exploratory scenario analyses. These results reflect the company's proposed patient access scheme (PAS) discount on the list price of brentuximab vedotin [redacted]. Confidential PAS discounts or confidential medicine unit (CMU) prices are available for subsequent lines of bleomycin, filgrastim, nivolumab and pembrolizumab and are included in the scenario and results provided in the confidential appendix.

The EAG scenario analyses were conducted deterministically given the alignment of deterministic and probabilistic outcomes. Across all scenarios A+AVD was found to generate more QALYs, while also being more costly compared to ABVD, with the resulting ICERs lying above the £30,000 ICER threshold in the northwest quadrant of the cost-effectiveness plane. [redacted]

Table 72. Results of the EAG's scenario analyses

	Results per patient	A+AVD	ABVD	Incremental value
0	Company corrected base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
1	Age weighted ICER MCM and EAG preferred distributions			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
2	EAG preferred adverse event durations and disutilities			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
3	Difference in time to resolution of peripheral neuropathy*			
	Total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
4	Accounting for lifelong peripheral neuropathy*			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
5	Company clinical expert subsequent treatment opinion & 5% of PD patients requiring radiation as a subsequent treatment			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]

*The scenario includes the assumptions of the previous scenario

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.3 EAG preferred assumptions

The EAG presents its preferred analysis for the cost-effectiveness of A+AVD for previously untreated late-stage classical Hodgkins's lymphoma compared to ABVD. The assumptions that form the EAG's preferred base case are listed below, with EAG base case results presented in Table 74.

1. Applying the same standardised mortality ratio (SMR) to both A+AVD and ABVD mortality rates (1.05);
2. Using the literature-based approach to calculate adverse event disutility;
3. Using the EAG preferred adverse event disutilities and durations;
4. Applying treatment specific mean time to peripheral neuropathy resolution;
5. Accounting for patients with lifelong peripheral neuropathy;
6. Informing subsequent treatment proportions from company clinical expert opinions;
7. Assuming 5% of progressed patients will require radiation as a subsequent treatment;
8. Weighting the ICER by the <60 and ≥60-year-old subgroups from ECHELON-1;
9. Modelling long term survival using MCMs and the EAGs preferred model distributions.

Table 73. EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company corrected base case	-	[redacted]	-

Applying the same SMR to both treatment arms (1.05)	4.2.7	[redacted]	[redacted]
Using the literature-based approach to calculate adverse event disutility	4.2.9	[redacted]	[redacted]
Using the EAG preferred adverse event disutilities and durations*	4.2.9	[redacted]	[redacted]
Applying treatment specific mean time to peripheral neuropathy resolution*	4.2.9	[redacted]	[redacted]
Accounting for patients with lifelong peripheral neuropathy*	4.2.9	[redacted]	[redacted]
Informing subsequent treatment proportions from company clinical expert opinions	4.2.10.4	[redacted]	[redacted]
5% of subsequent treatment patients receiving radiation*	4.2.10.4	[redacted]	[redacted]
Age-weighted ICER	4.2.3	[redacted]	[redacted]
Modelling long term survival using a MCM and the EAGs preferred distributions*	4.2.6	[redacted]	[redacted]

*Note: Assumption includes previous assumption.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 74. EAG base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
A+AVD	[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
A+AVD	[redacted]	[redacted]	[redacted]				
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

6.3.1 EAG sensitivity analysis

Given the EAG's preference for an age weighted ICER, separate sensitivity analyses were conducted for the <60 and ≥60-year-old age subgroups as presented below. Critically, while separate analyses have been provided, the EAG considers that the subgroups should not be considered separately in cost-effectiveness decision making and that an age-weighted ICER, based on the age proportions from ECHELON-1, is sufficient to account for the age bimodal incidence of disease within the population.

The EAG PSA scatterplot for <60-year-old patients is presented in Figure 35 and cost effectiveness acceptability curve (CEAC) in Figure 36. The reciprocal scatter plot and CEAC curve for the ≥60-year-old patient subgroup are provided in Figure 37 and Figure 38.

Figure 35. EAG PSA scatterplot for <60-year-old patients

Figure 36. EAG CEAC for <60-year-old patients

Figure 37. EAG ≥60-year-olds PSA scatter plot

Figure 38. EAG ≥60-year-olds CEAC

6.4 Conclusions of the cost effectiveness sections

In summary, the economic model broadly captures the major disease milestones of untreated late-stage classical Hodgkin lymphoma and reflects key changes in patient health related quality of life (HRQoL) while capturing the appropriate costs. In light of this, the EAG is concerned that the company has oversimplified the model in many aspects, leading to the avoidable and inappropriate loss of patient HRQoL and cost granularity.

The most prominent example of this is that while untreated late-stage classical HL effects the population bimodally, with 20–24 year and 75–79-year-olds being the most likely to have the condition, the company has preferred a simplistic approach based on mean age. The EAG considers the approach may not appropriately capture the health-related quality of life and cost outcomes of these key populations, with the model instead assuming a mean age between these groups of patients.

Furthermore, while the company is aware that the six cycle ABVD approach used in the ECHELON-1 trial and assumed to inform efficacy in the model is not reflective of current clinical practice, the EAG considers that the company has not provided robust evidence to support their assumption of equal efficacy between the approaches as has been assumed in the model. As discussed in the clinical section, while in clinical practice ABVD patients would be treated with a PET-adapted approach, allowing for those with a PET positive or negative scan to have their treatment escalated or de-

escalated respectively; ABVD treatment effects were derived from the ECHELON-1 trial which administered ABVD using a six-cycle approach. While RATHL concluded that de-escalated ABVD (AVD) was non-inferior to six-cycle ABVD, the EAG's clinical experts stated that escalated ABVD (escBEACOPDac) may be more effective than ABVD in PET-positive patients, given patients can be considered unresponsive to ABVD treatment. As such, the EAG considers that the ABVD treatment effect may be underestimated in the model when considering PET-positive patients, noting that 9% of ABVD patients were PET-positive in the ECHELON-1 trial.

With respect to the company's approach to survival modelling, the EAG considers that the company's modelling of progression free survival using a mixed cure model (MCM) is appropriate and robust, given the maturity of the data, that cure is well established in the clinical community, and that ECHELON-1 appears to support a cure fraction assumption. The EAG is therefore critically concerned with the company's use of a spline model to extrapolate the overall survival trial data given the additional modelling assumptions required for the spline model which can lead to bias and over fitting of curves. The company justifies their approach by stating that some of the MCM distributions provided implausible cure fractions under probabilistic conditions; however, the EAG considers that there are suitable and appropriate MCM distributions which should be preferred.

Finally, the EAG was critically concerned with the omission of peripheral neuropathy from the model given its identification as an adverse event of special interest in A+AVD treatment. Its exclusion was due to no single type of grade ≥3 peripheral neuropathy effecting patients ≥5% individually; however, when considered as a group, peripheral neuropathy incidence in A+AVD patient surpassed 10%. When peripheral neuropathy was considered by the company in a scenario analysis, only patients whose neuropathy resolved over time were accounted for with the EAG noting that a proportion of patients still experienced peripheral neuropathy at last follow-up (median follow up after end of treatment for A+AVD patients was [redacted] and [redacted] for ABVD patients). Given feedback from the EAGs clinical experts and the maturity of the data, those with unresolved peripheral neuropathy may have potentially lifelong symptoms which is critically not accounted for in the company's base case.

7 References

1. National Institute for Health and Care Excellence. Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including Review of TA594): Final scope, 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11384/documents/final-scope. Date accessed: 12 June 2024.
2. Cancer Research UK. What is Hodgkin lymphoma? 2020.
3. Singh D, Vaccarella S, Gini A, De Paula Silva N, Steliarova-Foucher E, Bray F. Global patterns of Hodgkin lymphoma incidence and mortality in 2020 and a prediction of the future burden in 2040. *International Journal of Cancer* 2022; **150**: 1941-7.
4. Shanbhag S, Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. *CA: a cancer journal for clinicians* 2018; **68**: 116-32.
5. Kaseb H, Babiker HM. *Hodgkin Lymphoma.* Hodgkin Lymphoma: StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499969/; 2023.
6. Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop-Evans E, et al. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. *British Journal of Haematology* 2022; **197**: 558-72.
7. Takeda. Data on file: Virtual advisory board. 2024 2024/01//. Report No.
8. Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, Carella A, et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *New England Journal of Medicine* 2016; **374**: 2419-29.
9. Borchmann P, Goergen H, Kobe C, Lohri A, Greil R, Eichenauer DA, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *The Lancet* 2017; **390**: 2790-802.
10. Casasnovas RO, Bouabdallah R, Brice P, Lazarovici J, Ghesquieres H, Stamatoullas A, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol* 2019; **20**: 202-15.
11. Nice. TA772 public committee slides. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies. Available at: https://www.nice.org.uk/guidance/ta772/documents/1 [last accessed: 10/03/2024]. 2021 2021. Report No.
12. Takeda. Data on file: medical advisory board. 2023 2023/12//. Report No.
13. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma. 2018.
14. Cancer Research UK. Hodgkin lymphoma statistics.
15. Rafiq M, Hayward A, Warren-Gash C, Denaxas S, Gonzalez-Izquierdo A, Lyratzopoulos G, et al. Socioeconomic deprivation and regional variation in Hodgkin's lymphoma incidence in the UK: a population-based cohort study of 10 million individuals. *BMJ open* 2019; **9**: e029228.
16. Cancer Research UKCI. Proportion Diagnosed by Stage (stacked chart). 2023.
17. Luminari S, Fossa A, Trotman J, Molin D, d'Amore F, Enblad G, et al. Long-Term Follow-Up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma Trial. *Journal of Clinical Oncology* 2024; **42**: 13-8.
18. Donato EM, Fernández-Zarzoso M, Hueso JA, de la Rubia J. Brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma: an evidence-based review. *OncoTargets and Therapy* 2018; **11**: 4583-90.
19. Schönberger S, van Beekum C, Götz B, Nettersheim D, Schorle H, Schneider DT, et al. Brentuximab vedotin exerts profound antiproliferative and pro-apoptotic efficacy in CD30-positive as

well as cocultured CD30-negative germ cell tumour cell lines. *Journal of Cellular and Molecular Medicine* 2018; **22**: 568-75.
20. Emc. Adcetris 50 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC). 2023.
21. Straus D, Collins G, Walewski J, Zinzani PL, Grigg A, Sureda A, et al. Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy. *Leukemia & Lymphoma* 2020; **61**: 2931-8.
22. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma | Addendum 3 - March 2024. 2024.
23. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
24. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health and Quality of Life Outcomes* 2007; **5**: 70.
25. Janssen MF, Pickard AS, Shaw JW. General population normative data for the EQ-5D-3L in the five largest European economies. *The European Journal of Health Economics* 2021; **22**: 1467-75.
26. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents). *NICE Decision Support Unit* 2016; **18**.
27. pCodr Expert Review Committee. Seattle Genetics Inc submission. For the treatment of previously untreated patients with stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine. FINAL RECOMMENDATION. 2020.
28. Brandt J, Dietrich S, Meissner J, Neben K, Ho AD, Witzens-Harig M. Quality of life of long-term survivors with Hodgkin lymphoma after high-dose chemotherapy, autologous stem cell transplantation, and conventional chemotherapy. *Leukemia & Lymphoma* 2010; **51**: 2012-20.
29. Ramchandren R, Advani RH, Ansell SM, Bartlett NL, Chen R, Connors JM, et al. Brentuximab Vedotin plus Chemotherapy in North American Subjects with Newly Diagnosed Stage III or IV Hodgkin Lymphoma. *Clinical Cancer Research* 2019; **25**: 1718-26.
30. Straus DJ, Długosz-Danecka M, Connors JM, Alekseev S, Illés Á, Picardi M, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *The Lancet Haematology* 2021; **8**: e410-e21.
31. Brazier J, Longworth L. NICE DSU Technical Support Document 8: an introduction to the measurement and valuation of health for NICE submissions. 2011.
32. Palmer S, Borget I, Friede T, Husereau D, Karnon J, Kearns B, et al. A guide to selecting flexible survival models to inform economic evaluations of cancer immunotherapies. *Value in Health* 2023; **26**: 185-92.
33. Office for National S. National life tables: UK. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. [Last accessed: 05/02/3034].
34. Nice. TA641: Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma. 2020.
35. Nice. TA874: Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta874/ [last accessed: 09/01/2024]. 2023 2023/03/01/. Report No.
36. Nice. TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta872/ [last accessed: 09/01/2024]. 2023 2023/02/28/. Report No.

37. Nice. TA677: Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta677/ [last accessed: 09/01/2024]. 2021 2021/02/24/. Report No.
38. Nice. TA567: Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta567/ [last accessed: 09/01/2024]. 2019 2019/03/13/. Report No.
39. Glimelius I, Ekberg S, Linderoth J, Jerkeman M, Chang ET, Neovius M, et al. Sick leave and disability pension in Hodgkin lymphoma survivors by stage, treatment, and follow-up time—a population-based comparative study. *Journal of cancer survivorship* 2015; **9**: 599-609.
40. Ramos-Cillan S, Castillo E, Riesco M, Herroro A, Pascual A, Lopez-Garcia A, et al. P079: PROCTCAE as a patient-reported outcome measurement (PROM) questionaire in patients with Hodgkin Lymphoma captures different adverse events profile than those reported by physicians. *HemaSphere* 2022; **6**: 36.
41. Dores GM, Curtis RE, Dalal NH, Linet MS, Morton LM. Cause-Specific Mortality Following Initial Chemotherapy in a Population-Based Cohort of Patients With Classical Hodgkin Lymphoma, 2000-2016. *Journal of Clinical Oncology* 2020; **38**: 4149-62.
42. Perez-Callejo D, Zurutuza L, Royuela A, Torrente M, Nunez B, Calvo V, et al. Long-term follow up of Hodgkin lymphoma. *Oncotarget* 2018; **9**: 11638-45.
43. Alava MH, Pudney S, Wailoo A. ESTIMATING EQ-5D BY AGE AND SEX FOR THE UK. 2022.
44. Dolan P. Modeling valuations for EuroQol health states. *Medical care* 1997: 1095-108.
45. Nice. TA478: Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma. 2017.
46. Nice. TA524: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 2018.
47. Nice. TA577: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma. 2019.
48. Nice. TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 2014.
49. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2008; **62**: 374-80.
50. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006; **95**: 683-90.
51. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008; **6**: 84.
52. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leuk Lymphoma* 2015; **56**: 1839-45.
53. Ansell SM, Radford J, Connors JM, Długosz-Danecka M, Kim W-S, Gallamini A, et al. Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. *The New England Journal of Medicine* 2022; **387**: 310-20.
54. N. H. S. England. 2021/22 National Cost Collection Data Publication (2023). Accessed at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. Last accessed on: 09/01/2024. 2023.
55. Jones, et al. Unit Costs of Health and Social Care 2022 Manual. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York).
56. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab Vedotin Plus Doxorubicin, Vinblastine, Dacarbazine (A+AVD) As Frontline Therapy Demonstrates Superior Modified Progression-Free Survival Versus ABVD in Patients with Previously Untreated Stage III or IV Hodgkin Lymphoma (HL): The Phase 3 Echelon-1 Study. *Blood* 2017; **130**: 6.
57. N. H. S. Kent & Medway Cancer Collaborative. ABVD. 2023.

