NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

# Committee Papers

NICE National Institute for Health and Care Excellence

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

**Contents:**



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

# Pre-meeting briefing
# Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

# Abbreviations

| | | | |
|---|---|---|---|
| ALCL | Anaplastic large cell lymphoma | OR | Objective response |
| ALK | Anaplastic lymphoma kinase | ORR | Overall response rate |
| ALK-ve | Anaplastic lymphoma kinase-negative | OS | Overall survival |
| ALK+ve | Anaplastic lymphoma kinase-positive | PD | Progressed disease |
| Allo-SCT | Allogeneic stem cell transplant | PFS | Progression-free survival |
| ASCT | Autologous stem cell transplant | PTCL | Peripheral T-Cell Lymphoma |
| CR | Complete remission | PR | Partial remission |
| ICER | Incremental cost effectiveness ratio | PS | Performance status |
| IRF | Independent review facility | QALY | Quality-adjusted life year |
| INV | Investigator | R/R | Relapsed or refractory |
| KM | Kaplan-Meier | sALCL | Systemic anaplastic large cell lymphoma |
| NPP | Named Patient Programme | SD | Stable disease |

# Key issues:
# Clinical management and clinical effectiveness

- Where in the treatment pathway would brentuximab vedotin be used?
- What is the rate of stem cell transplant post brentuximab and post-chemotherapy seen in clinical practice in England?
- What treatments are given in clinical practice on disease progression?
- How many cycles of brentuximab vedotin would a patient receive in clinical practice in England?
- How effective is brentuximab vedotin?
  - Phase II Single arm trial – 58 people
  - 2 retrospective studies
  - 3 Named Patient Programmes

# Key issues: Cost effectiveness
# Brentuximab vedotin (no SCT)

- PFS
  - Should the base case analysis use the per investigator or per independent review assessment of disease progression from SG035-0004?
  - Is it appropriate to use a mixture cure model?
- OS
  - Is it appropriate to use a mixture cure model?

# Key issues: Cost effectiveness Chemotherapy (no SCT)

- PFS
  - Which is the most appropriate source of data for chemotherapy?
    - Self control group from SG035-0004 (n=39/58, 67%): used in the base case analysis
    - Mak et al. :used in sensitivity analyses
  - Is it appropriate to use a different extrapolation approach for chemotherapy (no SCT) to that used for brentuximab vedotin (no SCT) i.e. use standard parametric models rather than mixture cure model?
- OS
  - Is it appropriate to use 2 alternative data sources for PFS and OS?
    - Company used self-control data from SG035-004 for PFS and Mak et al. for OS
    - ERG preferred Mak et al data to be used for both PFS and OS

# Key issues: Cost effectiveness

- There is uncertainty in the mortality rate for patients who are long term survivors compared with the general population
  - Is it appropriate to apply an additional excess mortality to all parametric OS extrapolations?
  - Which value is the most appropriate?
- What is the most appropriate distribution of post progression therapies to use in the model?
  - Trial based post-progression therapy distribution (ERG's preferred analysis)
  - Post-progression therapy based on clinical expert (Company's preferred analysis)
- What is the most plausible ICER?
- Is the end of life criteria met?
- Are there any additional benefits that have not been captured in the QALY?

# Systemic anaplastic large cell lymphoma

- Anaplastic large cell lymphoma (ALCL) is  rare disease which occurs most commonly in children and young people, representing around 40% of all non-Hodgkin Lymphoma diagnoses in paediatric populations and 2%-5% of all adult cases of non-Hodgkin Lymphoma
- 2 main types of ALCL: systemic ALCL (sALCL) and primary cutaneous ALCL
- CD30+ is invariably expressed on the surface of sALCL cells
- sALCL often presents as an aggressive stage III to IV disease, commonly with systemic symptoms and extranodal involvement
- 2 subtypes of sALCL: defined by presence or absence of anaplastic lymphoma kinase (ALK) protein expression
- People with ALK+ve ALCL tend to be younger than those diagnosed with ALK-ve ALCL
- Prognosis of ALK+ve ALCL is better than that of ALK-ve disease

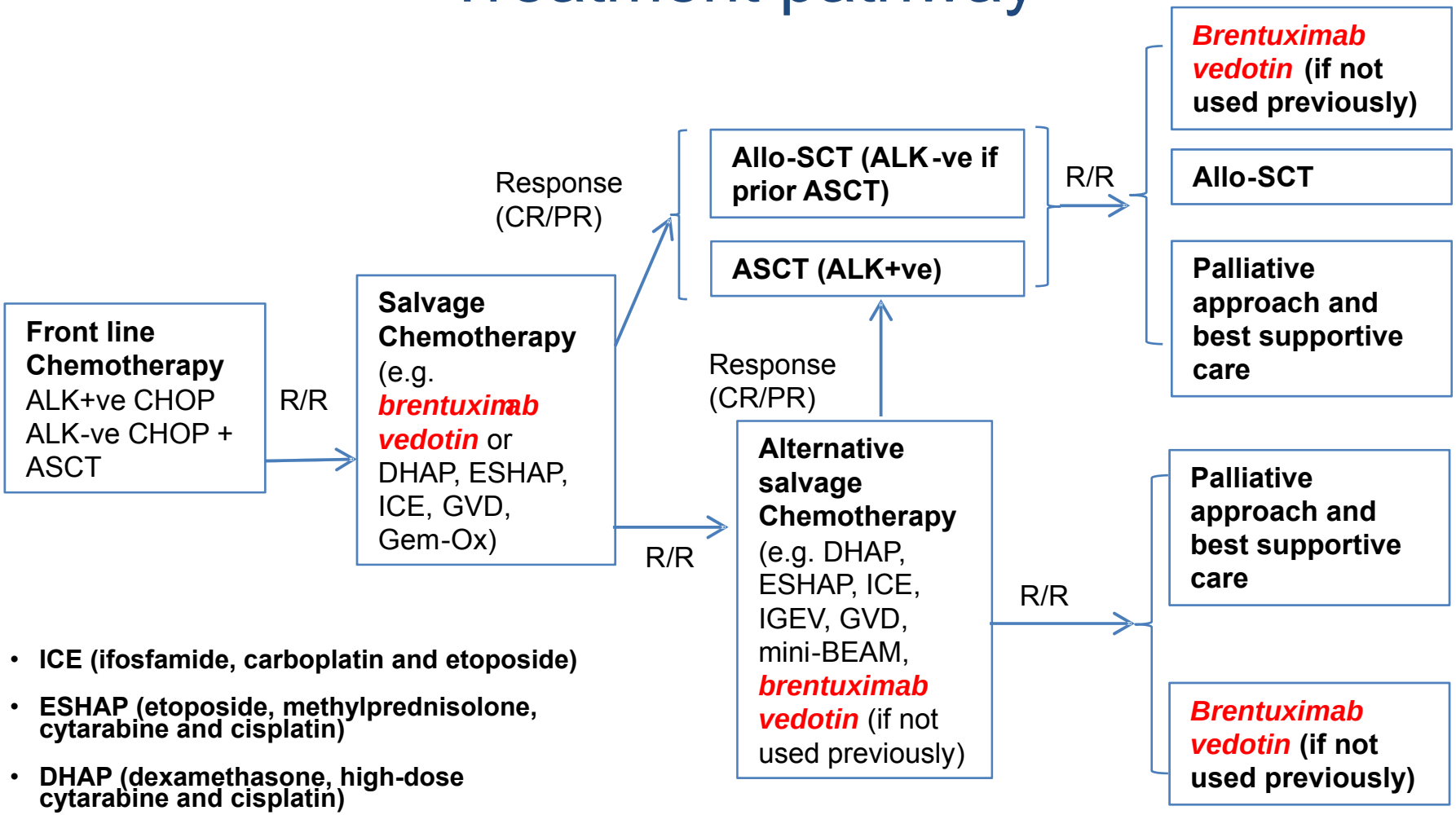
# Brentuximab vedotin

| | |
|---|---|
| **Mechanism of action** | Antibody–drug conjugate comprising an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to a potent chemotherapeutic agent. The antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells. |
| **Marketing authorisation** | "Brentixumab vedotin is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).<br><br>Brentuximab vedotin has been available through the Cancer Drugs Fund in England since April 2013 for "relapsed or refractory systemic anaplastic large cell lymphoma". |
| **Administration and dose** | 1.8 mg/kg administered intravenously over 30 minutes every 3 weeks |
| **Cost** | List price £2,500 per vial<br><br>Company has agreed a commercial access agreement with NHS England* |

# Decision problem

| | NICE scope | Company submission |
|---|---|---|
| **Population** | People with relapsed or refractory systemic anaplastic large cell lymphoma | Patients with relapsed or refractory systemic anaplastic large cell lymphoma who have received at least one prior regimen with curative intent:<br>• ALK+ve<br>• ALK-ve |
| **Comparator** | Established clinical management without brentuximab vedotin | Established clinical management without brentuximab vedotin |
| **Outcomes** | • Overall survival<br>• Progression-free survival<br>• Objective response rate<br>• Complete response rate<br>• Adverse effects of treatment<br>• Health-related quality of life<br>• Rate of stem cell transplantation | • As per NICE scope |

# Treatment pathway




- **ICE (ifosfamide, carboplatin and etoposide)**
- **ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin)**
- **DHAP (dexamethasone, high-dose cytarabine and cisplatin)**
- **GDP (gemcitabine, dexamethasone and cisplatin)**
- **Gem-P (gemcitabine, methylprednisolone and cisplatin)**

# Clinical expert's comments (1)

- sALCL in adults is a rare disease.
- It is now clear that there is significant clinical and biological heterogeneity particularly within ALK-ve sALCL
- The most commonly used first-line therapy for sALCL in the UK is CHOP (or CHOEP) chemotherapy. Some patients receive first-line consolidation with high-dose chemotherapy (most commonly BEAM) and ASCT
- The majority of patients with sALCL experience relapsed/refractory (R/R) disease. Such patients represent a major area of unmet clinical need
- There is a lack of clear consensus or strong evidence base on which to recommend second line therapies. Conventional salvage chemotherapy (e.g. ICE) is used, followed by either ASCT or allo-SCT; determined by clinician and patient preference influenced by a number of factors (e.g. patient age and fitness, nature and response to prior therapy(ies), donor availability and clinical trial options)
- Clinical experience of brentuximab vedotin as a treatment for R/R sALCL Has been possible through the CDF for R/R ALCL. Clinical experience has been that brentuximab vedotin is very well tolerated with a limited side-effect profile usually manageable with dose reductions or delays

# Clinical expert's comments (2)

- Typically, patients with R/R sALCL have received treatment with brentuximab vedotin with 2 strategies in mind (according to individual patient and disease characteristics and guided by regional lymphoma MDT discussion)
  - brentuximab vedotin as a first salvage therapy as a bridge to consolidation with either ASCT or allo-SCT. In this setting, response assessment with PET-CT imaging would typically be performed after 4 doses of brentuximab vedotin administered on a 21 day cycle.
- Brentuximab vedotin as a first salvage therapy without the intention to consolidate with SCT but the intention to deliver 16 cycles of brentuximab vedotin supported evidence of ongoing response and tolerability.
- A number of UK sites have participated in the ECHELON-2 phase III RCT (NCT01777152), which compared standard CHOP with CHP and brentuximab vedotin in patients with newly diagnosed CD30+ PTCL. This trial is closed to recruitment in 2016 and results are awaited