58. N. H. S. Northern Cancer Alliance. Escalated BEACOPDAC for Hodgkin's lymphoma.
59. N. H. S. South West Clinical Network. BEACOPDac-14/ EscalatedBEACOPDac.
60. N. H. S. South West Clinical Network. ABVD. 2020.
61. N. H. S. Thames Valley Strategic Clinical Network. ABVD.
62. N. H. S. Thames Valley Strategic Clinical Network. BEACOPDac - Escalated.
63. N. H. S. The Christie. Escalated BEACOPDac in Hodgkin lymphoma.
64. N. H. S. The Clatterbridge Cancer Centre. Escalated BEACOPDac High Grade Hodgkin Lymphoma.
65. N. H. S. The Clatterbridge Cancer Centre. ABVD. Hodgkin's Lymphoma. 2022.
66. N. H. S. The Royal Marsden. ABVD chemotherapy for Hodgkin lymphoma. 2020.
67. N. H. S. University Hospital Southampton. BLEOMYCIN-CYCLOPHOSPHAMIDE-DACARBAZINE-DOXORUBICIN-ETOPOSIDEPREDNISOLONE-VINCRISTINE (BEACOPDac Escalated).
68. N. H. S. University Hospital Southampton. BLEOMYCIN-DACARBAZINE-DOXORUBICIN-VINBLASTINE (ABVD). 2015.
69. NHS Cumbria NTWAT. ABVD (Hodgkin's Lymphoma). 2014.
70. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2023.
71. Nice. British National Formulary (BNF). 2023.
72. EMC. Neupogen 30 MU (0.3 mg/ml) solution for injection.
73. Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 2018; **29**: iv19-iv29.
74. Nice. TA446: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. 2017.
75. Nice. TA462: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. 2017.
76. N. H. S. Blood and Transplant. Price List 2023/24. NHS. Blood and Components - Contract Equivalent Cost per Item.
77. Armand P, Zinzani PL, Lee HJ, Johnson NA, Brice P, Radford J, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. *Blood* 2023; **142**: 878-86.
78. EMC. OPDIVO 10 mg/mL concentrate for solution for infusion. 2024.
79. NICE. NICE health technology evaluations: the manual (process and methods). Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 [Last accessed: August 2023]. 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Date accessed: 31 August 2023.
80. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ: British Medical Journal* 1996; **313**: 275.
81. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health technology assessment (Winchester, England)* 2004; **8**: iii-iv.
82. Büyükkaramikli NC, Rutten-van Mölken MPMH, Severens JL, Al M. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. *Pharmacoeconomics* 2019; **37**: 1391-408.

8 Appendices

8.1 Baseline characteristics for ECHELON-1 and RATHL

Table 75. Baseline characteristics from ECHELON-1 (ITT) and RATHL (Stage III and IV subgroup) (reproduced from CS appendices, Table 39)

Characteristic	ECHELON-1			RATHL Stage III&IV	SMD RATHL vs. A+AVD
	A+AVD	ABVD	Total		
Patients randomised – n‡	664	670	1,334	[redacted]	[redacted]
Age – Mean (SD)§	38.8 (15.8)	40.2 (16.1)	39.5 (15.9)	[redacted]	[redacted]
Age – n (%) ≤60 years >60 years	 585 (88.1) 79 (11.9)	 579 (86.4) 91 (13.6)	 1,164 (87.3) 170 (12.7)	[redacted]	[redacted]
Cancer stage n (%) Stage II Stage III Stage IV Missing	 0 237 (35.8) 425 (64.2) 2	 0 246 (36.9) 421 (63.1) 3	 0 483 (36.3) 846 (63.7) 5	[redacted]	[redacted]
Sex – n (%) Male Female	 378 (56.9) 286 (43.1)	 398 (59.4) 272 (40.6)	 776 (58.2) 558 (41.8)	[redacted]	[redacted]
Performance status – n (%)** 0 1 2 3 Missing ≥1	 376 (56.6) 260 (39.2) 28 (4.2) 0 0 288 (43.4)	 378 (56.6) 263 (39.4) 27 (4.0) 0 2 290 (43.4)	 754 (56.6) 523 (39.3) 55 (4.1) 0 2 578 (43.4)	[redacted]	[redacted]
B symptoms – n (%) Present Absent	 400 (60.2) 264 (39.8)	 381 (56.9) 289 (43.1)	 781 (58.5) 553 (41.5)	[redacted]	[redacted]
Number of IPS factors – n (%) 0–2 3–7 Missing	 330 (49.7) 334 (50.3) 0	 321 (47.9) 349 (52.1) 0	 651 (48.8) 683 (51.2) 0	[redacted]	[redacted]

The data presented for the Stage III or IV subgroup in RATHL include all eligible patients, regardless of PET adaptation. SMD was used to describe imbalances in patient characteristics between ECHELON-1 (the index study) and RATHL (the comparator study). SMD of 0.1 denoted meaningful imbalances in the patient characteristics. In the current assessment, an SMD between 0.1 and 0.25 was considered as moderate difference, and an SMD more than 0.25 was considered as substantial difference.

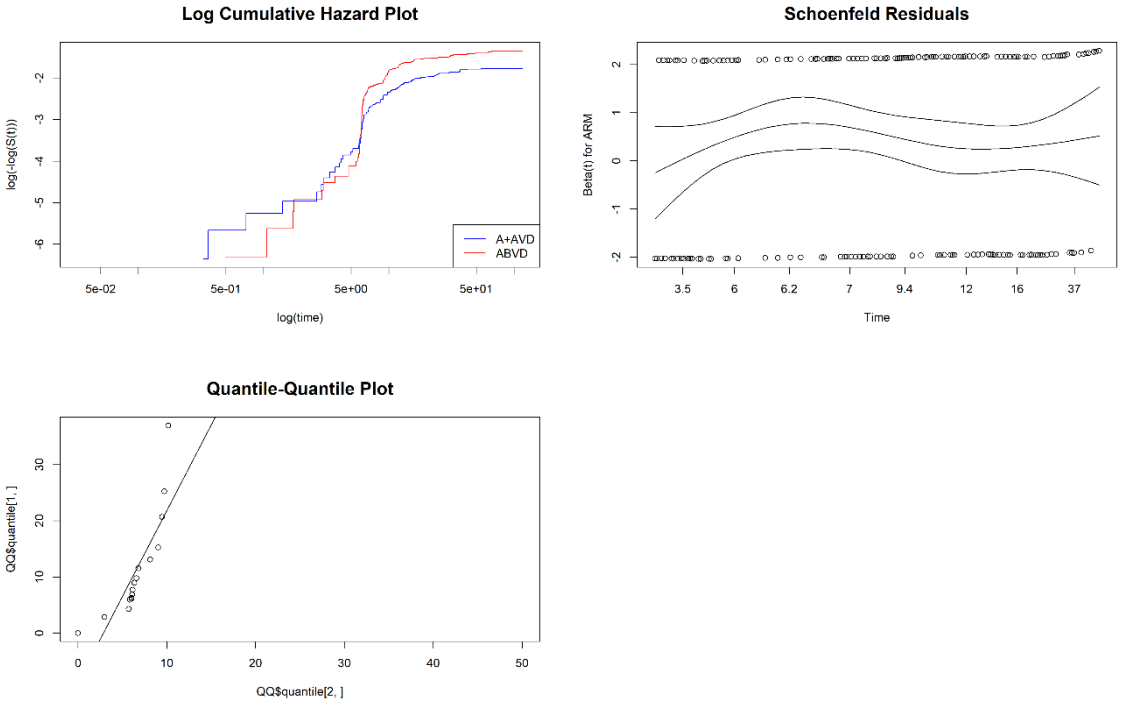
*The use of granulocyte colony-stimulating factor (G-CSF) was permitted, as per SmPC; †In RATHL, PET2-negative was defined as Deauville score 1–3 and PET2-positive was defined as Deauville score 4–5; ‡In RATHL, only patients with PET2-negative findings were randomised 1:1 to receive ABVD or AVD, following the first two cycles of ABVD; §Mean age for RATHL was reported for all patients in Stage III and IV; **ECOG performance status was reported for ECHELON-1 and

WHO performance status was reported for RATHL. However, both statuses were defined identically and can, therefore, be interpreted in the same way: 0, fully active, able to carry on all pre-disease performance without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2, ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; 3, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; 4, completely disabled; cannot carry on any selfcare; totally confined to bed or chair; 5, dead.
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AVD, doxorubicin, vinblastine, dacarbazine; BEACOPP-14, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone in 14-day cycle; escBEACOPP, escalated dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; G-CSF, granulocyte colony-stimulating factor; IQR, interquartile range; N, number; PET2, positron emission tomography after cycle 2; SMD, standardised mean difference; SmPC, summary of product characteristics.
Sources: Takeda ECHELON-1 CSR (2018); Luminari *et al,*(2023)

8.2 Mixed cure model extrapolation and fit statistics

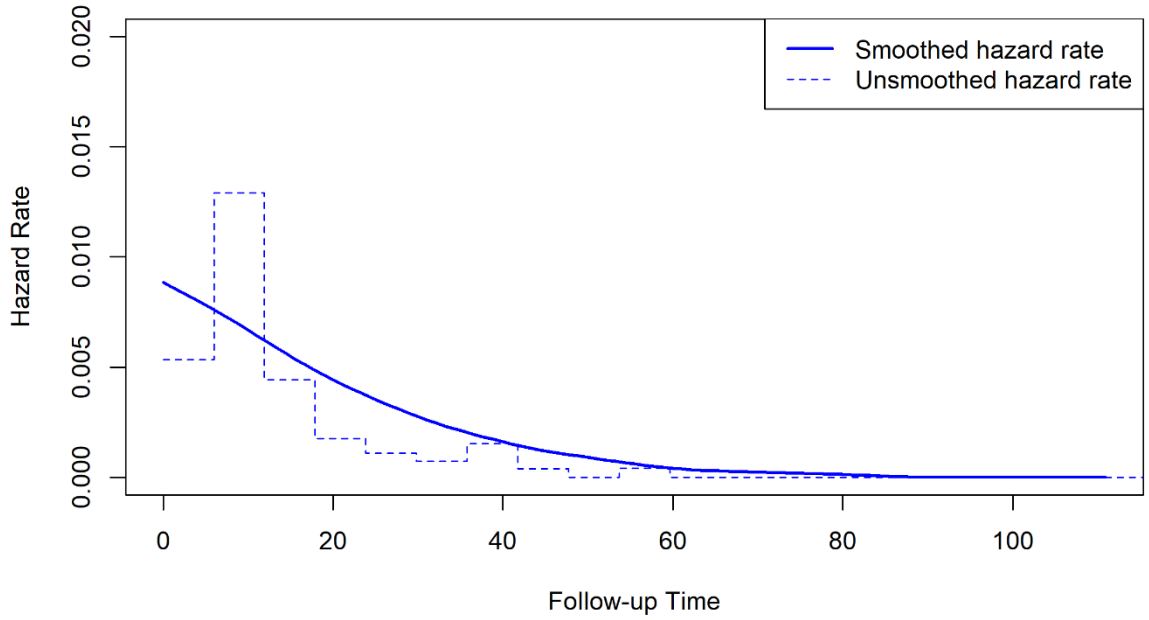
8.2.1 Age subgroup <60 years

Figure 39: PFS proportional hazards and accelerated failure time tests (reproduced from Figure 43 in the clarification response)



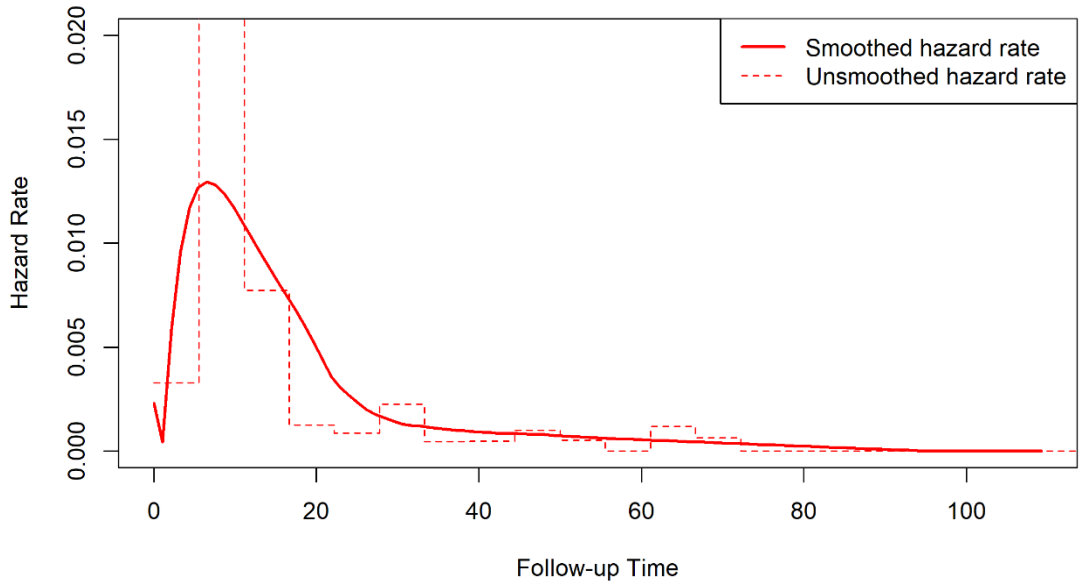
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 40: Observed hazards | A+AVD | PFS per INV (reproduced from Figure 44 in the clarification response)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

Figure 41: Observed hazards | ABVD | PFS per INV (reproduced from Figure 45 in the clarification response)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 42: PFS independent MCM parametric models | A+AVD (reproduced from Figure 50 in the company clarification response)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 76: PFS independent MCM parametric models AIC and BIC values (reproduced from Table 61 in the clarification response)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1094	7	1103	4
MCM: Weibull	1087	4	1101	3
MCM: Lognormal	1091	5	1104	6
MCM: Loglogistic	1080	1	1093	1
MCM: Gompertz	1094	6	1107	7
MCM: Generalised Gamma	1086	3	1103	5
MCM: Gamma	1085	2	1098	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 43: PFS independent MCM parametric models | ABVD (reproduced from Figure 52 in the clarification response)

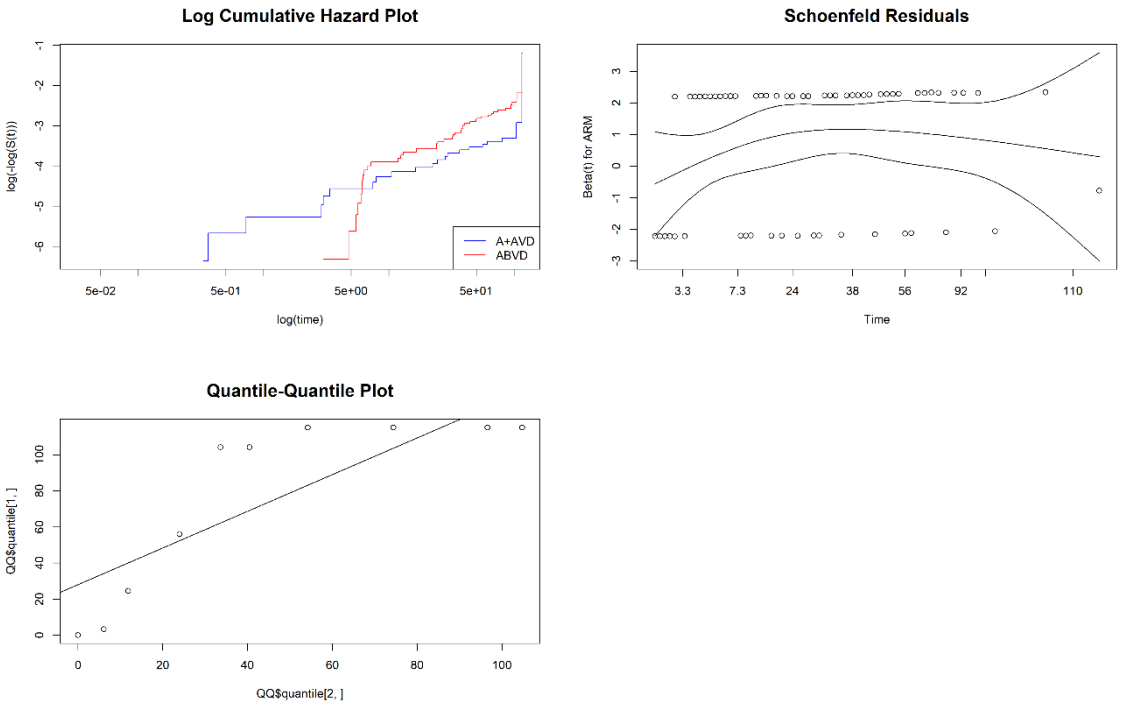
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 77: PFS independent MCM parametric models AIC and BIC values | ABVD (reproduced from Table 62 in the clarification response)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	1439	6	1448	6
MCM: Weibull	1433	5	1446	5
MCM: Lognormal	1399	2	1412	2
MCM: Loglogistic	1386	1	1399	1
MCM: Gompertz	1441	7	1454	7
MCM: Generalised Gamma	1401	3	1418	3
MCM: Gamma	1422	4	1435	4