# Patient perspective

- No patient expert statements received

# Clinical effectiveness

# Company's clinical evidence

| Company submission included: | |
|---|---|
| Main evidence: SG035-0004. 5 data up-dates, 2 presented in company submission:<br>• 16.8 months: primary end point data (Pro et al. 2012)<br>• 71.4 months: for up to 5-years follow-up (Pro et al. 2016) | See slides 13-22 in PMB<br>*Company submission:*<br>*pages 49-54 for trial details*<br>*pages 57-66 for trial results* |
| Supplementary evidence: 2 retrospective case series<br>• Gopel et al. 2014<br>• Chihara et al. 2015 | *Company submission:*<br>*pages 54-56 for details of trials*<br>*pages 66-67 for results of trials* |
| Supplementary evidence: 3 Named Patient Programmes | *Company submission:*<br>*pages 54-56 for details of trials*<br>*pages 56-57 for results of trials* |
| Mak et al. 2013: used in the unadjusted indirect comparison for the economic modelling | See slides 22-24 in PMB<br>*Company submission:*<br>*Pages 88-91*<br>*ERG report:*<br>*pages 46-49, 81* |

# SG035-0004 trial (Pro et al.)

| | |
|---|---|
| **Design** | Multicentre, phase II, open-label, single arm<br>22 centres in the US, Canada and Europe (UK 1 centre, 3 participants) |
| **Population (n=58)** | Patients with relapsed or refractory sALCL after treatment failure of at least 1 prior therapy with curative intent; age ≥12 years (USA) or ≥18years (other countries) |
| **Baseline characteristics** | Median age 52 years, predominantly ALK-ve and chemo-refractory disease (72%). 50% considered refractory, 50% experienced relapse; 62% primary refractory to front-line treatment (i.e. no CR or relapse within 3 months of front-line therapy), 22% not achieved an ORR to any previous therapy. Median number of prior chemotherapy regimens excluding ASCT=2 (range 1-6 regimens); 26% had previous ASCT before study enrolment. Most recent therapy before study enrolment ASCT or multi-agent chemotherapy for 91% of patients. |
| **Intervention** | Brentuximab vedotin 1.8 mg/kg every 3 weeks |
| **Treatment** | Maximum 16 cycles (approximately 1 year)<br>Median number of cycles 7<br>Among patients with an OR, median number of cycles was 8 |
| **Outcomes** | **Primary outcome**: ORR per independent review facility (IRF) (response criteria: Cheson 2007) **Secondary outcomes**: Duration of response per IRF, complete remission per IRF, PFS per IRF and OS |
| **Follow-up** | 5 year. Survival data reported after 3, 4 and 5 years separately |

# SG035-0004 results: Per IRF (median follow-up 16.8 months)

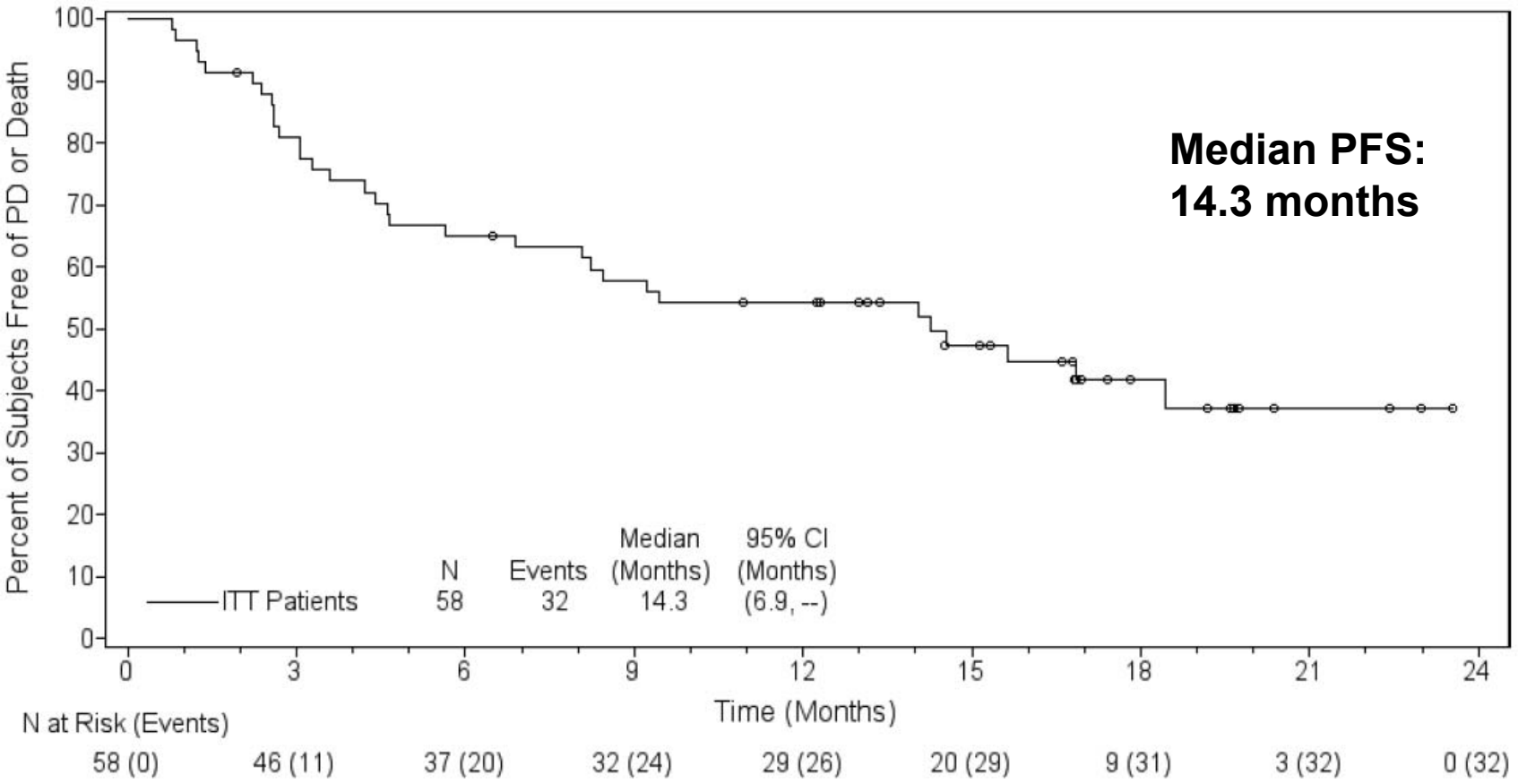
| Best clinical response (N=58) | IRF N (%) | 95% CI |
|---|---|---|
| Objective response rate (CR + PR) | 50 (86) | 74.6, 93.9 |
| • Complete remission (CR) | 34 (59) | 44.9, 71.4 |
| • Partial remission (PR) | 16 (28) | NA |
| Disease control rate (CR+PR+SD) | 52 (90) | 78.8, 96.1 |
| **Duration of response** | **Median per IRF** | **95% CI** |
| Objective response rate (CR + PR)* | 13.2 | 5.7, NE |
| Complete remission (CR) | Not reached | 13.0, NE |
| **Overall survival** | **Median** | **95% CI** |
| Median | Not reached** | 21.3, NE |

NE = Not estimable

* The range of DOR was 0.1+ months to 21.7+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 11.8 months.

** The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 months

# PFS: SG035-0004 (ITT set)
# Per IRF (median follow-up 16.8 months)



# Duration of response: SG035-0004 Per INV (median observation time 71.4 months)

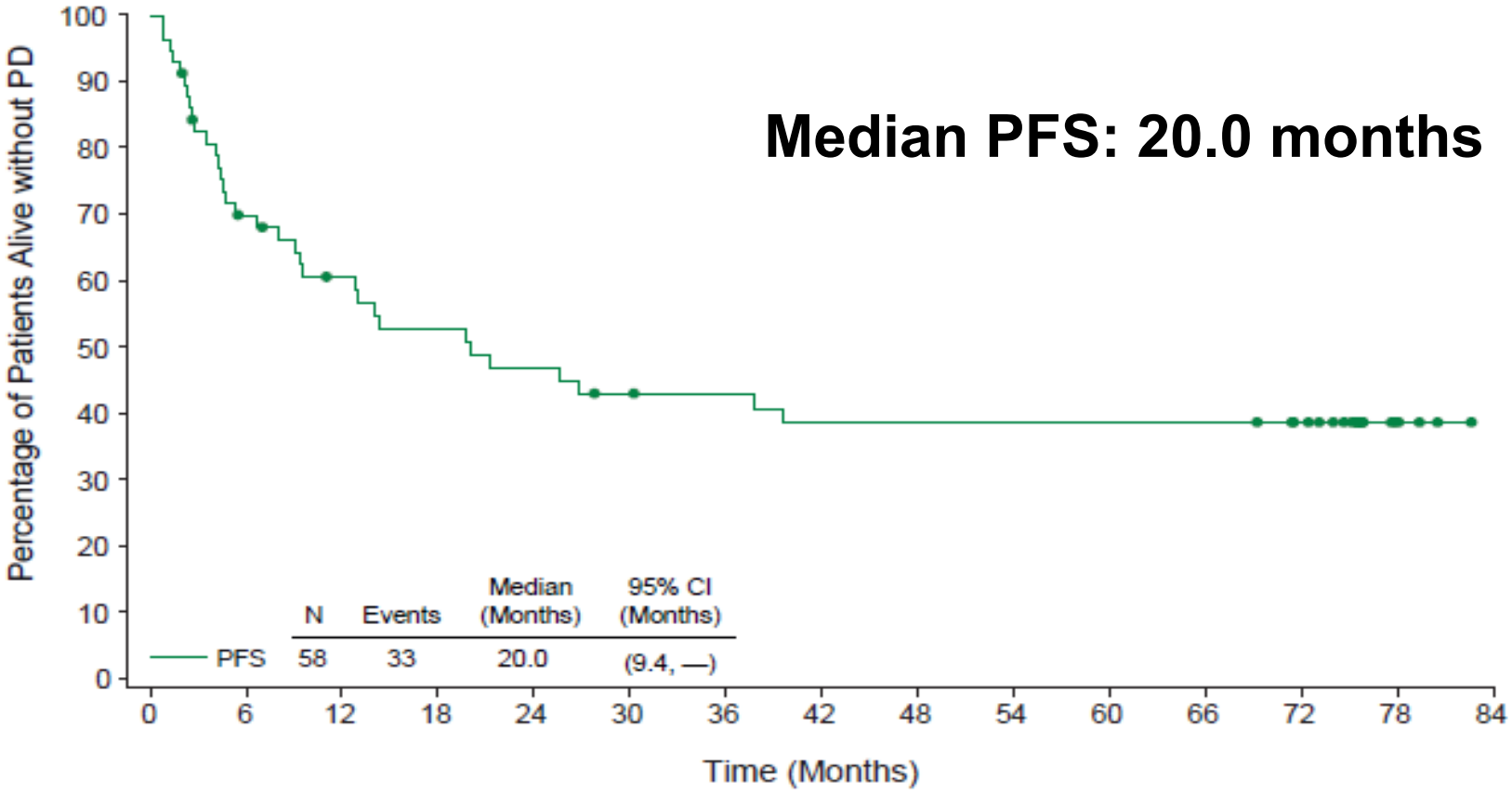
| | |
|---|---|
| **ORR** | 86% (n=50/58) |
| **CR** | 66% (38/58) |
| Of 38 CR patients: | |
| **DOR** | Not reached (95% CI: 20.0, -), range 0.9 to 79.7+ months |
| **Median OS** | Not reached |
| **Median PFS** | Not reached |
| Of 38 CR patients,16 underwent SCT after brentuximab vedotin: | |
| **Type of SCT** | 8 allo SCT, 8 ASCT |
| **Median OS** | Not reached |
| **Median PFS** | Not reached |
| Of 38 CR patients, 22 did not receive SCT after brentuximab vedotin: | |
| **Median OS** | Not reached |
| **Median PFS** | 39.4 months (95% CI: 14.3, -) |
| Of 38 CR patients, 16 still enrolled in trial and in remission without the start of new anticancer therapy, other than SCT | |
| **Median observation** | 75.4 months (range 69 to 82.4) |

# OS and PFS: SG035-0004
# Per INV (all enrolled patients, median follow-up 5 years)

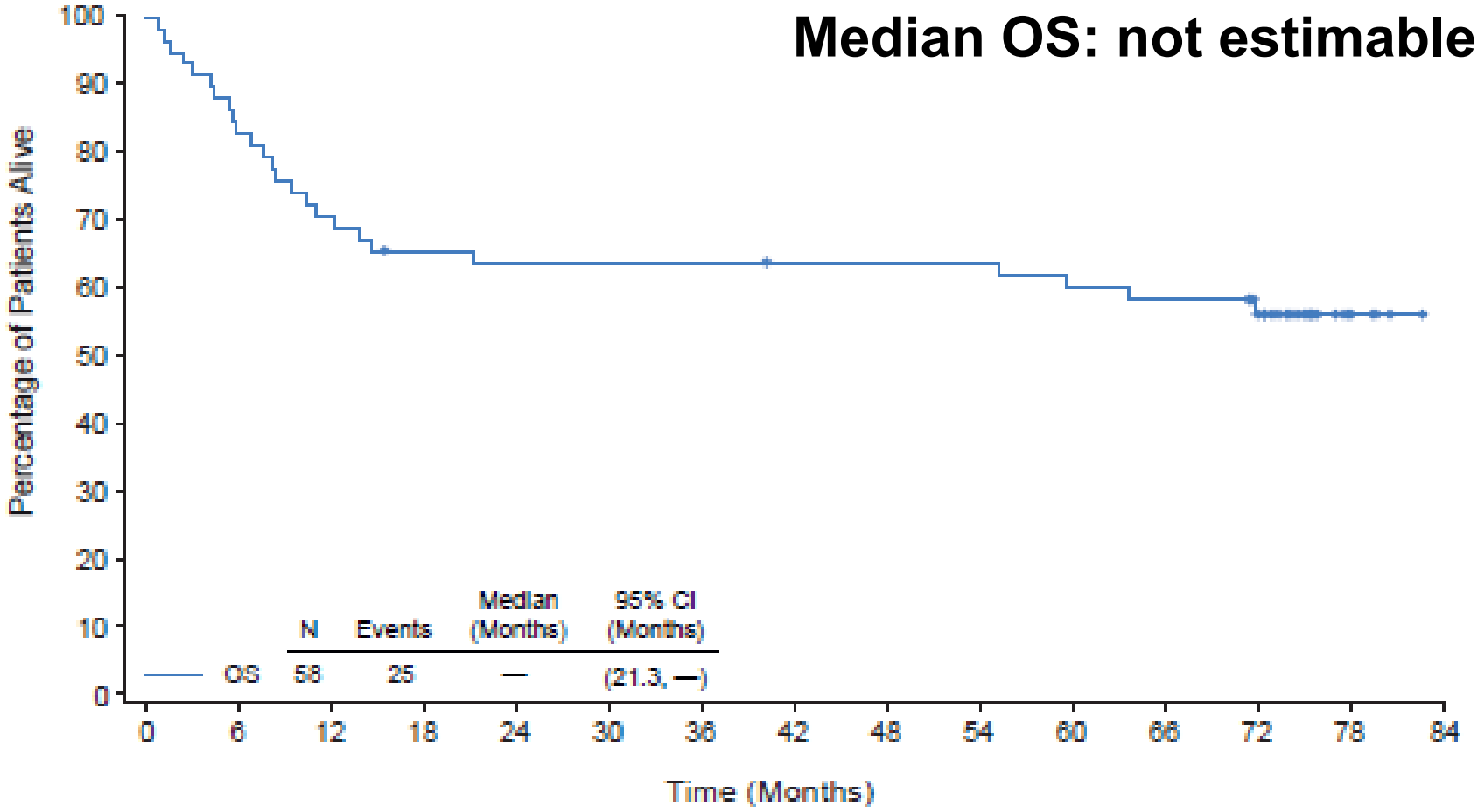
| | |
|---|---|
| Overall population | |
| Estimated 5-year OS rate | 60% (95% CI: 47, 73), |
| **Median OS** | Not estimable (95% CI: 21.3,-; range 0.8 to 82.4+ months) |
| **Median PFS** | 20.0 (95% CI: 9.4,-) * |
| Of 58 enrolled patients, 42 (72%) had ALK-ve disease: | |
| **Estimated 5-year OS** | 61% (95% CI: 47%, 76%) |
| **Median PFS** | 20 months (95% CI 6.7,-) |
| **Median OS** | Not reached |
| Of 58 enrolled patients, 16 (28%) had ALK +ve disease: | |
| **Estimated 5-year OS** | 56% (95% CI: 32%, 81%) |
| **Median PFS** | 25.5 months (95% CI 8.0,-) |
| **Median OS** | Not reached |

* Median PFS in patients who achieved a CR has not been reached

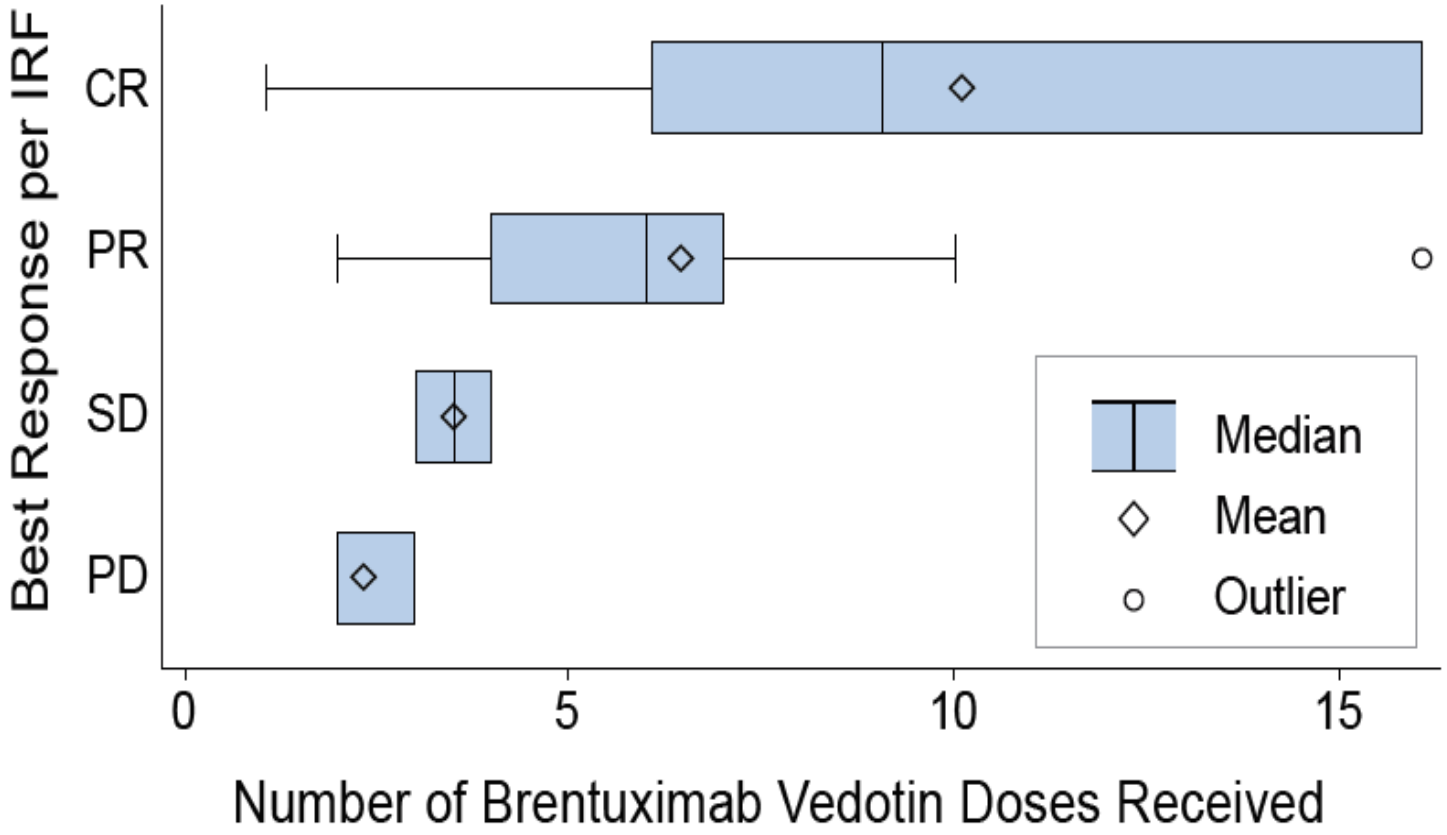
# PFS: SG035-0004
# Per INV (median follow-up 5 years)



# OS: SG035-0004
# Per INV (median follow-up 5 years)



# Number of cycles of brentuximab vedotin: SG035-0004 Per INV (median observation time 71.4 months)



# Adverse events reported by included studies

- Adverse events consistent across all studies with every patient experiencing at least one adverse event
- Sixteen serious adverse events in 11 patients related to brentuximab vedotin were reported by Pro et al. Two events were grade 4 and two were grade 2. Three of these events led to treatment discontinuation

# ERG's commentary: Clinical effectiveness evidence for brentuximab vedotin

- SG035-0004 is an appropriate source of evidence
- Rarity of disease and lack of standard comparator make randomised trial unfeasible, therefore single arm trial results acceptable
- Reported outcomes assessed by IRF support the efficacy of brentuximab vedotin
- OS, PFS and duration of response for patients still on study and in remission suggest long term efficacy with brentuximab vedotin
- The ERG noted that small patient numbers and unequal distribution between subgroup categories increase uncertainty in results, therefore appropriate to base economic model on whole trial population
- The ERG commented that whilst studies by Gopal et al. and Gibb et al. include small number of patients with ALCL, results support those of SG035-0004

# Indirect treatment comparison with chemotherapy (1)

- No data providing direct comparative evidence for brentuximab vedotin compared with chemotherapy.
- The company identified 2 studies through its systematic review; Mak et al. 2013 and Coiffier et al 2012
- The company focussed its submission on Mak et al. as Coiffier et al. evaluated romidepsin which does not have a marketing authorisation in the UK and the study had a shorter follow up. In addition the chemotherapy regimens administered in Mak et al. were reflective of those used in clinical practice in the UK
- Mak et al. reported PFS and OS data for a historical cohort of 153 patients with PTCL on the British Colombia Cancer Agency Lymphoid Cancer database who had relapsed or experienced progressive disease
- The company focussed its analyses on a subset of Mak et al. who had received systemic chemotherapy (n=89). Median follow-up 4 years. None had received SCT

# Indirect treatment comparison with chemotherapy (2)

- The company considered 2 subgroups of patients from the subset of Mak et al (n=89) as potentially relevant for informing PFS and OS for on chemotherapy arm in the economic model
  - A subgroup of patients with ALCL (n=17)
  - A broader subgroup which consisted of patients with PTCL and a performance status <2 (n=47)
- The company undertook an unadjusted indirect comparison of brentuximab vedotin with chemotherapy using a subgroup of patients from SG035-0004 who do not go on to receive SCT after discontinuation with brentuximab vedotin (n=41) and the subgroup of patients from Mal et al. with ALCL (n=17) and with PTCL with a performance status <2 (n=47). The company had to rely on an unadjusted indirect comparison because baseline characteristics of the subgroups in Mak et al. were not reported
- In response to clarification the company did explore whether a matched adjusted indirect comparison (MAIC) between SG035-0004 and Mak et al. could be undertaken. The company noted that following adjustment for available variables, the effective sample size for the MAIC would be 4.8, and therefore concluded that it was inappropriate to undertake an MAIC.