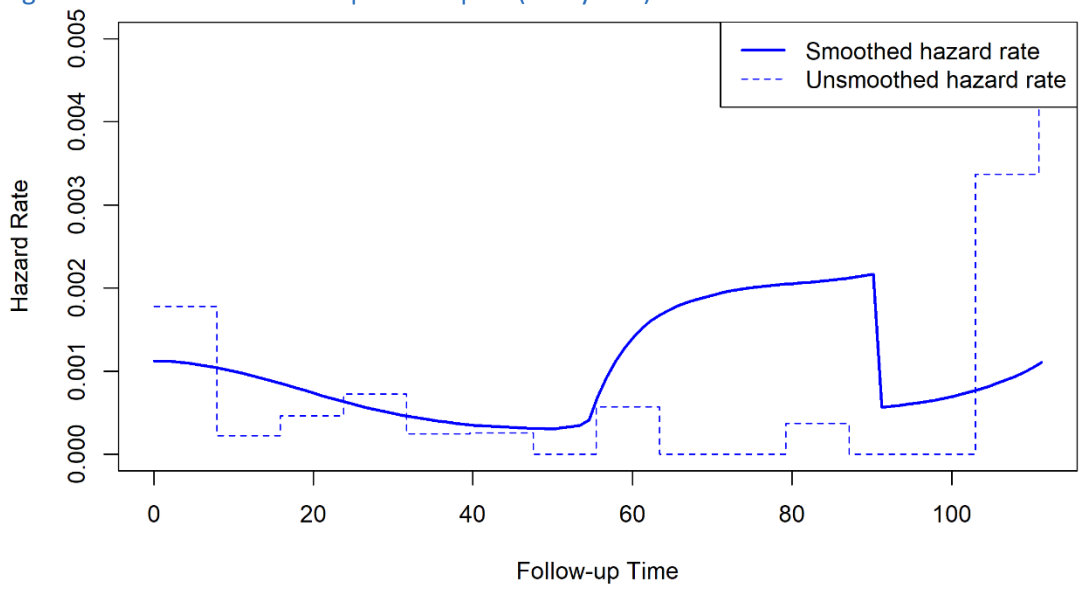
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 44: OS proportional hazards and accelerated failure time tests (<60-years)



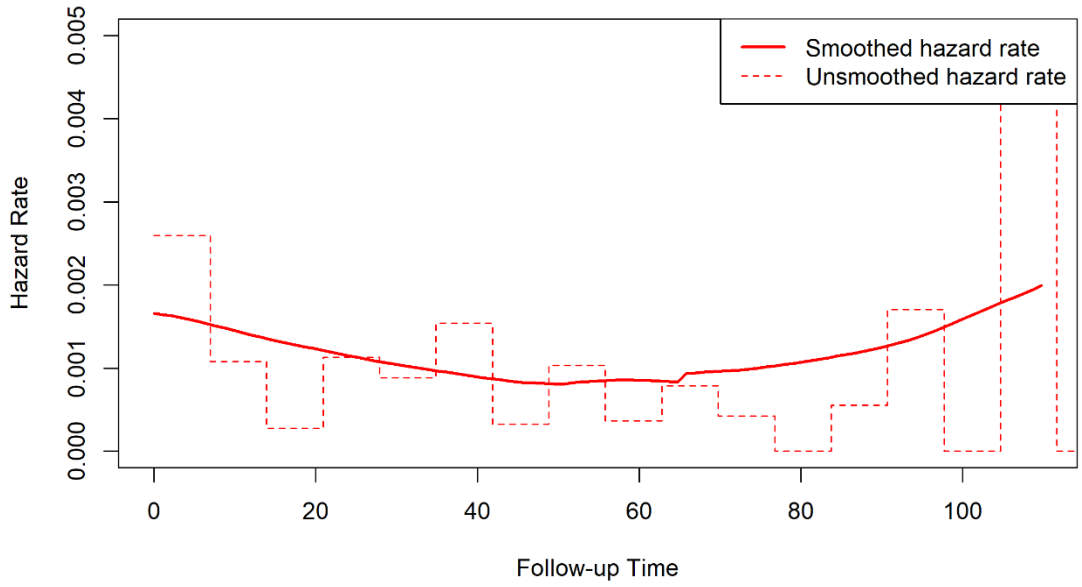
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival.

Figure 45: Observed hazards | A+AVD | OS (<60-years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 46: Observed hazards | ABVD | OS (<60-years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 47: OS independent MCM parametric models | A+AVD (<60-years)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 78: OS independent MCM parametric models AIC and BIC values | A+AVD (<60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	363	6	372	4

MCM: Weibull	359	3	372	3
MCM: Lognormal	359	1	372	1
MCM: Loglogistic	359	4	372	5
MCM: Gompertz	364	7	377	6
MCM: Generalised Gamma	361	5	378	7
MCM: Gamma	359	2	372	2

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 48: OS independent MCM parametric models | ABVD (<60-years)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 79: OS independent MCM parametric models AIC and BIC values | ABVD (<60-years)

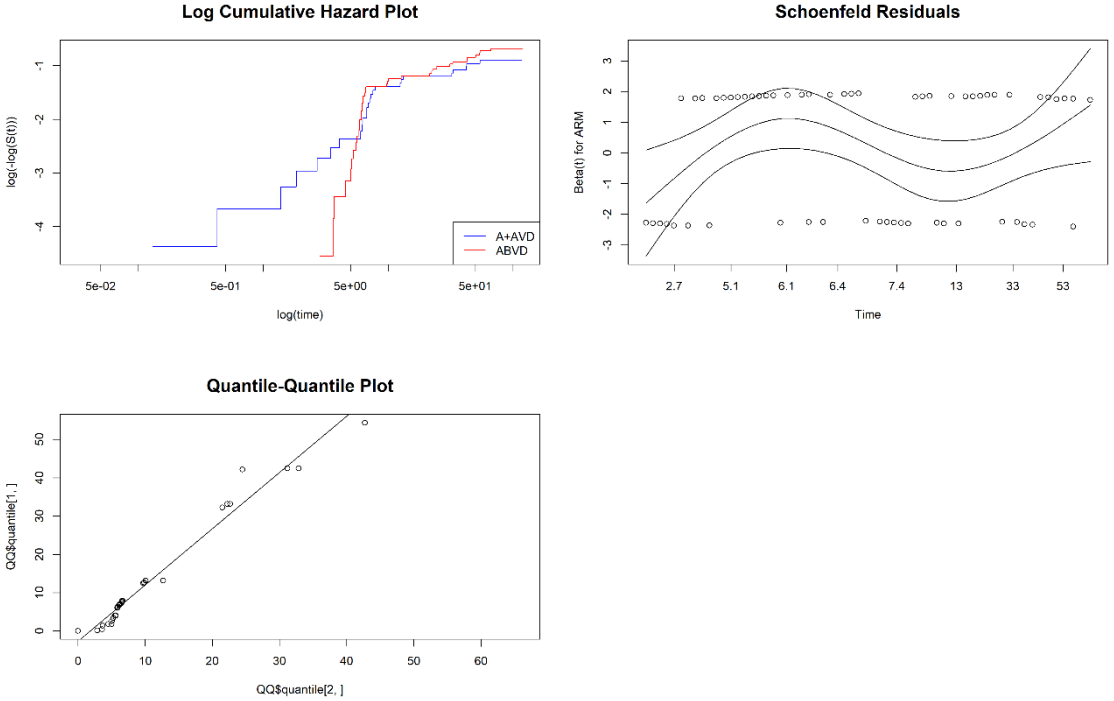
	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	621	3	630	1
MCM: Weibull	623	6	636	5
MCM: Lognormal	621	1	634	2

MCM: Loglogistic	623	4	636	3
MCM: Gompertz	623	5	636	4
MCM: Generalised Gamma	621	2	638	7
MCM: Gamma	623	7	636	6

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

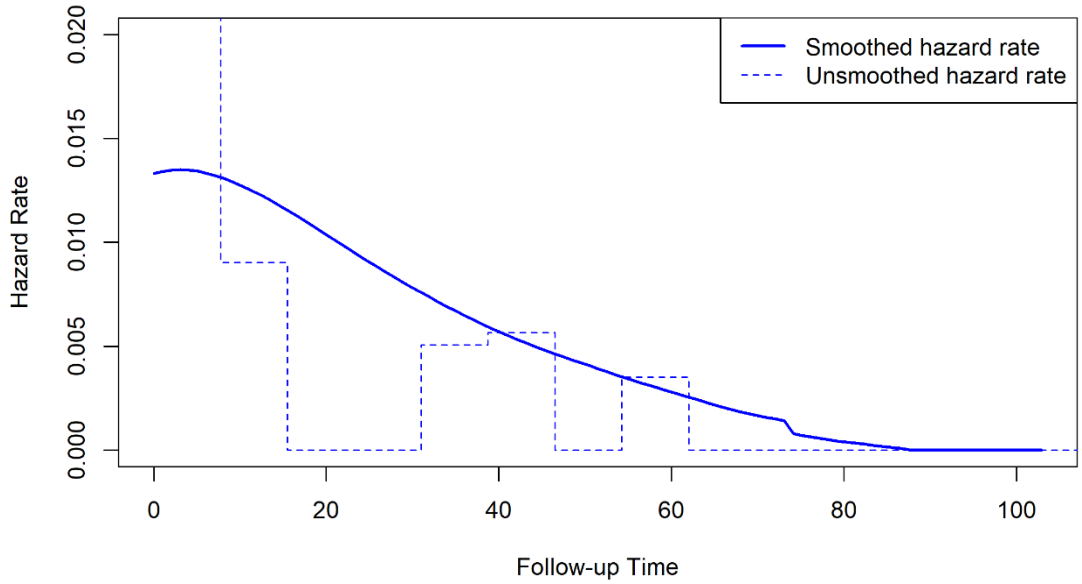
8.2.2 Age subgroup ≥60 years

Figure 49: PFS proportional hazards and accelerated failure time tests (≥60 years)



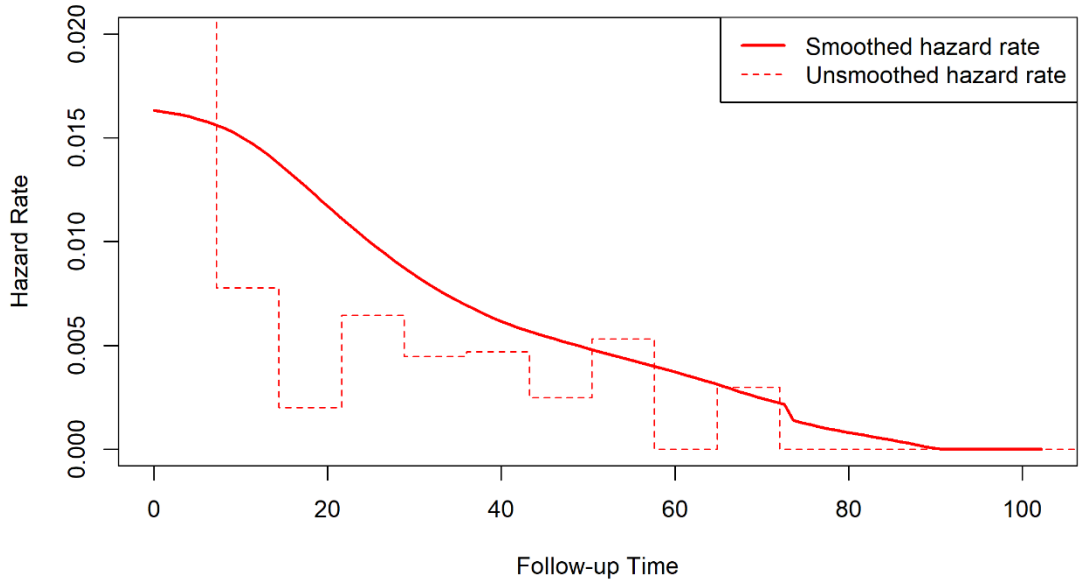
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 50: Observed hazards | A+AVD | PFS per INV (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival

Figure 51: Observed hazards | ABVD | PFS per INV (≥60 years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; PFS, progression-free survival.