# ERG's commentary: Indirect treatment comparison with chemotherapy

- Given the limited availability of data, the ERG agreed that the unadjusted indirect comparison offers the appropriate choice of comparison and that it was inappropriate to undertake a MAIC.
- The ERG noted that while the subgroup from MAK et al. with PTCL and a performance status<2 was not vastly different from the subgroup with ALCL, it may contain a number of histologies with inherently different responses and survivals
- The ERG agreed with the company that there was heterogeneity between the populations in SG035-0004 and Mak et al. particularly relating to age, stage of disease and performance status (all likely to bias in favour of brentuximab vedotin). However the ERG stated that by basing the analysis on the subgroup from Mak et al. with PTCL and performance status <2 (used in the company's base case analysis for OS and as a sensitivity analysis for PFS), this should improve comparability with SG035-0004 (where only 2% of patients in SG035-0004 had a performance status >2), assuming stage of disease and age are correlated with performance status

# Cost effectiveness

# Published economic evaluations

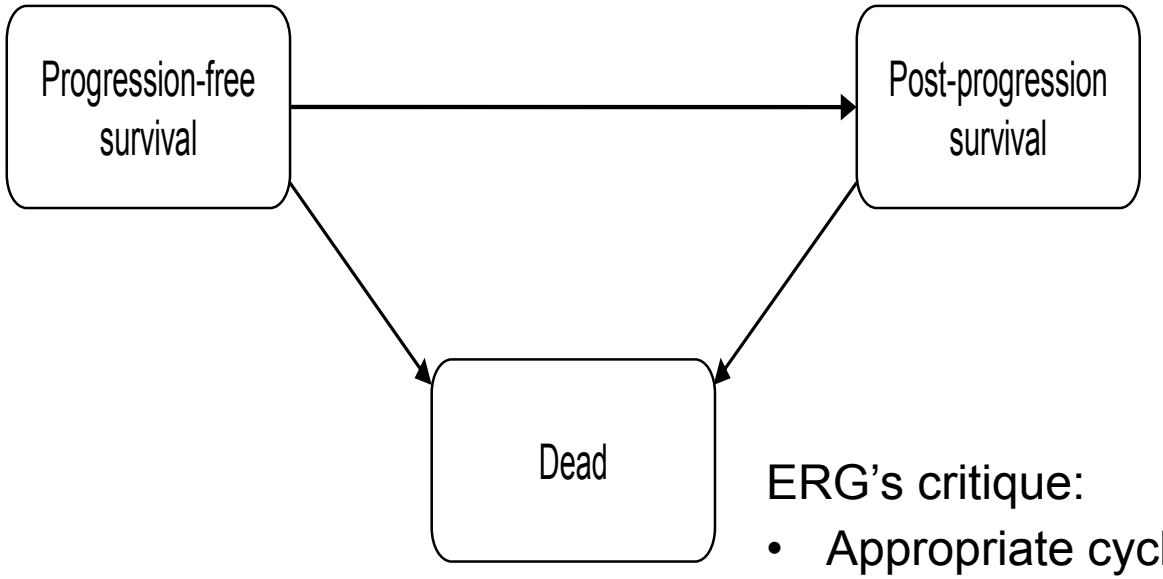
- The company identified 2 studies: Zou et al 2016 and Hux et al 2016 . Both compared brentuximab vedotin with chemotherapy in a population with R/R sALCL
- The company excluded Zou et al. because it adopted a Taiwanese perspective. The ERG commented that irrespective of the costings and outcomes perspective, the methods for extrapolating survival and simulating comparisons with chemotherapy may still have provided useful insights
- The ERG considered Hux et al. to be the most relevant study as it adopted a UK perspective. In response to clarification, the company provided reasons for the differences in the reported ICERs in the company submission and in Hux et al. (for further details see Table 2 [response to Question B1] in the company's response to clarification)
- The company's review of cost-effectiveness studies concluded that there was insufficient evidence to make a judgement on the cost-effectiveness in the UK setting. Given longer-term follow-up data for S035-0004 has become available since the publication of Hux et al., the ERG agreed with the company's conclusion. However, the ERG commented that Hux et al. provides a useful reference point to understand the key drivers behind the improved ICERs in the company's submission

# Company's model

## Partially consistent with NICE reference *case*

| | |
|---|---|
| **Type** | Partitioned-survival |
| **Population** | People with relapsed or refractory systemic anaplastic large cell lymphoma |
| **Comparators** | Revised model submitted after clarification with comparator as "established clinical management without brentuximab vedotin" (referred to as chemotherapy) |
| **Time horizon** | Lifetime (60 years)<br>Considered appropriate by the ERG who note 99% of modelled brentuximab vedotin patients have died by 50 years and 99% of modelled chemotherapy patients have died by 43 years |
| **Measure of health effect** | QALY |
| **Health states for QALY** | Deviated from reference case as health state vignettes were used based on a published study. Vignettes were not directly reflective of EQ-5D health states and additional clinical expert assumption was used to assign utility decrements from general population norms to long term survivors. |
| **Discount rate** | 3.5% rate applied to both costs and health effects |
| **Perspective** | Takes NHS perspective with PSS not considered |

# Company's model and ERG critique
## Partitioned-survival model structure




ERG's critique:

- Appropriate cycle length and half-cycle correction
- Modelling approach appropriate.
- Model structure represents treatment pathway

# Company's model: Population (1)

- The characteristics of the modelled cohorts are sourced primarily from SG035-0004 ITT population

Characteristics of the modelled cohorts

| Parameter | Mean | SD |
|---|---|---|
| Body weight | 76.35 | 20.385 |
| BSA ($m^2$) | 1.88 | 0.28 |
| Starting age (years) | 47.70 | 16.85 |
| Male | 57% | Std. Error: 7% |

# Company's model: Population (2)

6 cohorts modelled, depending on their treatment pathway (brentuximab vedotin or comparator), and whether or not they received an ASCT or allo-SCT

| Technology | Model cohort | Name | Description | Base case proportion |
|---|---|---|---|---|
| Brentuximab vedotin | 1 | Brentuximab vedotin, no SCT | Patients who only receive brentuximab vedotin | 71% |
| | 2 | Brentuximab vedotin + ASCT | Patients who receive brentuximab vedotin followed by ASCT | 14% |
| | 3 | Brentuximab vedotin + allo-SCT | Patients who receive brentuximab vedotin followed by allo-SCT | 16% |
| Chemotherapy | 4 | Chemotherapy, no SCT | Patients who only receive chemotherapy | 86% |
| | 5 | Chemotherapy + ASCT | Patients who receive chemotherapy followed by ASCT | 7% |
| | 6 | Chemotherapy + allo-SCT | Patients who receive chemotherapy followed by allo-SCT | 7% |

# Company's model: Intervention and comparators

- **Intervention**: **Brentuximab vedotin**
  - In line with the marketing authorisation, model assumes brentuximab vedotin was administered as a single outpatient IV infusion on day 1 of each 21-day cycle at a dose of 1.8 mg/kg
  - In line with marketing authorisation, patients in SG035-0004 could have continued on treatment until disease progression or unacceptable toxicity
  - Patients who achieved SD or better as assessed by INV were to receive a minimum of 8 cycles up to a maximum of 16 cycles
  - Mean number of cycles received by patients in SG035-0004 was 8 (range 1 to 16)
- **Comparator**: **established clinical management (referred to as chemotherapy)**
  - Modelled comparator consisted of a composite of multi-agent chemotherapy treatments given as salvage therapy. The multi-agent therapies were ICE, ESHAP, DHAP, GDP and Gem-P

# ERG's review: Intervention and comparators

- Brentuximab vedotin modelled according to the inclusions and exclusion criteria from SG035-0004 for a mixed cohort of patients who have progressed following either primary treatment (first line CHOP chemotherapy), previous salvage therapy, or a previous ASCT. Previous allo-SCT was excluded
- The ERG's clinical expert agreed that the chemotherapy regimens chosen by the company as the comparator was appropriate
- The company's original economic model included costs of subsequent brentuximab vedotin treatment for patients progressing following chemotherapy regimens. This was not consistent with the final scope issued by NICE which specified 'established clinical management with out brentuximab vedotin'. Therefore the economic model was corrected at clarification stage

# Company's model: treatment effectiveness and extrapolation

- Based on a combination of:
  - Clinical response rates (CR, PR, SD and PD)
  - SCT by response categories
  - PFS and OS by transplant status (no SCT, ASCT and allo-SCT)

- Those who receive a SCT: PFS and OS modelled to be equivalent irrespective of treatment arm

- Those who receive no SCT: Substantial differences in PFS and OS between brentuximab vedotin and chemotherapy. Therefore PFS and OS are based on the unadjusted indirect comparison

# Company's model: Data sources for PFS and OS Base case analysis

| Treatment | Endpoint data source | | Model cohort(s) * |
|---|---|---|---|
| | PFS | OS | |
| **Brentuximab vedotin, no SCT** | SG035-0004; patients who did not receive subsequent SCT (n=41) | SG035-0004; patients who did not receive subsequent SCT (n=41) | 1 |
| **Chemotherapy, no SCT** | SG035-0004; self-control patients (n=39) | Mak et al., 2013; PTCL patients with performance status<2 (n=47) | 4 |
| **ASCT** | Smith et al., 2013; ASCT patients (n=115) | Smith et al., 2013; ASCT patients (n=115) | 2,3,5,6 |
| **Allo-SCT** | Smith et al., 2013; allo-SCT patients (n=126) | Smith et al., 2013; allo-SCT patients (n=126) | 2,3,5,6 |

# Company's model: population receiving SCT (1)

- Model assumes brentuximab vedotin acts as a bridge to SCT for a proportion of patients
- Proportion of CRs and PRs receiving SCT based on 3 approaches:

| Approach | CR | PR | Economic Analysis |
|---|---|---|---|
| Response-based (SG035-0004, ITT population) | 42% | 8% | Base-case |
| Response-based (clinical expert opinion) | 69% | 35% | Sensitivity |
| Equal rate in both treatment arms (Mak et al., 2013) | 20% | 20% | Sensitivity |

- Response rates:
  - Brentuximab vedotin (SG035-0004)
  - Chemotherapy: Base-case (Self-control cohort, SG035-0004), sensitivity analyses (Dong and Crump)

| Response | Brentuximab vedotin | Chemotherapy | | |
|---|---|---|---|---|
| | | Self-control cohort | Dong (2013) | Crump (2004) |
| CR | 66% | 31% | 46% | 16% |
| PR | 21% | 13% | 42% | 33% |
| SD | 7% | 10% | 4% | 17% |
| PD | 3% | 36% | 8% | 17% |

# Company's model: population receiving SCT (2)

- NCCN clinical practice guidelines do not indicate how to identify which patients should undergo ASCT or allo-SCT.
- The base case analysis used the proportion of patients who went on to receive ASCT and allo-SCT from SGO35-0004, and sensitivity analysis used clinical expert opinion

| Approach | Proportion | |
|---|---|---|
| | ASCT | Allo-SCT |
| SG035-0004 (base case approach) | 47% (8/17) | 53% (9/17) |
| Clinical expert opinion (sensitivity analysis) | 25% | 75% |

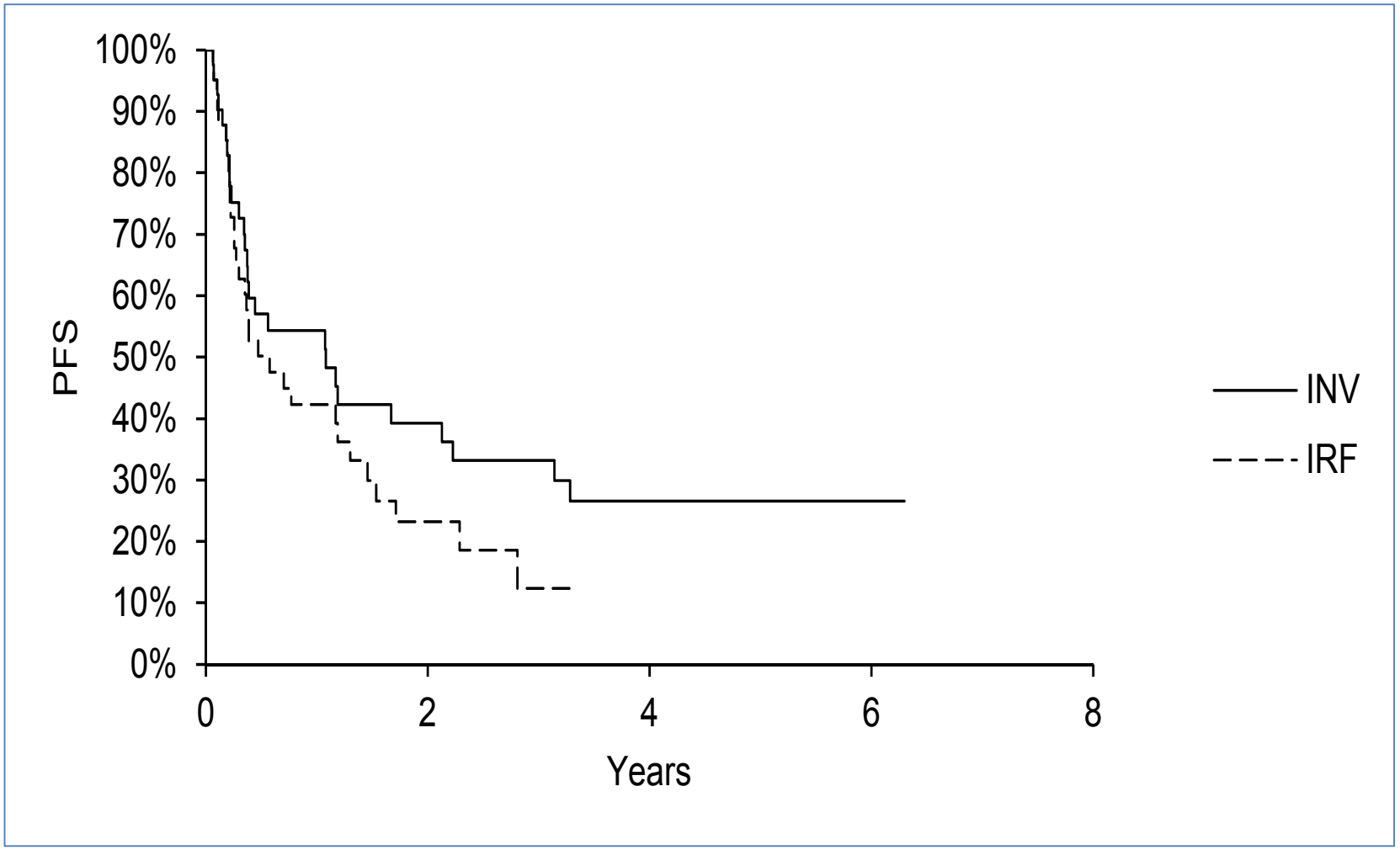
# ERG's critique
# Response rates and proportions receiving SCT

- Issues identified with using self-controls to estimate comparator response rates:
  - could not determine if prior treatments used to estimate response rates are representative of the chemotherapy comparators applied in the model
  - possible underestimation of complete response due to exclusion of patients who achieve long-term remission on chemotherapy or die prior to progression
  - alternative sources of limited value as they report on patients with predominantly newly diagnosed PTLC (Dong et al) or patients with recurrent/refractory B-Cell non-Hodgkin lymphoma (Crump et al)
- The ERG noted that the rates of bridging to ASCT (14%) and allo-SCT (16%) were higher with brentuximab vedotin than with chemotherapy (7% for both ASCT and allo-SCT). The ERG considered this assumption plausible, noting that an important role for brentuximab vedotin is its potential to bridge additional patients to SCT

# PFS: Brentuximab vedotin (no SCT)
## *Trial based data*

- PFS data sourced from the sub-group of patients in SG035-0004 (n=41/58 [71%]) who did not receive SCT
- Disease progression assessed by 2 alternative methods:
  - INV: pre-specified exploratory endpoint
  - IRF: pre-specified secondary endpoint
- INV used in base case analysis because:
  - provided longer follow-up data (71.4 months)
  - 'no SCT' subgroup, maximum INV follow-up 76 months compared with 40 months for IRF data
  - considered more reflective of the assessments used in the self control data

# PFS: brentuximab vedotin (no SCT)
# Kaplan-Meier curves



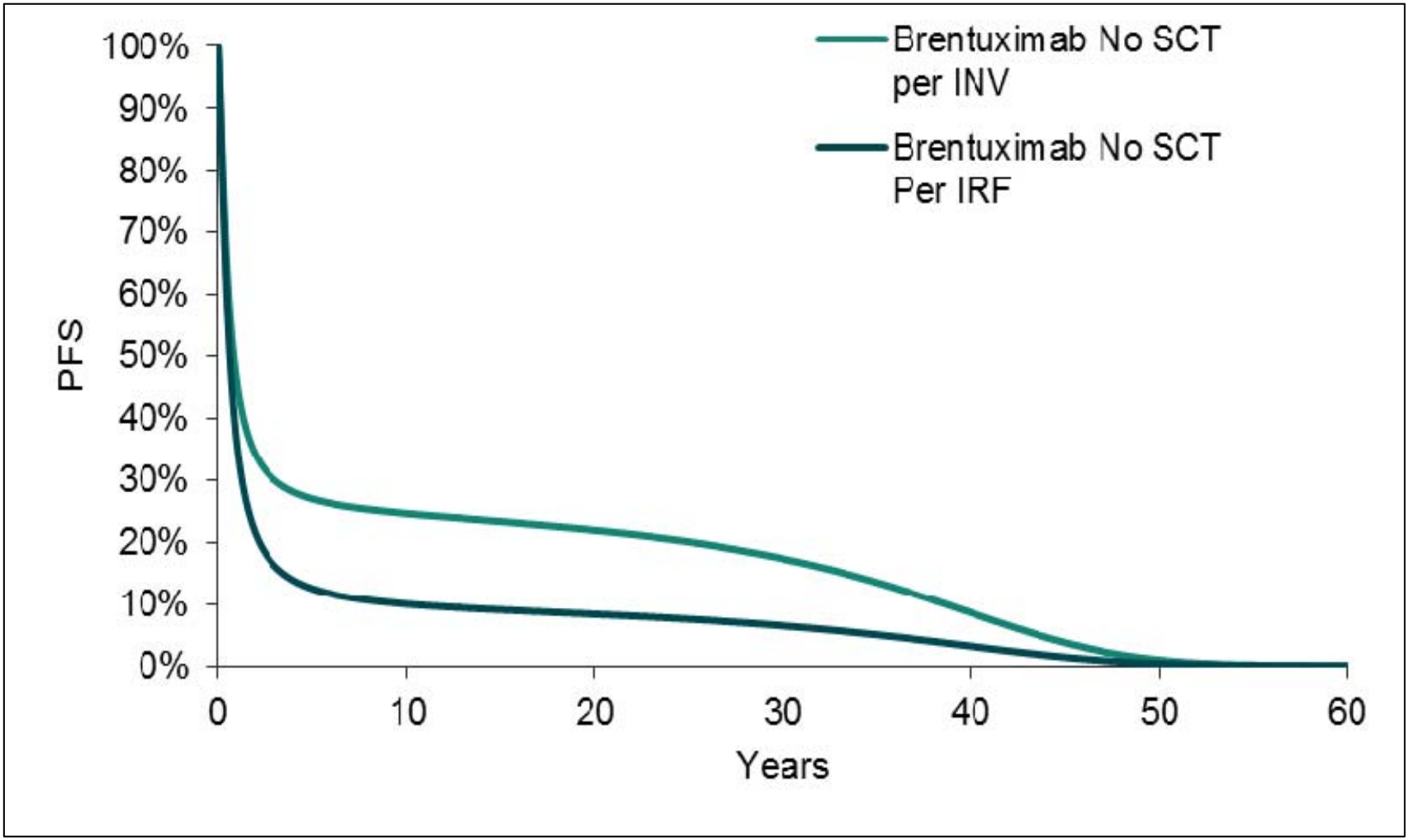
# PFS: Brentuximab vedotin (no SCT)
## *Extrapolation*

- Company assumed that the long plateau in the Kaplan Meier curve for the INV data is indicative of cure
- Company therefore estimated a mixture cure model where:
  - proportion of patients (cure fraction) were assumed to no longer be at risk of progression (PFS function tending towards general population mortality)
  - The remainder (uncured fraction) had a survival function tending towards zero
  - In all cases (cured or uncured), additional 5% excess mortality risk was applied
- Company chose a log-logistic curve, with a cure fraction of 24% (per INV data) or 9% (per IRF data) to extrapolate trial data