Figure 52: PFS independent MCM parametric models | A+AVD (≥60 years)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 80: PFS independent MCM parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	278	1	283	1
MCM: Weibull	279	4	286	4
MCM: Lognormal	280	6	287	6
MCM: Loglogistic	278	2	285	2
MCM: Gompertz	278	3	286	3
MCM: Generalised Gamma	281	7	290	7
MCM: Gamma	279	5	287	5

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 53: PFS independent MCM parametric models | ABVD (≥60 years)

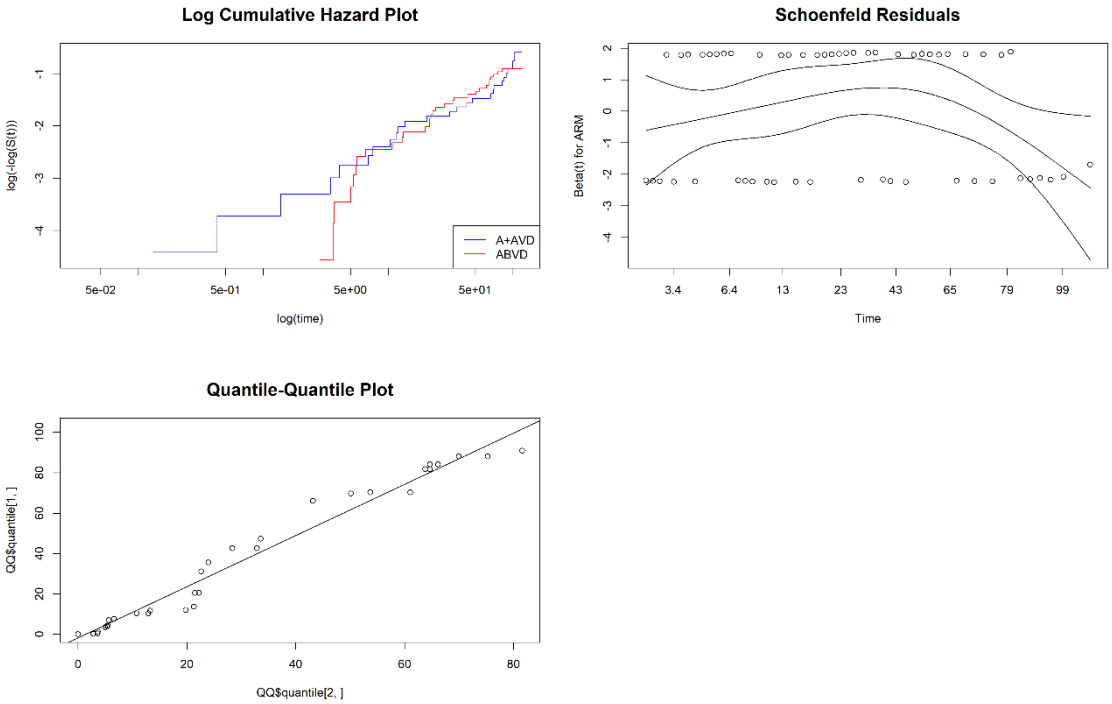
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 81: PFS independent MCM parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	412	4	417	4
MCM: Weibull	414	7	422	7
MCM: Lognormal	404	2	412	2
MCM: Loglogistic	406	3	414	3
MCM: Gompertz	413	6	421	6
MCM: Generalised Gamma	392	1	403	1
MCM: Gamma	413	5	421	5

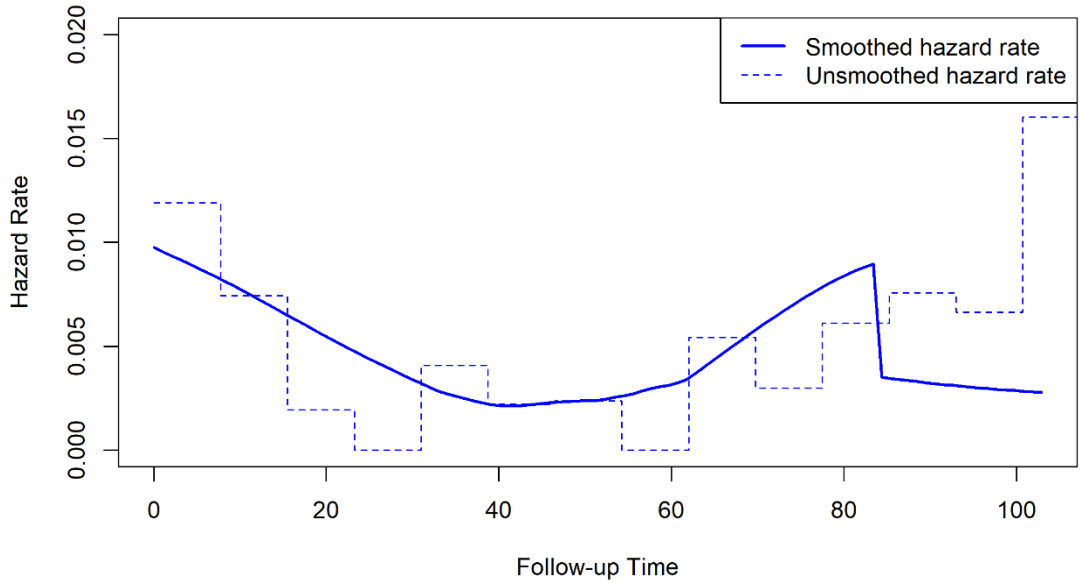
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; PFS, progression-free survival

Figure 54: OS proportional hazards and accelerated failure time tests (≥60 years)



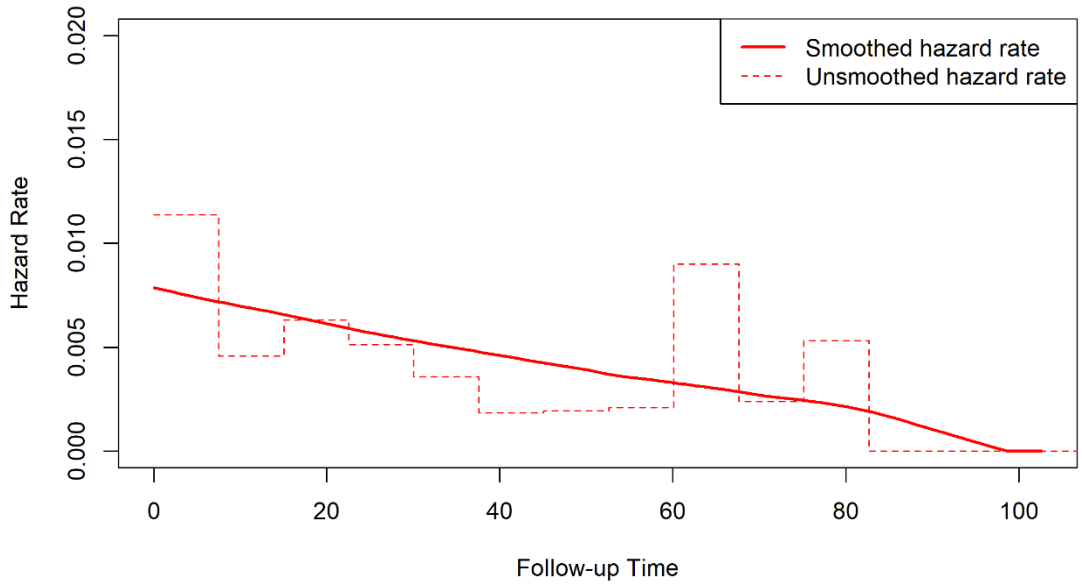
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival.

Figure 55: Observed hazards | A+AVD | OS (≥60 years)



Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 56: Observed hazards | ABVD | OS (≥60 years)



Abbreviations ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; INV, investigator; OS, overall survival

Figure 57: OS independent MCM parametric models | A+AVD (≥60 years)

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 82: OS independent MCM parametric models AIC and BIC values | A+AVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)

MCM: Exponential	323	6	328	3
MCM: Weibull	320	2	327	2
MCM: Lognormal	323	5	330	5
MCM: Loglogistic	321	3	328	4
MCM: Gompertz	325	7	332	7
MCM: Generalised Gamma	321	4	331	6
MCM: Gamma	320	1	327	1

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

Figure 58: OS independent MCM parametric models | ABVD (≥60 years)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival

Table 83: OS independent MCM parametric models AIC and BIC values | ABVD (≥60 years)

	AIC	Rank (AIC)	BIC	Rank (BIC)
MCM: Exponential	382	1	387	1

MCM: Weibull	384	7	392	6
MCM: Lognormal	382	2	390	2
MCM: Loglogistic	383	4	391	3
MCM: Gompertz	384	5	392	4
MCM: Generalised Gamma	383	3	393	7
MCM: Gamma	384	6	392	5

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; MCM, mixture cure model; OS, overall survival

8.3 Price sources for treatments included in the confidential appendix

Table 84. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Brentuximab vedotin	Simple PAS
Bleomycin	CMU price
Filgrastim	CMU price
Nivolumab	PAS
Pembrolizumab	CAA

Abbreviations: CAA, commercial access agreement; CMU, confidential medicines unit.

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

Addendum response

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 166073.

1 Introduction

In response to the External Assessment Group's (EAG's) single technology appraisal (STA) report evaluating the cost effectiveness of brentuximab vedotin with doxorubicin, dacarbazine and vinblastine (A+AVD) for previously untreated late-stage classical Hodgkin lymphoma the company has submitted an addendum to help address the key issues raised by the EAG.

In this report, the EAG evaluates and discusses the additional evidence and analysis provided by the company in the context of three key issues; namely, that the EAG considers that the clinical data for ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is not reflective of current standard care in UK clinical practice, that the age bimodal patient population is not accounted for in the model and lastly the exclusion of life-long peripheral neuropathy in the model.

2 EAG key issues

2.1 The clinical data for ABVD is not reflective of current standard care in UK clinical practice

The company used clinical efficacy data for six-cycle ABVD from the ECHELON-1 trial[1] to inform ABVD-based treatment in the economic model and assumed equal clinical efficacy between six-cycle and positron emission tomography (PET)-adapted ABVD. The company considered that the assumption of equal efficacy between ABVD-based treatments was supported by matching-adjusted indirect comparisons (MAICs), informed by data on PET-adapted ABVD from the Response-Adapted Therapy for advanced Hodgkin Lymphoma (RATHL)[2] trial.

The EAG lists below the company's key concerns, namely;

- outcomes for PET after cycle 2 (PET2)-positive patients who escalate treatment in the company MAICs;
- the face validity of results of the MAIC comparing six cycles of ABVD from ECHELON-1 versus PET-adapted ABVD from RATHL; and
- the proportional hazards assumption.

2.1.1 EAG critique

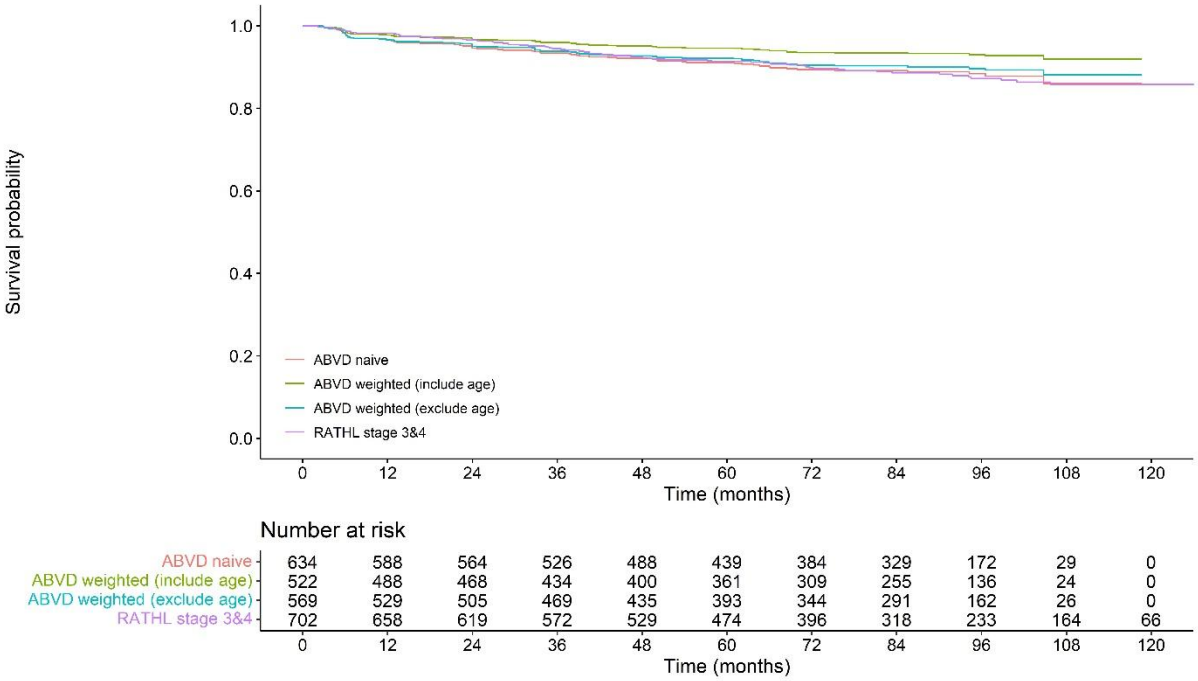
After reviewing the company's comments in the factual accuracy check (FAC), the EAG agreed that the RATHL data used in the company's MAICs included both patients who are de-escalated following

a negative PET2 scan as well as those whose treatment is escalated following a positive PET2 scan and made changes in the EAG report to reflect this. However, the EAG still considers the clinical efficacy of A+AVD versus PET-adapted ABVD to be uncertain.

In the company addendum, the company reported that they consider the results of the fully adjusted, unanchored MAIC comparing six-cycles of ABVD from ECHELON-1 vs PET-adapted ABVD from RATHL (adjusting for age, IPS, ECOG, stage, sex, B-symptoms, bulky disease and presence of extra-nodal sites [presented in the company response to clarification questions]), to be driven by matching on the age variable, similar to the MAIC presented in the company submission. The company noted that the RATHL population is younger than the ABVD (six cycles) arm of ECHELON-1, with a mean age of [redacted] and 40.2 years, respectively. In the addendum, the company have conducted a further MAIC removing adjustment for age but still adjusting for IPS, ECOG, stage, sex, B-symptoms, bulky disease and presence of extra-nodal sites (i.e. adjusting for all available baseline characteristics, excluding age) using six cycle ABVD data from ECHELON-1 and PET-adapted ABVD from the Stage III and IV subgroup of the RATHL trial.

The company presented the results of MAIC analyses for the outcomes of OS and PFS in the addendum (reproduced below as Figure 1 &Table 1 [OS], and Figure 2 & Table 2 [PFS]). The company considered that the removal of the adjustment for age from the fully adjusted MAICs resulted in the weighted ABVD (six cycles; ECHELON-1) and PET-adapted ABVD (RATHL) Kaplan–Meier curves appearing similar and overlapping at multiple timepoints and, that compared to the analysis matching on all baseline characteristics including age, there is no longer a visible difference between treatment arms (Figure 1).

Figure 1. Unweighted and weighted OS data for ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics, and adjusting for all baseline characteristics excluding age, for the MAIC analyses (Reproduced from company addendum Figure 1)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matching-adjusted indirect comparison; OS, overall survival; PET, positron emission tomography; RATHL, response-adapted trial.

The EAG notes that for OS, the relative efficacy of ABVD (six-cycles) compared to PET-adapted ABVD (RATHL) is associated with a HR of 0.88 (95% CI: 0.61 to 1.27, p=0.490) when excluding adjustment for age, whereas the fully adjusted MAIC was associated with a HR of 0.59 (95% CI: 0.40 to 0.85, p=0.005) (Table 1).