# ERG's critique
# PFS: Brentuximab vedotin (no SCT)

- The ERG noted:
  - IRF assessment may have a lower risk of bias and be more objective, however INV provided best available long term data.
  - Both assessments subject to a censoring at later follow-up time points; tails of Kaplan Meier curves subject to a high degree of uncertainty
- The ERG queried the appropriateness of a mixture cure model for 2 reasons:
  - the IRF data did not show evidence of cure, though the company explained that this was likely because of insufficient follow-up
  - the IRF Kaplan Meier curve showed lower PFS at the end of follow-up than the INV curve; indicative that the cure fraction may be over-estimated in the INV data
- The ERG used data available in the company's economic model to compare the company's chosen extrapolation approach for PFS over the full model time horizon.
  - The ERG noted substantial additional PFS gain using INV data compared with IRF

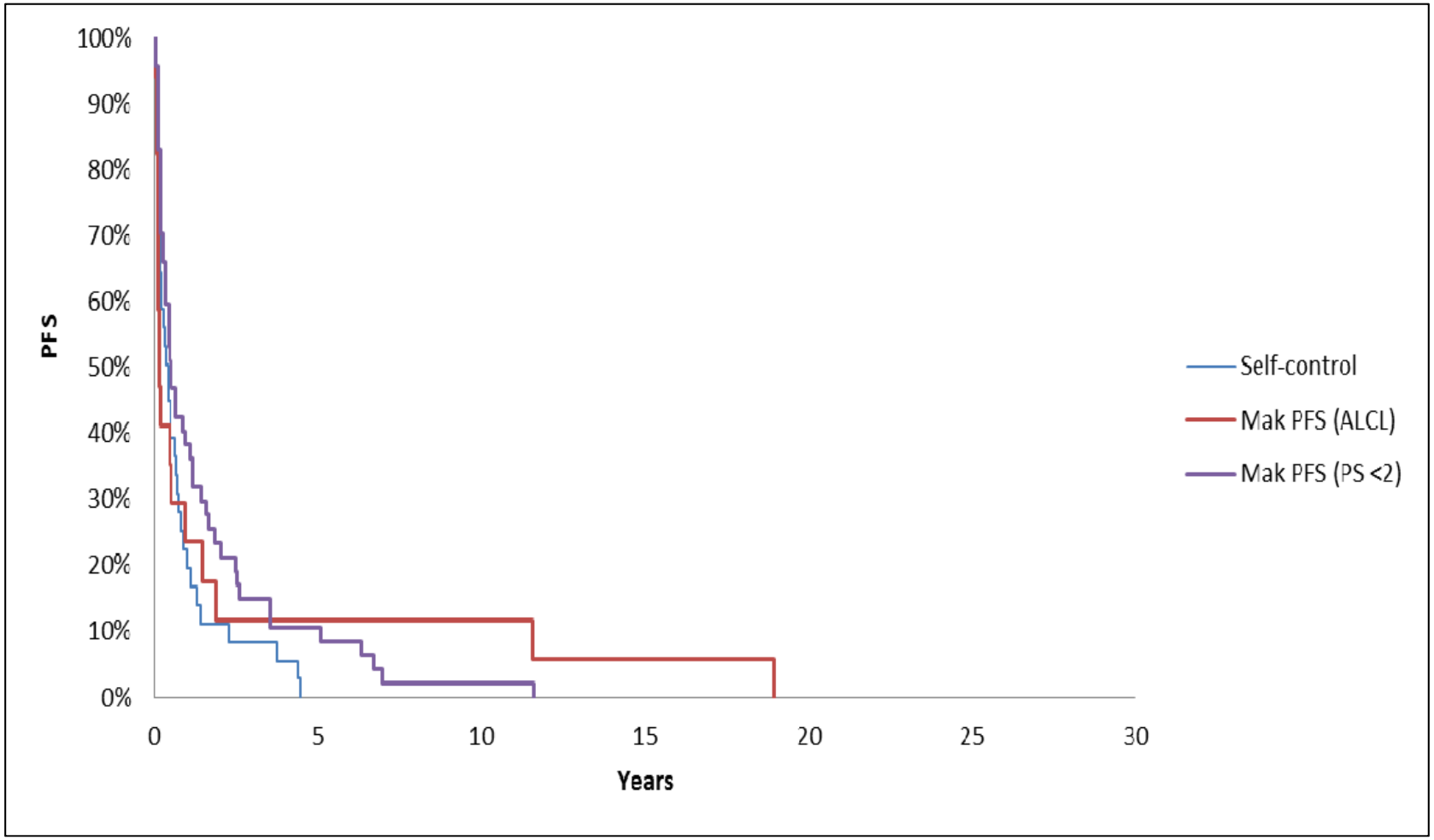
# ERG's critique
# PFS comparison per IRF/INV
# brentuximab vedotin (no SCT)



# PFS: chemotherapy (no SCT)
## *Trial based data*

- The company's model provided PFS data for 3 alternative analyses:
  - **Base case:** internal self-controls from SG-35-0004 consisting of subgroup of patients (n=39/58 [67%]) who had previously had salvage chemotherapy for R/R disease.
  - **Sensitivity analysis:** subgroup from Mak et al. with ALCL (n=17)
  - **Sensitivity analysis:** subgroup from Mak et al. with PTCL and a performance status <2 (n=47)

# PFS: chemotherapy (no SCT)
# Kaplan-Meier curves



# ERG's critique
# PFS: chemotherapy (no SCT)
## *Trial based data*

- The ERG disagreed with the company's choice of data and analytical approach for PFS.
  - The ERG noted patients achieving a long term remission on chemotherapy will not have been captured in the analysis (likely to create a bias in favour of brentuximab vedotin)
  - The ERG noted there were no deaths in the self-control group data which does not equate with PFS or time to progression (for the latter outcome as patients would be censored at time of death). Therefore it is not suitable to combine with OS data from an alternative source in a partitioned survival model.
- The ERG preferred data from the Canadian registry data reported in Mak et al. as source for PFS to counter potential biases associated with the internal self-control used in the company's base case

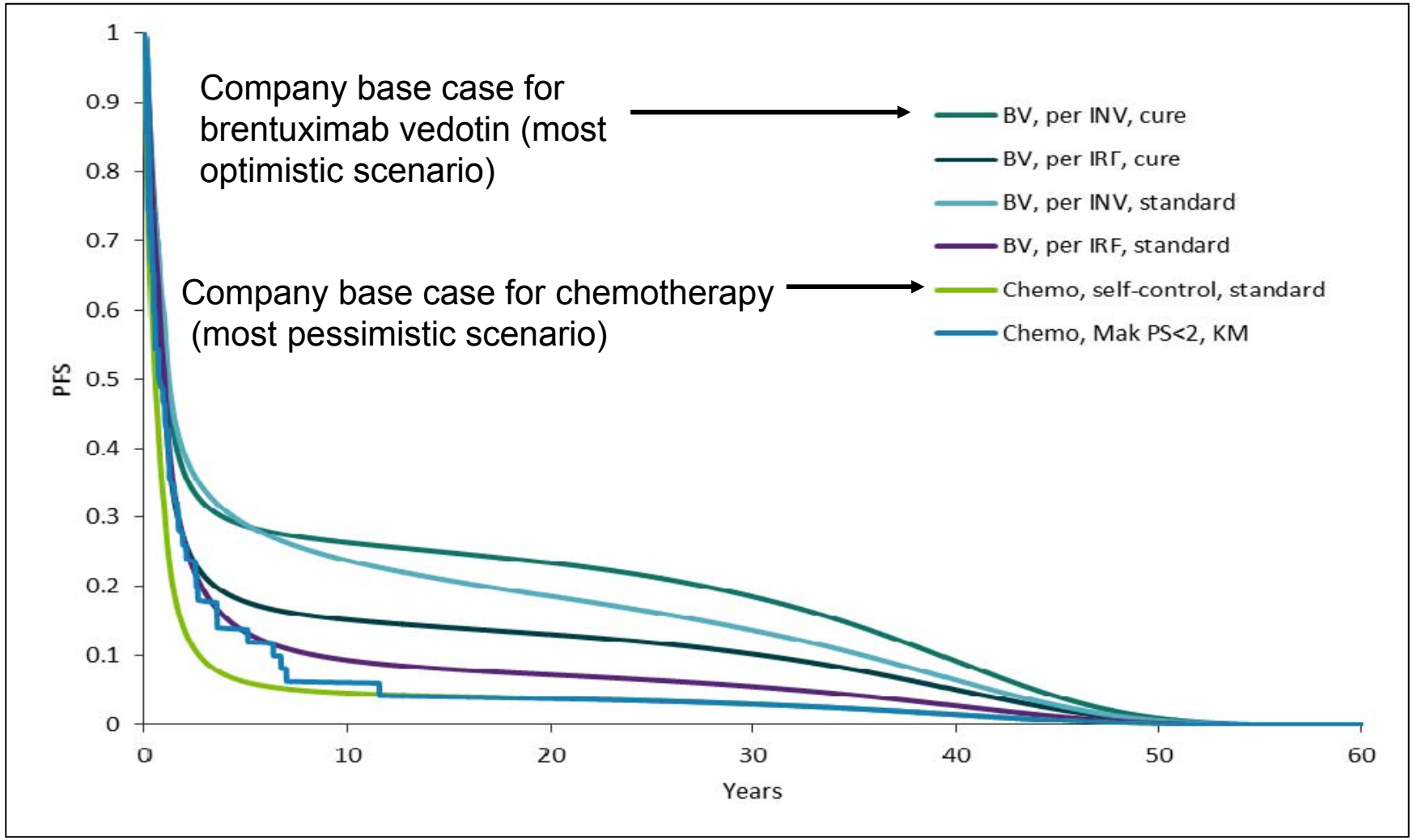
# PFS: Chemotherapy (no SCT)
## *Extrapolation*

- The company used standard parametric models rather than cure models to extrapolate chemotherapy PFS
- For the base-case analysis (based on the self-control data), a log-normal parametric model was selected
- The company's model only allowed PFS based on Mak et al. to be modelled using the raw Kaplan Meier data, as there was no flexibility in the model for alternative survival functions to be fitted to Mak et al. data for PFS

# ERG's critique
# PFS: chemotherapy (no SCT)
# *Extrapolation*

- The ERG's clinical advice suggested that a small proportion of patients could be expected to achieve a long term remission (and thus be considered cured) using salvage chemotherapies. The ERG commented that the Kaplan Meier curve from the subgroup of patients in Mak et al. with ALCL illustrated this point (see slide 47)
- The ERG was of the opinion that mixture-cure models for brentuximab vedotin (no SCT), and standard survival models for chemotherapy (no SCT) may generate a bias in favour of brentuximab vedotin
- The ERG considered that a more conservative analysis where both brentuximab vedotin and chemotherapy are modelled using standard parametric survival models more appropriate.
- The ERG presented 6 different survival curves for PFS that could be implemented in the model to illustrate the range of uncertainty underpinning the choice of data (see slide 51)
- The ERG noted that there was a substantial difference in the excess PFS benefit of brentuximab vedotin, depending on the sources and extrapolation approach used