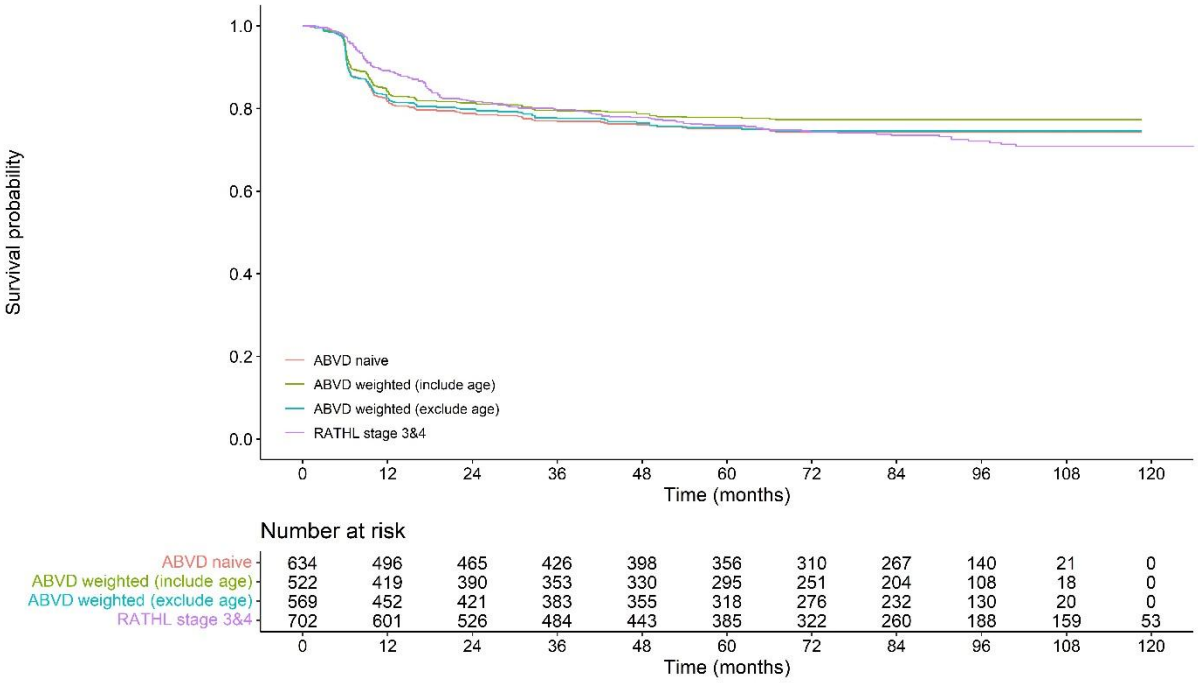
Table 1. Results of the ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL) MAIC analyses for OS, including analyses previously presented and new analysis matching based on all baseline characteristics, excluding age (Reproduced from company addendum Table 2)

Variables matched	Analysis	ESS	HR (95% CI)	Log rank p-value
Age + IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.02 (0.73 to 1.42)	0.987
	Weighted	553.22 (82.8%)	0.63 (0.44 to 0.89)	0.010
IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.02 (0.73 to 1.42)	0.909
	Weighted	619.42 (92.7%)	0.88 (0.62 to 1.23)	0.443
All baseline characteristics (response to EAG clarification questions)	Unweighted	634 (100.0%) ‡	1.00 (0.71 to 1.40)	0.996
	Weighted	441.72 (69.7%)	0.59 (0.40 to 0.85)	0.005
All baseline characteristics excluding age (new analysis)	Unweighted	634 (100.0%) ‡	1.00 (0.71 to 1.40)	0.071
	Weighted	512.74 (80.9%)	0.88 (0.61 to 1.27)	0.490

[†]2 patients from ABVD arm of ECHELON-1 who did not have ECOG information were excluded from the analysis. [‡] 36 patients from ABVD arm of ECHELON-1 who did not have stage, ECOG, bulky disease, or extranodal site information were excluded from the analysis.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IPS, International Prognostic Score; MAIC, matching-adjusted indirect comparison; OS, overall survival; PET, positron emission tomography; RATHL, response-adapted trial.

The results of the MAIC comparing ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL Stage III/IV subgroup), for PFS adjusting for all available baseline characteristics, excluding age are presented in Figure 2 and Table 2, respectively. The company consider that when age is excluded from the MAIC, the Kaplan-Meier curves appear to be similar and overlap at multiple timepoints, and the PFS HR is closer to one than the MAIC where age is adjusted for (1.01, 95% CI: 0.80 to 1.27, p=0.960).

Figure 2. Unweighted and weighted PFS data for ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL Stage III/IV subgroup) adjusting for all baseline characteristics, and adjusting for all baseline characteristics excluding age, for the MAIC analyses (Reproduced from company addendum Figure 2)



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MAIC, matching-adjusted indirect comparison; PET, positron emission tomography; PFS, progression-free survival; RATHL, response-adapted trial.

Table 2. Results of the ABVD (six cycles; ECHELON-1) vs PET-adapted ABVD (RATHL) MAIC analyses for PFS, including analyses previously presented and new analysis matching based on all baseline characteristics, excluding age (Reproduced from company addendum Table 3)

Variables matched	Analysis	ESS	HR (95% CI)	Log rank p-value

Age + IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.03 (0.83 to 1.27)	0.818
	Weighted	553.22 (82.8%)	0.92 (0.73 to 1.17)	0.505
IPS + ECOG (original Company submission)	Unweighted	668 (100.0%) †	1.02 (0.82 to 1.26)	0.878
	Weighted	619.42 (92.7%)	0.99 (0.79 to 1.24)	0.937
All baseline characteristics (response to EAG clarification questions)	Unweighted	634 (100.0%) ‡	1.03 (0.83 to 1.27)	0.818
	Weighted	441.72 (69.7%)	0.89 (0.70 to 1.13)	0.342
All baseline characteristics excluding age (new analysis)	Unweighted	634 (100.0%) ‡	1.03 (0.83 to 1.27)	0.818
	Weighted	512.74 (80.9%)	1.01 (0.80 to 1.27)	0.960

†2 patients from ABVD arm of ECHELON-1 who did not have ECOG information were excluded from the analysis. ‡ 36 patients from ABVD arm of ECHELON-1 who did not have stage, ECOG, bulky disease, or extranodal site information were excluded from the analysis.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IPS, International Prognostic Score; MAIC, matching-adjusted indirect comparison; PET, positron emission tomography; PFS, progression-free survival; RATHL, response-adapted trial.

The company reported that the results from these new MAICs where adjustment for age is removed, indicate that the results of the fully adjusted MAICs presented in the company's response to clarification questions were "driven by matching on the age variable, due to the RATHL population being younger than the ECHELON-1 population" and "When adjusting for all possible variables, including age, the company believes that the residual difference between the OS Kaplan-Meier curves for ABVD (six cycles) and PET-adapted ABVD specifically may be due to heterogeneity in treatment practices across regions." However, the EAG does not consider this to be sufficient justification for the removal of age from the MAICs and the EAG remains concerned about the face validity and generalisability of the findings from the MAIC analysis.

With regards to proportional hazards (PH), the EAG notes that the assumption of proportional hazards was shown not to hold in the MAICs where full adjustment for all baseline characteristics was made. If the method of calculating the reported HRs is dependent on PH holding, then the EAG considers that the reported HRs from the unanchored MAICs are potentially flawed and should be interpreted with caution.

The EAG agrees with the company that the most robust source of evidence for the comparison of A+AVD with ABVD is currently the ECHELON-1 trial, but the EAG is also concerned that the ABVD arm of ECHELON-1 comprises of six-cycle ABVD rather than the PET-adapted ABVD which is used in UK clinical practice.

2.2 The age bimodal patient population is not accounted for in the model

The EAG lists below the company's key concerns, namely;

- That subgroup analysis based on age would not impact the way that clinicians would treat patients considered suitable for ABVD. Therefore, assessing the cost-effectiveness based on age is not appropriate.
- That utilising age subgroup data breaks randomisation.
- There are fewer patients informing the subgroup analysis versus the intention to treat (ITT) analysis (1,334 patients; A+AVD, 664; ABVD, 670). For the age ≥60 years subgroup, data are available for 84 and 102 patients in the A+AVD and ABVD arms respectively.
- The EAG's preferred age weighted incremental cost-effectiveness ratio (ICER) still uses a mean age-based approach.
- The company considers the EAG's preferred approach may lead to the population subgroups being considered separately for decision-making.
- The EAG's preferred age weighted ICER has not fully characterised the uncertainty, instead it provides a deterministic and not probabilistic ICER.

In addition to raising these considerations, the company explored an alternative approach to addressing the bimodal patient population compared to the EAG's age-weighted ICER. The company conducted a probabilistic scenario analysis where instead of assuming a starting age in the model using the mean patient age and standard error as in the base case, age was instead sampled from the list of patients ages who participated in the study. The company's scenario led to an increase in the company's base case ICER from [redacted] to [redacted] and was found to be less than the EAG's age-weighted ICER scenario [redacted]

2.2.1 EAG critique

The EAG agrees with the company that a subgroup analysis based on age would not impact how patients suitable for ABVD would be treated; however, considers that this does not make the age-weighted ICER inappropriate. Both the company's and EAG's clinical experts have raised how late-stage classical Hodgkin lymphoma presents age bimodally, with incidence being highest earlier and later in life. The EAG therefore considers that it would be inappropriate to not account for the age bimodal population and assess the cost effectiveness uncertainties in these key populations.

The EAG also agrees with the company that the age subgroup analysis breaks randomisation. However, the EAG considers it crucial to account for the age bimodal patient population, as this allows the patient population to be more generalisable to patients in clinical practice. As such, the EAG considers that the additional uncertainty introduced by breaking randomisation is outweighed by the benefits of accounting for these distinct patient subgroups in the overall population; and that the uncertainty introduced due to assessing subgroups rather than the overall population may be adequately controlled for when generating probabilistic outcomes.

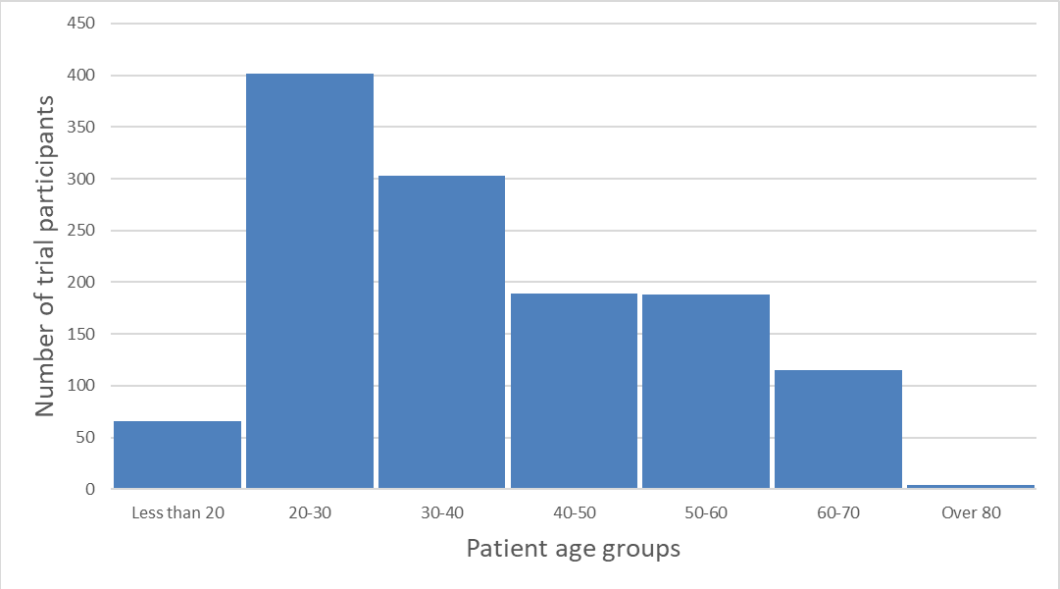
The EAG also agrees that the age weighted ICER uses a mean age-based approach. The EAG notes that the age weighted ICER utilises the mean ages within each subgroup of the age bimodal distribution of patients (34 and 68 years old for the <60 and ≥60-year-old subgroups respectively) rather than the overall mean age of the ITT population (39.5) which the EAG considers is less appropriate given the patient age distribution.

The company also raised concern on the separate reporting of the age subgroup cost-effectiveness outcomes. Considering that this may allow the outcomes to be interpreted separately by decision makers, leading to health inequities. As indicated in the EAG report, the EAG considers that the cost-effectiveness results for the individual subgroups should not be considered separately in decision making. It is the EAG's view that an age-weighted ICER, based on the age proportions from ECHELON-1, is sufficient to account for the age bimodal incidence of disease within the population and is suitable for decision making.

The company includes in the addendum that the EAG has provided a deterministic and not probabilistic weighted base case ICER for decision making. The EAG notes that the EAG's probabilistic base case ICER was calculate using the mean of 1000 probabilistic samples from the <60-year-old age subgroup and the mean of 1000 probabilistic samples from the ≥60-year-old age subgroup and weighted by the number of patients in each subgroup in ESCHELON-1. As such, the EAG considers that the resulting ICER can be considered probabilistic. The EAG acknowledges that the weighting of the age subgroups has not been included in the PSA, however, in the absence of information relating to the true proportion of patients in each age group that would be treated in clinical practice, the EAG considers using the proportions from ECHELON-1 is reasonable.

The company has also provided an additional scenario analysis which uses the raw patient age data to sample starting age in the PSA. Figure 1 presents the patient age frequencies.

Figure 3. Distribution of ECHELON-1 trial participant ages



As presented, the distribution of patient ages is not aligned to the opinion of the EAG's and company's clinical experts, with the study participants showing a right skew compared to a more bimodal distribution as would be expected in clinical practice. This may be expected given the inclusions and exclusion study criteria, however, the issue that the trial age distribution is not reflective of what would be expected in clinical practice remains.

Additionally, the EAG notes that the mean age and standard error of the raw patient data used in the company's updated sampling approach are the same as that previously assumed in the model. Therefore, within a probabilistic analysis, the EAG considers that sampling ages from the trial participant ages will lead to results similar to those of the previous mean age based approach, while still not accounting for the age bimodal patient population. As such, the EAG considers that the age-weighted ICER remains the most appropriate method to account for the age bimodal patient population.

A scenario analysis has been conducted using the EAG's preferred assumptions and the company's updated probabilistic age sampling approach. The scenario assumes a mixed cure model for both OS and PFS, modelling PFS using a loglogistic distribution for both A+ABD and ABVD as it provided the lowest AIC and BIC score. Overall survival was modelled with a

Gompertz and exponential distribution for A+AVD and ABVD, respectively, as these provided the best statistical and visual fit to the underlying Kaplan-Meier data extrapolations.

2.3 Treatment-related lifelong peripheral neuropathy

The EAG lists below the company's key concerns, namely;

- The inclusion of lifelong peripheral neuropathy (PN) in the model,
- The method of modelling life-long PN,
- The proportion of patients assumed to have lifelong PN,
- The disutility associated with PN.

The company also conducted an alternative multivariate utility analysis using the trial data to identify a grade ≥3 PN specific disutility, which was calculated to be -0.0836. The company aimed to externally validate the calculated disutility, identifying a paper by Hirose *et al.* 2020[3] which showed that peripheral sensory neuropathy reduced utility by -0.06. The company acknowledged that the study was associated with many limitations, such as the study being conducted in a Japanese patient population with a variety of cancers, of which malignant lymphoma only account for 6.7%.

The company also considered that the EAG's assumed proportion of patients with lifelong PN was overestimated, stating that without long-term follow up, data on the duration of PN in these patients was limited, especially for those who were lost to follow up or withdrew from the study. As such, there remains uncertainty regarding whether these patients go on to have life long PN and these data may in fact overestimate the proportion of patients with life long PN. When consulting their clinical experts, the clinicians expressed that patients who had at least three years of unresolved grade ≥3 PN could be considered as having life long PN. Table 1 presents the number of patients who had ongoing grade ≥3 PN at the end of trial follow up, were alive at the end of follow-up and had at least 3 years of unresolved PN at their last follow-up.

Table 3. Ongoing Grade ≥3 peripheral neuropathy at last follow-up (March 2023) (reproduced from Table 5 in the addendum)

	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing Grade ≥3 PN at last follow-up, n (%)	16 (2.4%)	4 (0.6%)

Patients with ongoing Grade ≥3 PN at last follow-up, who were alive at end of follow-up, n (%)	13 (2.0%)	2 (0.3%)
Patients with ongoing Grade ≥3 PN at last follow-up, who were alive at end of follow-up and had Grade ≥3 PN for at least 3 years prior to their last follow-up date, n (%)	[redacted]	[redacted]
End of study status of patients with ongoing Grade ≥3 PN at last follow up, who were alive at end of follow-up and had at least 3 years of unresolved Grade ≥3 at their last follow-up		
Lost to follow-up, n (%)	[redacted]	[redacted]
Withdrawal by subject, n (%)	[redacted]	[redacted]
Still active, n (%)	[redacted]	[redacted]

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PN, peripheral neuropathy.

Lastly, the company identified a potential error in the EAG's method of modelling lifelong PN. In the EAG's approach, PN disutility was applied to the total undiscounted QALYs per health state across the model time horizon. This method, however, applied the disutility at a constant rate over time and therefore failed to account for the mortality of patients with lifelong PN. As such, the company adapted the model to allow life long PN disutility to adjust over time, in line with mortality.

The company conducted a scenario analysis using their preferred PN disutility, proportion of patients with lifelong PN and correction in how the disutility was applied in the model leading to an increase in the company's updated base case ICER from £[redacted].

2.3.1 EAG critique

In the company's addendum, the company makes reference to the inclusion of life long PN being unprecedented. The company highlights that while PN has been included in previous brentuximab-related submissions (TA641, TA478, TA446/TA534, TA577) using the disutility identified by Swinburn *et al.*, none have modelled lifelong PN. The EAG notes that compared to the TAs highlighted, where the clinical trial length was between two to three years, the ECHELON-1 study enrolled patients in 2012 with final long-term follow-up in 2023. As such, the EAG considers that the longer study duration has provided greater insight into treatment safety and shown that a proportion of patients may have treatment-related long term PN, which in shorter term study may have been assumed to resolve over time. The EAG therefore considers it would be inappropriate not to model lifelong PN given the evidence in the ECHELON-1 clinical trial and its substantial burden to health-related quality of life.

With respect to the method of modelling lifelong PN, the EAG thanks the company for identifying the error of applying a constant rate of disutility and therefore not accounting for mortality. This correction has been included in the EAG's updated base case.

The company considers that only patients with ongoing grade ≥3 PN at last follow-up, who were alive at end of follow-up and had grade ≥3 PN for at least 3 years prior to their last follow-up date should be considered to have lifelong PN. Breaking this apart into its constituents, the EAG agrees with the inclusion of patients with ongoing grade ≥3 PN at last follow-up, however, questions the appropriateness of including only those alive at the end study and with grade ≥3 PN for at least 3 years prior to their last follow-up.

With respect to including only patients alive at the end of study, the EAG considers this would exclude patients who had chronic PN and died before the end of the study. Therefore, their exclusion may underestimate the proportion of patients with lifelong PN.

Similarly, only including those with three years of grade ≥3 PN prior to end of study would exclude patient with chronic PN whose symptoms only progress to grade ≥3 less than three years before the end of the study.

The EAG notes that data relating to the number of patients who had at least three years of grade ≥3 PN by last follow up was not included in the clinical study report (CSR) or its addendums. When requested for the source of the date, the company confirmed that patient data relating to the duration of time with grade ≥3 PN was not in the CSR and that the analysis had been conducted using the final cut of the ECHELON-1 data given the company's clinical expert opinion. As such, no other data relating to the length of patient PN was provided.

Given the remaining uncertainty around the true proportion of patients who can be considered to have lifelong PN following treatment, the EAG considers that a conservative approach is associated with the lowest decision risk. As such, the previous EAG assumption of 2.4% and 0.6% of patients receiving A+AVD and ABVD, respectively, having lifelong PN is assumed in the EAG base case. For completeness, a scenario analysis using the EAG's preferred assumptions and company preferred lifelong PN proportions of [redacted] and [redacted] has also been conducted.

The company was also concerned with the disutility used to model grade ≥3 PN, reflecting that it lacked face validity given the greater utility loss associated with PN compared to disease

progression. The disutility was sourced from Swinburn *et al*.[4], and as identified by the company, has previously been used to model the disutility of grade ≥3 PN in NICE TA641, TA478, TA446 and TA524 with TA577 also using PN disutility from Swinburn *et al.*[4] but only for grades 1 and 2. To identify the disutility associated with grade ≥3 PN, the company conducted a multivariate utility analysis using the ECHELON-1 trial data, which calculated the grade ≥3 PN specific disutility to be -0.0836.

The EAG is concerned with the validity of the regression and its outcomes given that the company's previous utility regression used to calculate adverse event disutility in the company submission lacked face validity. In the company's previous utility regression, the disutility calculated when considering a combination of all appropriate grade ≥3 AEs (anaemia, febrile neutropenia, neutropenia, neutrophil count decreased) was -0.02. Comparing these to the wider literature, anaemia independently was associated with a disutility of -0.17, with febrile neutropenia associated with a -0.12 disutility, a -0.09 disutility for neutropenia and -0.05 for neutrophil count decrease. As such, the EAG considers that the company's utility regression analysis lacks face validity and is likely to be underestimating the disutility for PN.

Similarly, the EAG considers that the disutility identified by Hirose *et al.*[3], may not be directly relevant to grade 3≥ PN in the context of this technology appraisal. As acknowledged by the company, the study was conducted in a Japanese patient population with a variety of cancers, of which malignant lymphoma only account for 6.7%. Additionally, the study only included 36 patients, included those with grade 2 PN without providing a disutility by grade or the proportion of patients with each grade, and finally, only included patients with sensory PN and not other forms of PN such as motor PN as was also measured in ECHELON-1.

As such, in the absence of alternative sources from which to assign a disutility to grade ≥3 PN, the EAG considers that the disutility calculated by Swinburn *et al.*[4] is most appropriate to use in the model and that its use is consistent with previous brentuximab NICE TAs.

3 EAG scenario analysis

Table 4 presents the EAG conducted scenario analyses. Scenario one includes the correction in the application of PN disutility as identified by the company which is then included in the subsequent scenarios and the updated EAG base case.

Table 4. Results of the EAG's scenario analyses

	Results per patient	A+AVD	ABVD	Incremental value
0	Previous EAG base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
1	Corrected EAG base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
2	Corrected EAG base case & sampling age from patient data in the PSA (ITT population)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
3	Corrected EAG base case & company preferred proportion of patients with lifelong PN			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

4 EAG updated base case

Table 5 presents the EAG base case, corrected to allow the total disutility from lifelong grade ≥3 PN to adjust according to mortality.

Table 5. EAG base case

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
A+AVD	[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
A+AVD	[redacted]	[redacted]	[redacted]	-	-	-	-
ABVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

5 References

1. Takeda. Data on file: Clinical study report. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma | Addendum 3 - March 2024. 2024.
2. Luminari S, Fossa A, Trotman J, Molin D, d'Amore F, Enblad G, et al. Long-Term Follow-Up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma Trial. *Journal of Clinical Oncology* 2024; **42**: 13-8.
3. Hirose C, Fujii H, Iihara H, Ishihara M, Nawa-Nishigaki M, Kato-Hayashi H, et al. Real-world data of the association between quality of life using the EuroQol 5 Dimension 5 Level utility value and adverse events for outpatient cancer chemotherapy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2020; **28**: 5943-52.
4. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leuk Lymphoma* 2015; **56**: 1839-45.

Single Technology Appraisal

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma (including review of TA594) [ID6334]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 3 July 2024** 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.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Company's MAIC and associated base case are not reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The MAICs conducted by the Company have not been presented in the EAG report. Similarly, the associated alternative base case submitted by the Company, which utilises the MAIC comparing A+AVD from ECHELON-1 with ABVD from RATHL, has not been reported in the EAG report. This issue is first reported at: **Section 3.4, page 63** '*However, following review of the results of the fully adjusted MAIC comparing six-cycle ABVD from ECHELON-1 with PET-adapted ABVD from RATHL, the EAG considers the results of the MAIC likely to be unreliable and*	The Company proposes that the EAG amend the report so that it reflects the totality of evidence presented by the Company. It is proposed that the EAG include both base cases provided in response to clarification questions, and relevant information around all the MAICs (comparing six-cycles ABVD from ECHELON-1 with PET-adapted ABVD from RATHL and comparing A+AVD from ECHELON-1 with PET-adapted ABVD from RATHL) to ensure the Committee has a complete picture of the evidence base.	The Company disagrees with the EAG's decision not to include full details of the Company's MAICs in the report alongside the current commentary. Two Company base cases were provided in response to clarification questions. It is often not clear which is being referred to, potentially leading to commentator and committee confusion, or why only one is presented. The Company proposes that the results using the alternative base case be included, alongside the additional MAICs provided by the Company, as the report does not currently reflect the full Company submission and evidence base. Inclusion of these MAICs is important because the Company believes the EAG has dismissed the	Not a factual inaccuracy, no change required. The EAG report refers to the company base case and directs readers to the company response to clarification, should they want to consider the company alternative base case.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
therefore the EAG does not discuss this MAIC further' Further instances – not exhaustive – are as follows: **Section 3.5, page 68** **Section 4.2.4.1, page 80** The EAG concludes on **page 88** by stating *"the EAG strongly considers that no robust conclusions can be draw from the naïve comparisons between the ECHELON-1 trial and RATHL, and by extension the model".* The Company believes that this statement, while the EAG's opinion, doesn't take into account the MAICs provided by the Company, and therefore doesn't reflect the totality of the evidence submitted by the Company.		Company MAICs due to potential confusion around the generalisability of the RATHL study (see subsequent issues).	

Issue 2 Description of PET de/escalation in the RATHL study

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report incorrectly states that the RATHL data informing the Company MAICs did not include patients who were PET2 positive and escalated to a BEACOPP-based regimen. **Section 3.4, page 63** '*The EAG considers it important to highlight that the data from RATHL in the Company's MAICs only comprise of patients who are de-escalated following a negative PET2 scan. The RATHL data thus does not include the outcomes for PET2 positive patients who would receive treatment escalation to escBEACOPDac in clinical practice.*' **Section 2.3.3, page 39**	The Company proposes that relevant statements throughout the EAG report are updated to reflect that the RATHL data includes both patients who are de-escalated following a negative PET2 scan as well as those whose treatment is escalated following a positive PET2 scan.	Both ECHELON-1 and the RATHL data used in the naïve, unadjusted indirect comparisons and the MAICs included patients who were PET2 positive, and the RATHL data therefore includes patients who underwent treatment escalation. From the RATHL study, a total of N=702 patients (Stage III and IV) contributed to the PFS and OS data; n=99 of these patients were PET2 positive and received BEACOPP-based regimens (the EAG's clinical experts stated that they expect BEACOPP-14 to be equivalent to escBEACOPP and escBEACOPDac; page 29). Therefore, the impact of treatment escalation is	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text relating to the PET-adapted ABVD data from RATHL in the report on pages 39, 63, 68 and 80-81.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'*The EAG notes that the six-cycle ABVD data includes patients who are PET2 positive and who would be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac.*' **Section 3.4.1, page 64** '*In addition, the EAG notes that the six-cycle ABVD data includes patients who are PET2 positive (9%) and who would be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac'* **Section 3.5, page 68** '*In addition, the EAG notes that the RATHL data in this analysis do not fully reflect the use of PET-adapted ABVD in UK clinical practice*…'		reflected in the data informing all MAICs presented in the Company response to the EAG's clarification questions. The Company acknowledges the opinion of the EAG that the clinical efficacy of A+AVD vs PET-adapted ABVD is uncertain and that outcomes in UK practice may not be accurately reflected (page 69). However, the Company is concerned that this conclusion is based on an assumption that the RATHL data informing the analyses only include patients who are de-escalated following a negative PET2 scan, which is an inaccurate interpretation of the data informing the MAICs presented by the Company in the Company submission and response to the EAG's clarification questions.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4.1, page 80 '…*the RATHL data in this MAIC do not fully reflect the use of PET-adapted ABVD in UK clinical practice*…'			
The EAG report asserts as fact, rather than opinion, that there are differences in outcomes between therapeutic regimens without providing supporting clinical evidence. **Section 3.5, pages 67–68** '*The EAG notes that the six-cycle ABVD data includes patients who are PET2 positive and who would be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac. The EAG thus considers the results of the MAIC to contradict the findings in the RATHL trial of noninferiority for PFS and no*	The Company proposes the text is amended to the following: *"The EAG notes that the six-cycle ABVD data includes patients who are PET2 positive and who <u>may</u> be expected to have worse outcomes if remaining on ABVD compared to if they escalated to escBEACOPDac."*	It is unclear on what basis the assumption is made of patients having worse outcomes if PET2 positive and remaining on ABVD compared with escalation to escBEACOPDac. Expert opinion received by the Company, and outcomes from the RATHL study, do not provide clear clinical evidence that this is the case.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text from 'would' to 'may' in the EAG report on pages 39, 64 and 67.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
significant difference in OS for de-escalated ABVD/AVD compared with six-cycle ABVD.'			

Issue 3 Generalisability of RATHL

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.1, page 35 *"The EAG's clinical experts also reported that the proportion of Stage III patients (36.3%) was lower than expected in UK clinical practice and the proportion of Stage IV patients (63.7%) was higher than expected; clinical experts reported a more even split would be expected."* This is stated as multiple points in the EAG report as follows:	Amendment of statements that ECHELON-1 staging split is not reflective of UK clinical practice. Where the proportions of patients with Stage III and IV disease in RATHL are described in the EAG report, it should also be clarified in each instance that the proportions refer to those patients with Stage III or IV disease only, and not to the ITT population in RATHL (which also included some Stage II patients). The Company proposes that the report is also amended to reflect the fact that the proportions of patients with Stage III and IV disease in	The Company acknowledges that these statements are based on feedback from the EAG's clinical expert; however, consider it important to highlight that the RATHL trial (Johnson et al. 2016), which shaped UK clinical practice for the management of first-line HL patients enrolled a total of 363 Stage III HL patients (30.2% of ITT population). As reported in Section B.2.3.3 in the CS, UK-based clinical expert advisors concluded	The EAG thanks the company for highlighting this and has updated the text in the EAG report to include the Cancer Research UK (CRUK) data on page 35 and amended the text relating to the generalisability of ECHELON-1 on pages 30, 31, 36, 45 and 66.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, Table 9, page 31 *"the EAG's clinical experts reported that the baseline characteristics of patients in the trial are broadly consistent with patients with [redacted] in the UK population, although they noted that the proportion of Stage IV (compared to Stage III) patients in the trial is possibly slightly higher than expected in clinical practice in the UK."* **Section 3.5, page 67** *"In addition, the EAG's clinical experts raised concerns around the proportions of Stage III and IV patients in the ECHELON-1 trial potentially not reflecting the UK patient*	ECHELON-1 are reflective of the UK disease patient landscape.	that the patient population included in ECHELON-1 is reflective of the patients they would see in routine clinical practice.[36, 131] Moreover, the proportion of patients with Stage III vs. Stage IV disease is reflective of what is observed in UK clinical practice, aligning with Cancer Research UK (CRUK) data for HL, where 325 and 497 patients were diagnosed with Stage III and Stage IV disease, respectively, in England in 2021 (representing 39.5% and 60.5% of advanced HL for Stage III and Stage IV disease, respectively).[131]	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
population. The proportion of Stage III patients (36.3%) in ECHELON-1 was lower than expected in UK clinical practice, and the proportion of Stage IV patients (63.7%) was higher than expected; clinical experts reported a more even split would be more reflective of patients presenting in the UK."			

Issue 4 Differences in second malignancies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Table 5, page 24 *"The EAG notes that rates of secondary malignancies were similar between treatments"*	The Company proposes that the text is amended to "*The EAG notes that rates of second malignancies were numerically different between treatments, occurring in [redacted] and [redacted] patients in the A+AVD and ABVD groups, respectively"*	Rates of malignancies were numerically different between treatment arms, occurring in 33 and 39 patients in the A+AVD and ABVD groups, respectively. This represents an approximately 20% difference between treatment groups over the time period of data	Not a factual inaccuracy, no change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		collection. Across a lifetime horizon, a 20% difference in malignancies is not insubstantial, and while ECHELON-1 was not powered to detect differences in second malignancies, factual reporting of the second malignancy rates is preferred.	
The text does not state that the description of the treatment difference for second malignancies is the EAG's opinion. **Section 4.2.9.4, page 120** "*The difference in incidence of secondary malignancies between patients receiving A+AVD and patients receiving ABVD is very small*…"	The Company proposes that the text is amended to: "*The difference in incidence of <u>second</u> malignancies between patients receiving A+AVD and patients receiving ABVD is <u>considered by the EAG to be</u> very small*…"	To clarify that this is the opinion of the EAG, not the Company. To clarify that the text refers to second, and not secondary, malignancies	The text has been updated to report the percentage difference in secondary mortalities between treated groups.
"Secondary malignancies" should be amended to "second malignancies".	The Company proposes to amend all instances in the text to:	Clinical expert feedback to the Company has been that there is a subtle but important difference	The EAG thanks the company for identifying the factual inaccuracy and has

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Company believes all instances should be changed throughout the EAG report**.**	"*Second malignancies*"	between "second" and "secondary" malignancies. In the context of ECHELON-1 it is correct to use "second malignancies" i.e. a second malignancy, unrelated to the initial HL.	updated the report accordingly.