# ERG's critique
# PFS: chemotherapy (no SCT)
# Exploration of impact of alternative data choices



# OS: Brentuximab vedotin (no SCT)
## *Trial based data and extrapolation*

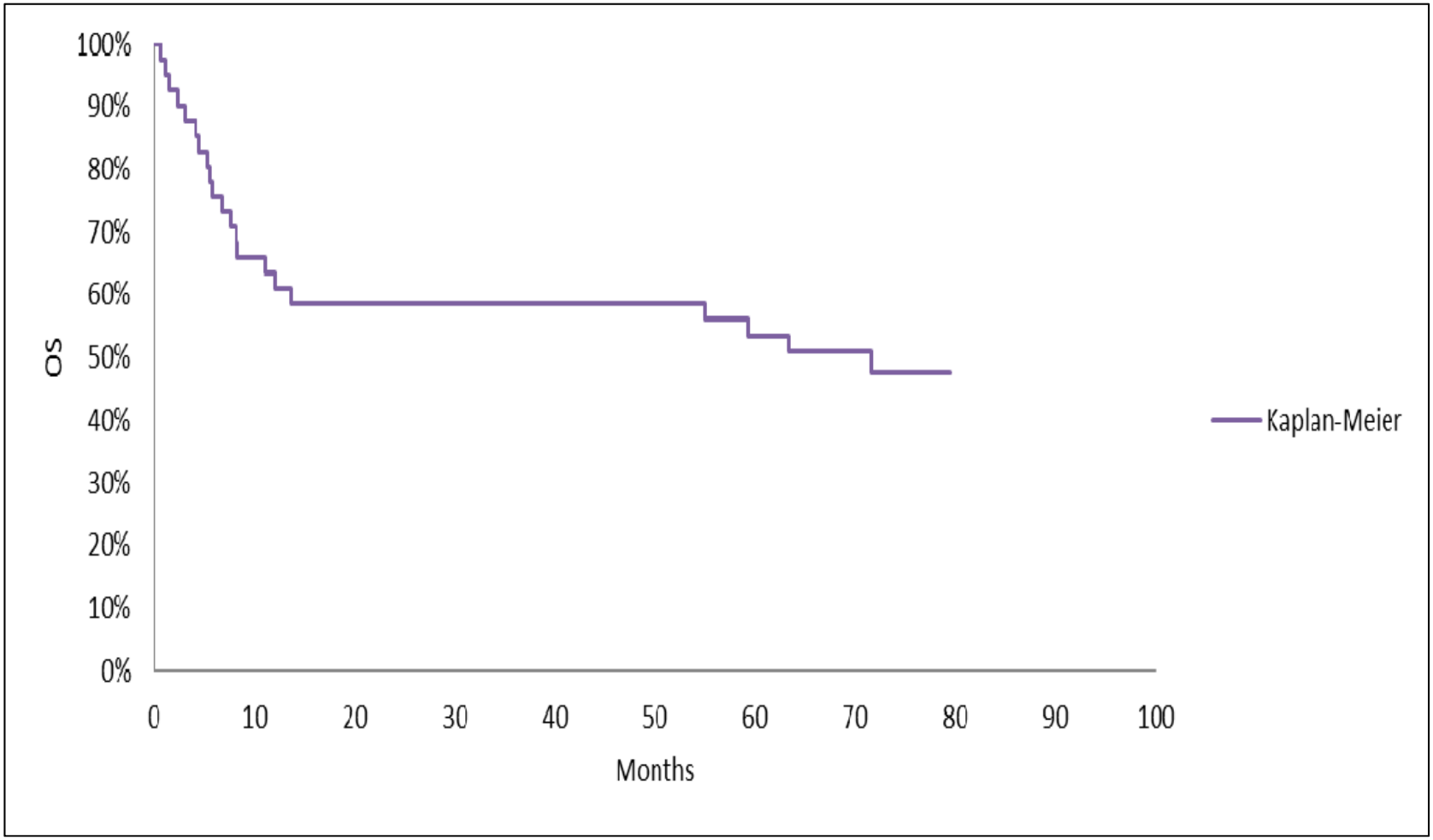
Trial based data

- OS data reported according to SG035-0004 (n=41 patients with no SCT)
- 5-year OS for the 'no SCT' subgroup not reported; model trace showed 49% remained alive at 5 years

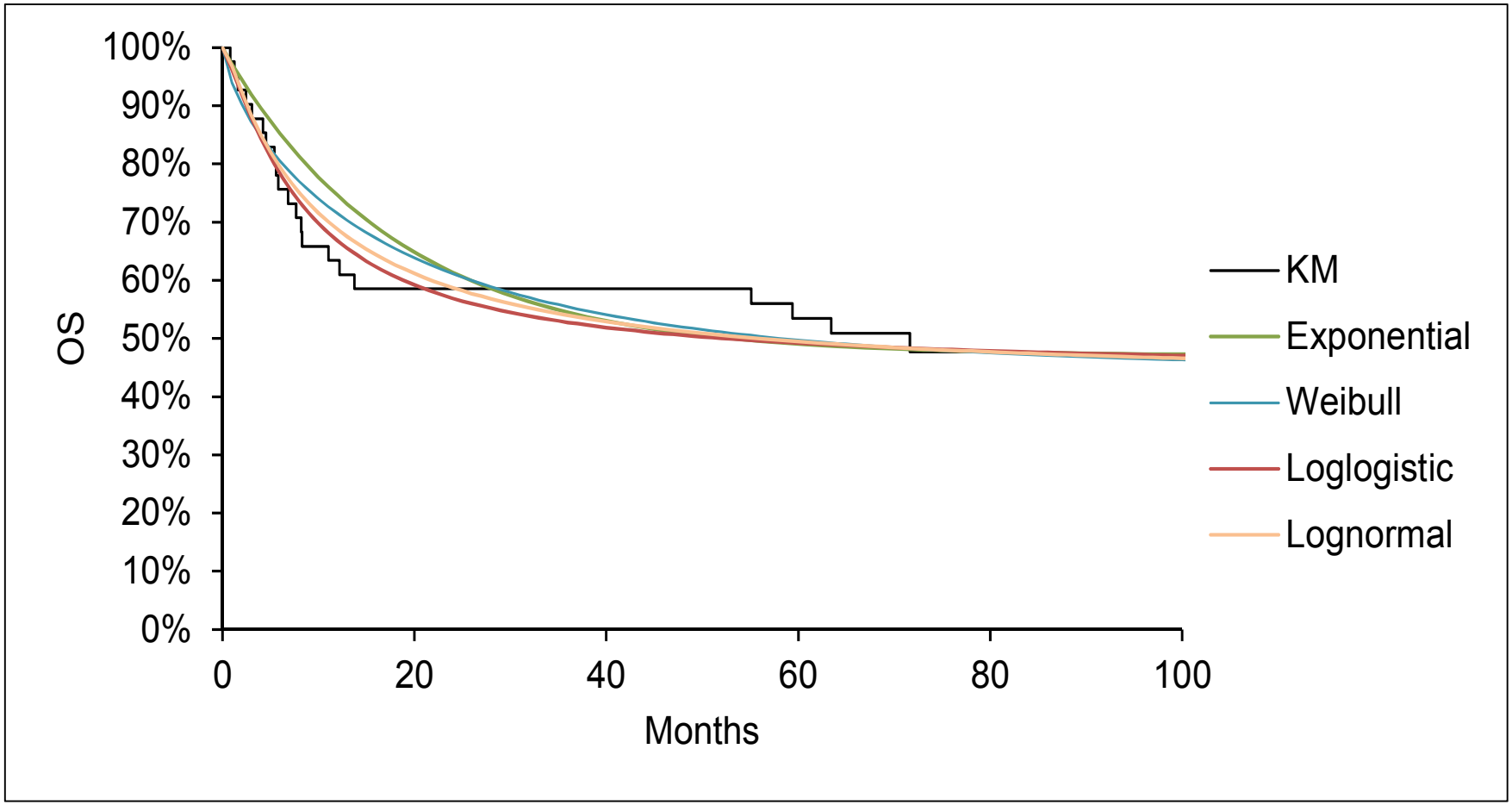
Extrapolation

- Similar plateau in OS Kaplan Meier curve was observed as with PFS; similar mixture-cure model applied for OS extrapolations
- Additional 5% excess mortality applied, based on expert clinical opinion, to all parametric OS extrapolations
- All models explored had similar predicted cure fractions ranging between 44% (log-logistic and log-normal) to 47%(exponential)
- Company chose log-logistic parametric model

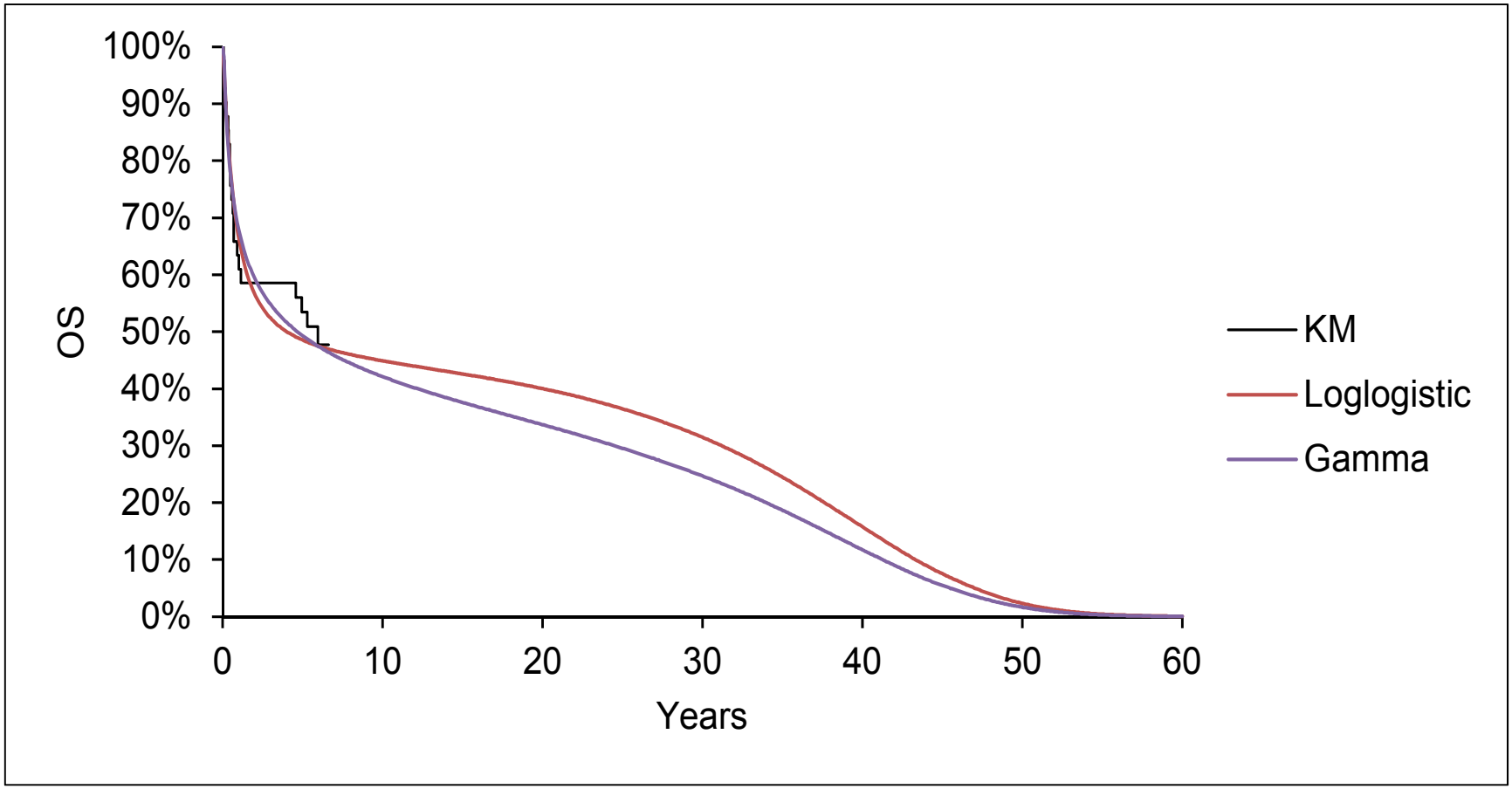
# OS: Brentuximab vedotin (no SCT)
# Kaplan-Meier curves