Issue 5 Statement that final HRQL assessment data were not provided in the CS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
This EAG report states: **Section 2.3.4, page 41** "*The EAG also considers it important to highlight that the EQ-5D-3L data presented in the clinical effectiveness section of the CS…relate to the 20 April 2017 data cut rather than the final data-cut (11 March 2023) but it is reported in the cost-effectiveness section…that the results from the final data cut were used in the economic model. The EAG also considers that data from the EORTC QLQ-C30 assessments should also be available from the final data-cut and notes that these were not provided in the CS."*	The Company proposes that these statements are amended to reflect the correct data cuts presented in the clinical effectiveness section of the Company submission and utility analyses in the economic model.	The Company apologises for the lack of clarity, which is caused by conflicting utilisation of the wording 'final data cut' in the Company submission. The results provided for both EORTC QLQ-C30 and EQ-5D-3L in the clinical effectiveness section of the CS were from the April 2017 data cut. The Company acknowledges that this has caused confusion, as elsewhere, 11 March 2023 is described as 'the final data cut-off'; however, no data are available for EORTC QLQ-C30 or EQ-5D-3L from this later data cut. For clarity, the utility analysis that informs the economic model uses the EQ-5D-3L data from the 01 June 2021 data cut of ECHELON-1. The use of the wording "final data cut" comes	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text on page 41 to refer to 01 June 2021 as the final data-cut for EQ-5D-3L data from ECHELON-1 and the text on page 52 to state the EQ-5D-3L data used in the model were from the final data-cut.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.9.1.1, page 110 "*HRQoL inputs were informed by EQ-5D-3L data collected from patients in the ECHELON-1 trial, based on the 11 March 2023 data cut."*		from the fact that collection of both EORTC QLQ-C30 and EQ-5D-3L ceased by 36 months from the end of treatment, and this was the final data cut that informed analysis of these outcomes. The Company acknowledges that this has caused confusion. All other data are from the final ECHELON-1 analysis, dated 11 March 2023, including the data informing the progressed disease covariate in the utility analysis.	The EAG thanks the company for identifying the factual inaccuracy and has updated the model accordingly.

Issue 6 Exclusion of information provided in response to clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The tables contain data from ECHELON-1 that do not match the data provided in the Company response to clarification questions. This occurs in the following instances in the EAG report: **Section 3.4.2, Table 21, page 65** **Section 4.2.8, Table 40, page 106–107** **Section 4.2.8, Table 41, page 107**	The Company proposes to update these data with the most up to date data from ECHELON-1 presented in the Company clarification responses dated 28th May 2024, namely: • Table 20. p63 • Table 21. p64 • Table 22. p64	The Company provided data from the March 2023 data cut, which is considered more appropriate to report in these instances.	The EAG thanks the company for identifying the factual inaccuracy. The EAG has updated Table's 21, 40 and 41 in the EAG report using the most up to date data from Table's 20 and 21 in the clarification response.

Issue 7 Amendments to report text for greater clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
It is not specified which Company base case is referred to. **Section 1.4, Table 7, page 25** The EAG reports the "*Company corrected base case*" in Table 7. **See also:** • **Section 4, Table 22, page 70** • **Section 4.2.10.6, Table 65, page 133** • **Section 4.2.10.6, Table 66, page 134–135** • **Section 4.2.10.6, Table 67, page 135** • **Section 4.2.10.6.1, page 136** "*Using the duration of subsequent pembrolizumab from the KEYNOTE-087 trial marginally reduced the ICER, with the updated subsequent treatment duration assumed in the Company base case.*" In this instance, we appreciate that the EAG is repeating text from the responses to clarification questions.	Please clarify which one (or both if applicable) of the Company base cases are being referred to in each instance.	Two Company base cases were provided in response to the EAG's clarification questions. The current text is unclear which is being referred to.	The corrected base case refers to the inclusion of the corrected treatment costs, outlined in the model corrections section, to the company base case. Throughout the EAG report only the company base case, and not the alternative base case, has been reported and so it should be clear which base case is being referred to.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• **Section 4.2.10.6.1, page 137** "*For completeness the Company conducted a scenario using 240mg every two weeks directly which led to no change in the ICER*." • **Throughout Section 5** • **Section 6.1, page 143** "*The External Assessment Group (EAG) identified a number of lower treatment costs compared to those included in the model (Table 70). The model has therefore been updated to reflect these corrections, resulting in the Company corrected base case presented in Table 71*." **Section 6.1, Table 71, page 143**			The EAG has updated the wording to "*led to no change in the company base case ICER"*. This section provides the rationale and description of the corrected company base case.
The report states that the EAG's clinical experts advised that PET-adapted treatment is the recommended approach in the UK and that PET scans are widely available (page 28). The EAG report also states that the PET-adapted approach is the approach used in clinical practice. However, it is noted on page 121 that both PET-adapted and six-cycle ABVD are per NHS England protocols. **Section 4.2.4.1, page 80**	The Company proposes to amend the text to: **Section 4.2.4.1, page 80** "*The EAG's clinical experts agreed that the PET-adapted ABVD was the more appropriate*	To clarify that while PET-adapted ABVD is commonplace across the UK, there are centres that do not use PET adaptation (i.e. treat with six cycles of ABVD rather than via the RATHL	Not a factual inaccuracy, no change required..

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"*The EAG's clinical experts agreed that the PET-adapted ABVD was the more appropriate comparator due to its routine use in clinical practice following the RATHL trial and thereafter its recommendation withing BSH guidelines. The EAG notes that their clinical experts could not consider under what circumstances a six-cycle approach may be preferred to PET-adapted, given the utility of escalating and de-escalating treatment in reaction to a positive or negative PET scan*." … "*The modelled ABVD treatment effect is therefore highly uncertainty and potentially underestimated given treatment effects are derived from the six-cycle used in the ECHELON-1 trial compared to the PET-adapted approach used in clinical practice*." **Section 6.4, page 149** *"while in clinical practice ABVD patients would be treated with a PET-adapted approach"*	*comparator <u>because it is often used</u> in clinical practice…"* "…*derived from the six-cycle used in the ECHELON-1 trial compared to the PET-adapted approach <u>often</u> used in clinical practice*." **Section 6.4, page 149** *"while in clinical practice ABVD patients <u>should</u> be treated with a PET-adapted approach"*	strategy),[36] and the CS is intended to reflect this.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The text referred to below does not reflect all cost impacts of brentuximab vedotin. **Section 1.2, page 22** *"Overall, the technology is modelled to affect costs by:* • *Being more costly than the comparator;* • *Fewer patients requiring subsequent treatments;* • *Fewer patients requiring monitoring and follow up care; and* • *More patients requiring adverse event treatments."* Brentuximab vedotin also reduces administration costs vs. ABVD; however, this is not mentioned.	For completeness, the Company proposes to add "*Reducing administration costs*" to the bulleted list.	To provide clarity about the cost impacts of brentuximab vedotin.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.
It is unclear whether the EAG are proposing to model long-term PFS or OS or both using an MCM **Section 1.4, Table 7, page 25** "*Modelling long term survival using a MCM and the EAGs preferred distributions*"	The Company proposes to amend to include "*PFS*", "*OS*" or "*PFS and OS*" instead of "survival" to ensure it is clear whether survival' refers to overall survival and/or progression-free survival.	The current text does not state which endpoint is being referred to.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
As discontinuations from the study vary based on the data-cut assessed, it is important to clarify which data cut is being presented in the statement below. **Section 3.2, Table 11, page 45** *"Discontinuation from the study was reasonably well balanced across the two study arms with 318 patients (48%) discontinuing from follow-up in the A+AVD group and 346 patients (52%) in the ABVD treatment group."*	The Company proposes to state that the data are from the March 2023 data cut.	Discontinuation data are understood best in the context of the timeframe over which they have been collected.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text in the EAG report to: "*Based on the March 2023 data cut-off, discontinuation from the study….*"
The text states that AE data for ABVD were from RATHL. However, this excludes the 10% of patients whose AEs were informed by the ABVD arm of ECHELON-1. **Section 3.3, page 47** "…*AE data for ABVD in the model were obtained from the RATHL trial*…"	The Company proposes to amend the text to: "…*AE data for <u>PET-adapted ABVD in the model were</u> obtained from the RATHL trial<u>, and obtained from ECHELON-1 for six-cycle ABVD</u>* …"	The current text does not accurately describe the source of AE data for ABVD-based treatment.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text in the EAG report to "*AE data for PET-adapted ABVD in the model were obtained from the RATHL trial and AE data for six-cycle ABVD were*

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td></td><td>obtained from ECHELON-1”.</td></tr>
<tr><td>It is unclear what the overall cost referred to includes, as this does not align with the Company analyses for A+AVD over the model time horizon. The relevant column is in bold and underlined below.
Section 4.2.10.3, Table 59, page 127
<table>
<tr><th>Regimen</th><th>Treatment</th><th>Cost per cycle</th><th><u>Overall cost</u></th></tr>
<tr><td>A+AVD</td><td>A+AVD</td><td>£678.44</td><td><u>£1,289.69</u></td></tr>
<tr><td rowspan="3">ABVD</td><td>ABVD</td><td>£18.92</td><td rowspan="3"><u>£286.76</u></td></tr>
<tr><td>AVD</td><td>£18.92</td></tr>
<tr><td>escBEACOPDac</td><td>£348.57</td></tr>
</table></td><td>The Company recommends providing clarification on what overall cost includes and confirm that the overall cost presented for A+AVD is not an error.</td><td>The overall cost for A+AVD does not align with the Company analyses which estimate the escBEACOPDac cost as £348.57, and ABVD overall cost as £286.75.</td><td>The EAG thanks the company for identifying the factual inaccuracy. The overall A+AVD cost was calculated in error and has been corrected. Due to the lack of clarity of the overall cost compared to cost per cycle, the overall cost column has been removed from the table.</td></tr>
<tr><td>Drug-related adverse events are not mentioned for the April 2017 data cut-off.
Section 3.3.6, page 57</td><td>The Company proposes that the text is amended to:
“The EAG notes that the treatment-emergent adverse events (TEAEs),</td><td>To clarify that data provided from this data cut included drug-related adverse events.</td><td>This is not a factual inaccuracy. The EAG considers that treatment-emergent adverse</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The EAG notes that the treatment-emergent adverse events (TEAEs) from ECHELON-1 were collected from the 20 April 2017 data cut-off…"	*<u>including drug-related adverse events,</u> from ECHELON-1 were collected from the 20 April 2017 data cut-off*…"		events captures all adverse events during the period of treatment and so no additional specification is required.
It is not clear which rows in the table are related due to unclear formatting. **Section 3.3.6.4, Table 19, page 61**	The Company proposes to adjust indentation within the table to provide greater clarity about the data presented.	Adjusting the table formatting would provide greater clarity, for example showing via indentation that some of the rows below "*Status of PN AEs*…" are related to peripheral neuropathy events.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text in the EAG report.
The 2-year cure timepoint is from the end of treatment; however, this is unclear in the EAG report. **Section 2.2.1, page 29** "…*the Company reported that patients are usually followed up for 2 years*…" **Section 4.2.2, pages 73–74**	The Company proposes that the text is amended to: "…*the point at which progression-free patients were considered to be functionally cured…was*	To clarify to the readers that the two-year cure timepoint is in addition to the treatment period.	The report has been amended in line with the recommendation.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"*The Company's clinical experts outlined that 24 months was a reasonable cure timepoint…"* **Section 4.2.10.4, page 128** "…*the point at which progression-free patients were considered to be functionally cured…was assumed to be two years…"*	*assumed to be two years <u>after the EOT</u>…"*		
The text identified below does not list all the Company's reasons for not considering separate patient populations. **Section 4.2.3.1, page 78** "*The Company…did not believe it appropriate to consider the patient populations separately, given a potential negative impact on health inequities*."	The Company proposes that the EAG include all of the Company's reasons for not considering separate patient populations, or state that multiple reasons were given, of which health inequities were one.	The current text incorrectly implies that potential health inequities were the sole reason considered by the Company.	The EAG has added the additional reasons listed in the company's clarification response.
No cost-effectiveness threshold is provided. **Section 4.2.3.1, page 78** "…but accounting for these differences has no inference to if the ICER lies above or below the cost effectiveness threshold…"	The Company proposes that the text is amended to: *"but accounting for those differences does not change whether the ICER is above or below the cost-effectiveness*	The current text does not make clear which cost-effectiveness threshold is referred to.	The report has been amended in line with the recommendation.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	threshold of £30,000 per QALY"		
The impact of disease progression is not explained. **Section 4.2.7, page 103** "…*given ABVD is a bleomycin containing treated and therefore is associated with elevated risk of pulmonary toxicity in addition to being associated with increased secondary malignancies and disease progression."*	The Company proposes that the text is amended to: "…*given ABVD is a bleomycin containing treated and therefore is associated with elevated risk of pulmonary toxicity in addition to being associated with increased <u>second</u> malignancies and disease progression<u>, and therefore more subsequent therapies including stem cell transplantation</u>."*	To clarify the patient and system impact of disease progression.	The report has been amended in line with the recommendation.
The text omits administration costs for subsequent therapies that were included in the Company's economic modelling. **Section 4.2.10, page 120** "*Administration costs for first line treatments;*"	The Company proposes that the text is amended to: "*Administration costs for first line <u>and subsequent</u> treatments;*"	To clarify that subsequent treatment administration costs were included in modelling.	The EAG thanks the company for identifying the factual inaccuracy and has updated

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td></td><td>the wording accordingly.</td></tr>
<tr><td>It is unclear where the data (bold and underlined below) in the anti-infectives and pain management rows of the table have come from, as they do not align with the analyses conducted by the Company.
Section 4.2.10.3, Table 57, page 126
<table>
<tr><th>Treatment category</th><th>Treatment</th><th>Proportion receiving treatment, A+AVD</th><th>Proportion receiving treatment, ABVD</th></tr>
<tr><td rowspan="2">Anti-infectives</td><td>Acyclovir</td><td><u>21.2%</u></td><td><u>15.7%</u></td></tr>
<tr><td>Levofloxacin</td><td><u>20.5%</u></td><td><u>17.2%</u></td></tr>
<tr><td rowspan="2">Pain management</td><td>Oxycodone</td><td><u>13.2%</u></td><td><u>8.5%</u></td></tr>
<tr><td>Tramadol</td><td><u>13.0%</u></td><td><u>9.4%</u></td></tr>
</table></td><td>The Company proposes that the EAG provide an explanation for these data in/near the table.</td><td>The data do not align with the analyses conducted by the Company.</td><td>The EAG thanks the company for identifying the factual inaccuracy and has updated the table accordingly.</td></tr>
<tr><td>The text does not specify that only efficacy is informed by six-cycle ABVD in the model.
Section 6.4, page 149
“…the six cycle ABVD approach used in the ECHELON-1 trial and assumed in the model…”</td><td>The Company proposes that the text is amended to:
“…the six cycle ABVD approach used in the ECHELON-1 trial and assumed in the model <u>for</u></td><td>To clarify that this applies only to efficacy within the model.</td><td>The report has been amended in line with the recommendation.</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	the purposes of informing efficacy…"		

Issue 8 Incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The cure timepoint scenario analysis of 1 year is incorrect. **Section 4.2.2, page 74** "*The Company therefore assumed a two-year cure time point in their base case, with additional scenario analysis conducted using one and five years timepoints*."	The Company proposes that the text is amended to: "*The Company therefore assumed a two-year cure time point in their base case, with additional scenario analysis conducted using three and five years timepoints*."	A 3-year timepoint was analysed in a scenario; a 1-year timepoint was not explored.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.
The reference to the figure number in the CQ response is incorrect. **Section 4.2.2.1, Figure 10, page 77**	The Company proposes that the text is amended to: "*Figure 10. Combined treatments (ITT population) smoothed hazard plots*	To accurately reference the relevant figure in the CQs.	The EAG thanks the company for identifying

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"*Figure 10. Combined treatments (ITT population) smoothed hazard plots (reproduced from Figure 26 in the CQ response)"*	*(reproduced from Figure 23 in the CQ response)"*		the factual inaccuracy and has updated the report accordingly.
The dependent scenario analysis is incorrectly listed. **Section 4.2.6.2, page 90** "…*with dependent and parametric models explored in scenario analyses*."	The Company proposes that the text is amended to: "…*with independent standard parametric models and independent MCMs explored in scenario analyses*."	To correctly describe the scenarios analysed; dependent models were not explored in scenario analyses.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.
The text states "*no*" rather than "*one or less*" differences, which is incorrect. **Section 4.2.6.2, page 93** "…*between the models with no differences in AIC or BIC values between the A+AVD extrapolations*…"	The Company proposes that the text is amended to: "…*between the models with differences of one or less in AIC or BIC values between the A+AVD extrapolations*…"	To accurately reflect the data presented by the Company, and to make the text consistent with that describing the extrapolations for ABVD.	The EAG thanks the company for identifying the factual inaccuracy and has

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			updated the report accordingly.
The relationship between utility values (see underlined text below). **Section 4.2.9.2.1.1, page 114** "…*is consistently higher than the utility value for a patient*…"	The Company proposes that the text is amended to: "…*is consistently lower than the utility value for a patient*…"	To correctly reflect the difference between utility values for patients in the progression-free and progressed health states.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.
The text refers to "*durations"* rather than "*decrements*". **Section 4.2.9.3.1, page 118** '…*this allows durations of adverse events to be applied individually*…'	The Company proposes that the text is amended to: "…*this allows decrements of adverse events to be applied individually*…'	The Company believes the text should refer to HRQoL decrements instead of durations, as durations were the same in both scenarios.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect reporting of A+AVD total costs. **Section 4.2.10.1, Table 55, page 124** [redacted] *(with PAS)"*	The Company proposes that the text is amended to: [redacted] *(with PAS)"*	The cost currently provided is incorrect.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.
Incorrect statement around cost of concomitant medications. **Section 4.20.3, page 126** *"Costs for concomitant medications were applied to patients receiving active first line treatment; for patients in the ABVD arm, it was assumed that 10% receive concomitant medications relevant to the six-cycle ABVD regimen, while the remaining 90% receive concomitant medications in line with the PET-adapted ABVD regimen*."	The Company proposes that the text is amended to: *"Costs for concomitant G-CSF were applied to patients receiving active first line treatment; for patients in the ABVD arm, it was assumed that 10% receive concomitant G-CSF relevant to the six-cycle ABVD regimen, while the remaining 90% receive concomitant G-CSF in line with the PET-adapted ABVD regimen. All other concomitant medication use for ABVD was in line with ECHELON-1.*"	To correctly reflect the Company approach.	The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>The text incorrectly states equal AE frequencies between PET-adapted and six-cycle ABVD in the model.

Section 4.2.10.5, page 129

“…the frequency of adverse events for patients receiving PET-adapted ABVD was assumed to be the same as the frequency for patients receiving the six-cycle ABVD regimen.”</td>
<td>The Company proposes that the text is amended to:

“…the frequency of adverse events for patients receiving PET-adapted ABVD was <u>sourced from the RATHL study and weighted by 90%, and</u> the frequency <u>of adverse events for patients receiving six-cycle ABVD was per ECHELON-1 and weighted by 10%</u>.”</td>
<td>To correctly reflect frequency of AEs in the model.</td>
<td>The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.</td>
</tr>
<tr>
<td>The price per pack and total cost per cycle are incorrectly reported for both oxycodone and tramadol.

Section 4.2.10.3, Table 58, page 127
<table>
<tr><th>Treatment category</th><th>Treatment</th><th>Price per pack</th><th>Total cost per cycle</th></tr>
<tr><td rowspan="2">Pain management</td><td>Oxycodone</td><td><u>£1.69</u></td><td><u>£13.53</u></td></tr>
<tr><td>Tramadol</td><td><u>£0.28</u></td><td><u>£0.59</u></td></tr>
</table>
</td>
<td>The Company proposes that the table is amended to:
<table>
<tr><th>Treatment category</th><th>Treatment</th><th>Price per pack</th><th>Total cost per cycle</th></tr>
<tr><td rowspan="2">Pain management</td><td>Oxycodone</td><td><u>£13.53</u></td><td><u>£1.69</u></td></tr>
<tr><td>Tramadol</td><td><u>£0.59</u></td><td><u>£0.28</u></td></tr>
</table>
</td>
<td>To correctly reflect costs.</td>
<td>The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.</td>
</tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Incorrect number of administrations per cycle for Ondansetron.
Section 4.2.10.3, Table 59, page 127
<table>
<tr><th>Treatment category</th><th>Treatment</th><th>Dose per admin</th><th>Admins per cycle</th></tr>
<tr><td rowspan="5">Anti-emetics</td><td>Dexamethasone (day 1)</td><td>8 mg</td><td>2</td></tr>
<tr><td>Dexamethasone (days 2-3)</td><td>4 mg</td><td>4</td></tr>
<tr><td>Ondansetron</td><td>8 mg</td><td><u>8</u></td></tr>
<tr><td>Aprepitant (day 1)</td><td>125 mg</td><td>2</td></tr>
<tr><td>Aprepitant (day 2-3)</td><td>80 mg</td><td>4</td></tr>
</table>
</td>
<td>The Company proposes that the table is amended to:
<table>
<tr><th>Treatment category</th><th>Treatment</th><th>Dose per admin</th><th>Admins per cycle</th></tr>
<tr><td rowspan="5">Anti-emetics</td><td>Dexamethasone (day 1)</td><td>8 mg</td><td>2</td></tr>
<tr><td>Dexamethasone (days 2-3)</td><td>4 mg</td><td>4</td></tr>
<tr><td>Ondansetron</td><td>8 mg</td><td><u>2</u></td></tr>
<tr><td>Aprepitant (day 1)</td><td>125 mg</td><td>2</td></tr>
<tr><td>Aprepitant (day 2-3)</td><td>80 mg</td><td>4</td></tr>
</table>
</td>
<td>To correctly reflect administrations per cycle.</td>
<td>The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.</td>
</tr>
<tr>
<td>The overall cost for ABVD is incorrect.
Section 4.2.10.3, page 127
<table>
<tr><th>Regimen</th><th>Treatment</th><th>Cost per cycle</th><th>Overall cost</th></tr>
<tr><td>A+AVD</td><td>A+AVD</td><td>£678.44</td><td>£1,289.69</td></tr>
<tr><td>ABVD</td><td>ABVD</td><td>£18.92</td><td><u>£286.76</u></td></tr>
</table>
</td>
<td>The Company proposes that the table is amended to:
<table>
<tr><th>Regimen</th><th>Treatment</th><th>Cost per cycle</th><th>Overall cost</th></tr>
<tr><td>A+AVD</td><td>A+AVD</td><td>£678.44</td><td>£1,289.69</td></tr>
<tr><td>ABVD</td><td>ABVD</td><td>£18.92</td><td><u>£286.75</u></td></tr>
</table>
</td>
<td>To correctly reflect the overall cost of ABVD.</td>
<td>The EAG thanks the company for identifying the factual inaccuracy and has</td>
</tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td><table><tr><td></td><td>AVD</td><td>£18.92</td><td></td></tr><tr><td></td><td>escBEACOPDac</td><td><u>£348.57</u></td><td></td></tr></table></td><td><table><tr><td></td><td>AVD</td><td>£18.92</td><td></td></tr><tr><td></td><td>escBEACOPDac</td><td><u>£348.56</u></td><td></td></tr></table></td><td></td><td>updated the report accordingly.</td></tr>
<tr><td>Minor error in annual cost data.
Section 4.2.10.4, Table 62, page 129<table><tr><th>Health state</th><th>Total monitoring/follow-up cost per year</th></tr><tr><td>Pre-progression, 0-6 months</td><td>£2,407.57</td></tr><tr><td>Pre-progression, 6 months - cure</td><td>£427.8<u>4</u></td></tr><tr><td>Progressed disease</td><td>£3,498.42</td></tr></table></td><td>The Company proposes that the table is amended to:<table><tr><th>Health state</th><th>Total monitoring/follow-up cost per year</th></tr><tr><td>Pre-progression, 0-6 months0.</td><td>£2,407.57</td></tr><tr><td>Pre-progression, 6 months - cure</td><td>£427.8<u>3</u></td></tr><tr><td>Progressed disease</td><td>£3,498.42</td></tr></table></td><td>To correctly reflect annual cost data.</td><td>The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly.</td></tr>
<tr><td>An incorrect cost-per-event for neutropenia is provided.
Section 4.2.10.5, Table 63, page 130<table><tr><th>Adverse event</th><th>Cost per event</th></tr><tr><td>Neutropenia</td><td>£<u>655.34</u></td></tr></table></td><td>The Company proposes that the table is amended to:<table><tr><th>Adverse event</th><th>Cost per event</th></tr><tr><td>Neutropenia</td><td>£<u>387.69</u></td></tr></table></td><td>To correctly reflect neutropenia event costs.</td><td>The EAG thanks the company for identifying the factual inaccuracy and has updated the report accordingly</td></tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Incorrect proportions receiving radiation are provided.

Section Table 64, page 132
<table>
<tr><th>Treatment</th><th>Proportion receiving treatment, A+AVD (ECHELON-1)</th><th>Proportion receiving treatment, ABVD (ECHELON-1)</th></tr>
<tr><td>Radiation</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>The Company proposes that the table is amended to:
<table>
<tr><th>Treatment</th><th>Proportion receiving treatment, A+AVD (ECHELON-1)</th><th>Proportion receiving treatment, ABVD (ECHELON-1)</th></tr>
<tr><td>Radiation</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>To correctly reflect the proportion receiving radiation therapy of those patients who go on to receive subsequent anticancer therapy.</td>
<td>The EAG considers that this is not a factual inaccuracy. In the company’s response to clarification question B13 the company outlines that [redacted]% and [redacted]% of A+AVD and ABVD patients received radiation as a subsequent anti-cancer therapy based on the</td>
</tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			March 2023 data-cut.
The number and proportion of patients in the A+AVD arm who experienced Grade ≥3 peripheral neuropathy is incorrect and should be updated to reflect the data provided in answer to the EAG's clarification question A7b. **Section 3.3.6.4, page 60** **And** **Section 3.5, page 68** "…*72 A+AVD patients (11%) had a Grade ≥3 peripheral neuropathy TEAE*…"	The Company proposes that the text is amended to: "*The EAG also notes that 68 A+AVD patients (10%) had a Grade ≥3 peripheral neuropathy TEAE*…"	To provide correct data.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text in the EAG report.
Some instances of escBEACOPP described in the EAG report refer to prednisone instead of prednisolone. **Section 2.2.1, page 28** "…*escalated treatment with bleomycin, etoposide, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine and prednisone (escBEACOPP)*…"	The Company proposes that 'prednisone' is amended to 'prednisolone'.	Per the EAG's suggested correction of prednisone to prednisolone for escBEACOPDac (clarification question B23), this is also applicable for escBEACOPP.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
This change should also be made in the following locations in the EAG report: **List of abbreviations, page 17** **Section 4.2.10.1, Table 53, page 122**			text in the EAG report.
Section 2.3.1, page 36 "*The EAG also notes that there was a similar proportion of patients aged <60 years and ≥60 years in RATHL ([redacted]% and [redacted]%, respectively) compared to in ECHELON-1 (87.3% and 12.7%, respectively).*"	The Company proposes that the text is amended to: "*The EAG also notes that there was a similar proportion of patients aged <60 years and ≥60 years in the Stage III and IV RATHL cohort ([redacted]% and [redacted]%, respectively) compared to in ECHELON-1 (86.1% and 13.9%, respectively).*"	To provide correct data.	The EAG thanks the company for highlighting this factual inaccuracy and has updated the text in the EAG report.

Issue 9 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5, page 68 "and 16 of the A+AVD patients (2%) had ongoing	The Company proposes that the text is amended to:	Typographical error	The EAG thanks the company for identifying the inaccuracies and has

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
had a Grade ≥3 peripheral neuropathy TEAE...”	“and 16 of the A+AVD patients (2%) had an ongoing Grade ≥3 peripheral neuropathy TEAE...”		updated the report accordingly.
Section 4.2.4, page 80 “highly uncertainty”	The Company proposes that the text is amended to: “highly uncertain”	Typographical error	
Section 4.2.4, page 80 “60 cycles”	The Company proposes that the text is amended to: “60 years”	Typographical error	
Section 4.2.6, page 88 “no robust conclusions can be draw”	The Company proposes that the text is amended to: “no robust conclusions can be drawn”	Typographical error	
Section 4.2.6, page 90 “Proportional hazards and accelerate failure time assumptions”	The Company proposes that the text is amended to: “Proportional hazards and accelerated failure time assumptions”	Typographical error	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6, page 93 "there is little difference in statistical fitted"	The Company proposes that the text is amended to: "there is little difference in statistical fit"	Typographical error	
Section 4.2.6, page 96 "Gompertz MCM produced implausible probabilistic cure fractions within the confident intervals"	The Company proposes that the text is amended to: "Gompertz MCM produced implausible probabilistic cure fractions within the confidence intervals"	Typographical error	
Section 4.2.7, page 103 "while also considering SMRS"	The Company proposes that the text is amended to: "while also considering SMRs"	Typographical error	
Section 4.2.7, page 103 "in all NICE TA"	The Company proposes that the text is amended to: "in all NICE TAs"	Typographical error	
Section 4.2.7, page 104	The Company proposes that the text is amended to:	Typographical error	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“ABVD patients experiences”	“ABVD patients experience”		
Section 4.2.8, page 107 “A+ABD patients”	The Company proposes that the text is amended to: “A+AVD patients”	Typographical error	
Section 4.2.9, page 109 “health state utility values (HSVUs)“	The Company proposes that the text is amended to: “health state utility values (HSUVs)”	Typographical error	
Section 4.2.10, page 131 “As such, adverse event costs for both A+ABD”	The Company proposes that the text is amended to: “As such, adverse event costs for both A+AVD”	Typographical error	
Section 6.3.1, page 146 “the EAH considers that the subgroups”	The Company proposes that the text is amended to: “the EAG considers that the subgroups”	Typographical error	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.3.1, page 149 “given patients can be considers unresponsive to ABVD treatment”	The Company proposes that the text is amended to: “given patients can be considered unresponsive to ABVD treatment”	Typographical error	