# OS: Brentuximab vedotin (no SCT) Parametric models for extrapolation based on self-controls from SG035-0004



# OS: Brentuximab vedotin (no SCT) Comparison of cure and standard parametric models



# OS: chemotherapy (no SCT)
## *Trial based data and extrapolation*

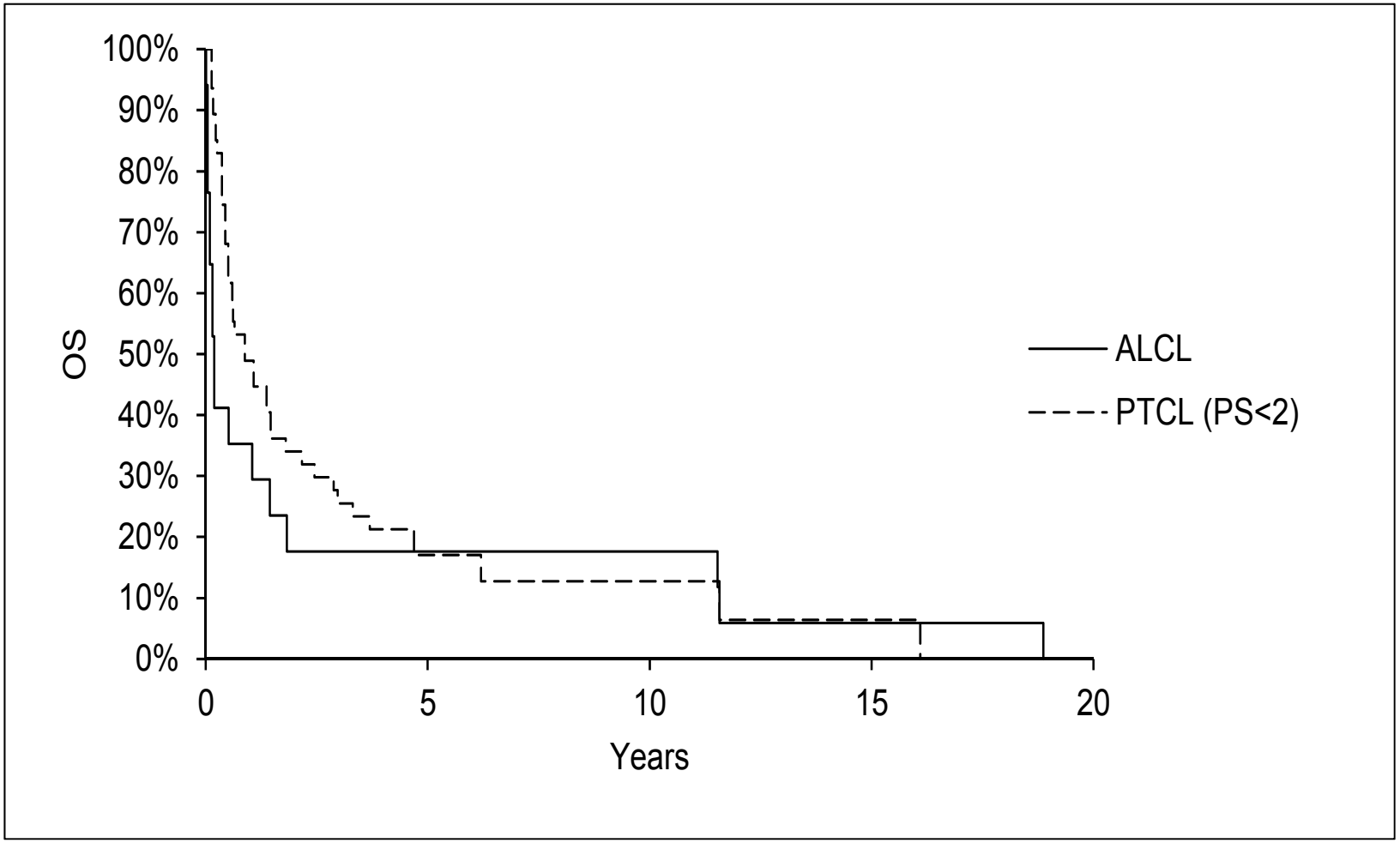
Trial based

- Kaplan Meier curves from Mak et al. used to estimate OS probability at each time point for the chemotherapy comparator
  - both subgroups (ALCL [n=17], and PTCL with performance status <2, [n=47]) considered
- Company used data from the subgroup of patients from Mak et al. with PTCL and performance status <2 (n=47) in base case:
  - ALCL subgroup generated implausible results
  - Approach accounted for potential bias introduced through differences in performance status between patients in SG035-0004 and Mak et al.

Extrapolation

- Standard parametric models, rather than cure models, were used given conventional chemotherapy approaches are not curative.
- The company chose the log-normal parametric model for its base case analysis

# OS: Chemotherapy (no SCT)
# Kaplan-Meier curves



# ERG's critique
# OS: Chemotherapy (no SCT)

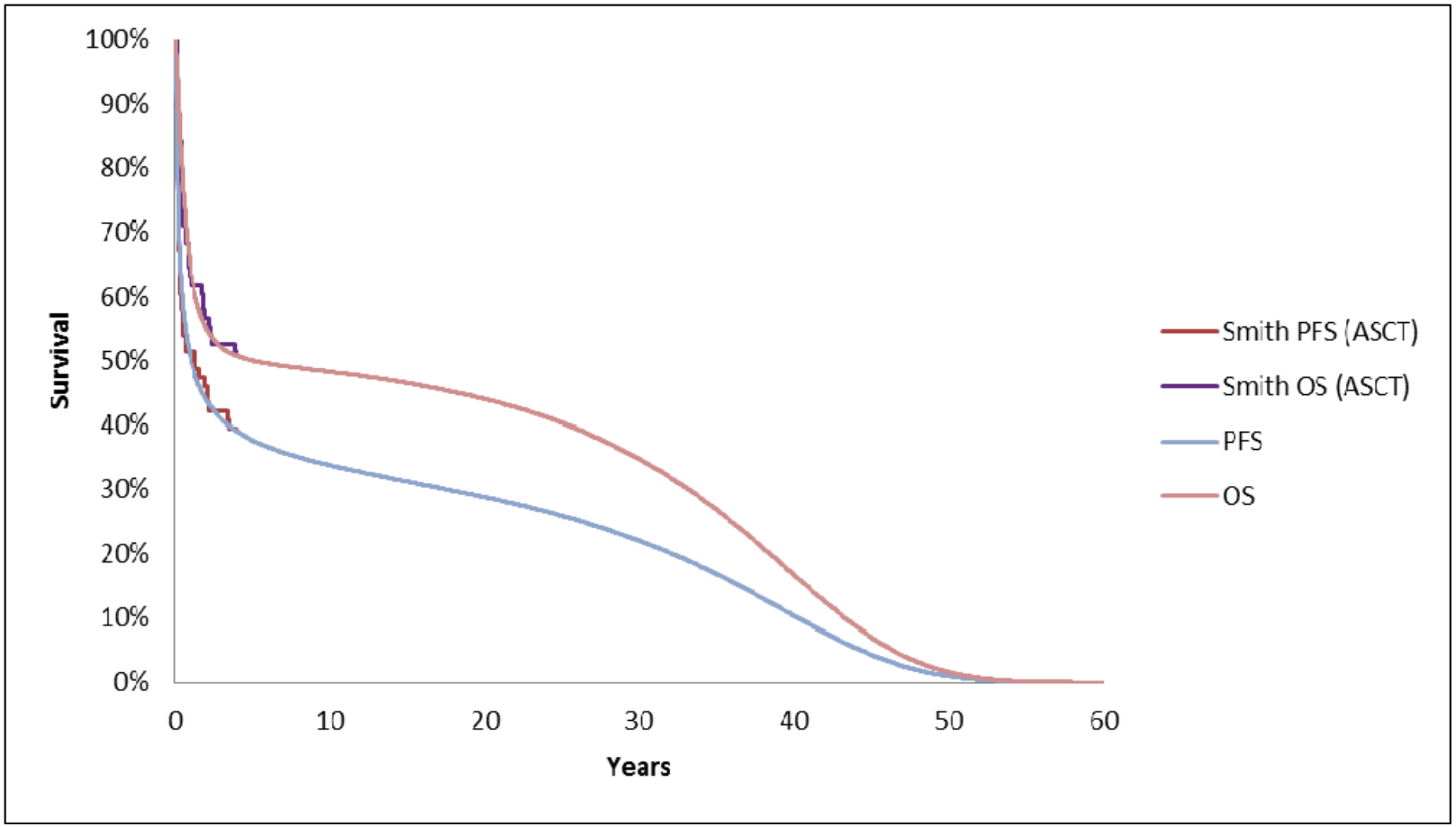
- The ERG considered the use of data from Mak et al. to be appropriate
- The ERG considered the use of different data sources for PFS and OS to be inappropriate
  - The ERG preferred the use of Mak et al. data for both PFS and OS to avoid mis-match
- The ERG questioned why Hux et al., which used individual data on 40 patients with sALCL from the Canadian BC Cancer registry was not considered for modelling PFS and OS
  - The company noted that Mak et al. data was used because this decision was in line with NICE guidance. ERG acknowledged that the cohort used by Hux et al. came from same source as Mak et al. and the Kaplan Meier curves for both were similar suggesting there is likely a high degree of overlap between the cohorts.
- The ERG considered the company's preference of log-normal and gamma distributions to model parametric distribution for OS considered to be appropriate. However, the ERG noted that there was substantial uncertainties driven by the long tail on the Kaplan Meier curve for OS noted

# PFS and OS: ASCT and allo-SCT
## *Trial based data and extrapolation*

- PFS and OS data sourced from Smith et al. (Subgroup of patients who received ASCT [N=115], subgroup of patients who received alloSCT [n=126])
- Mixture cure models were fitted in a similar manner to that used for the brentuximab vedotin (no SCT)
- ASCT:
  - Base case analysis for PFS used a gamma parametric survival model and for OS, a log-normal parametric model
- Allo-SCT:
  - Base case analysis used a log-normal parametric model for PFS and OS

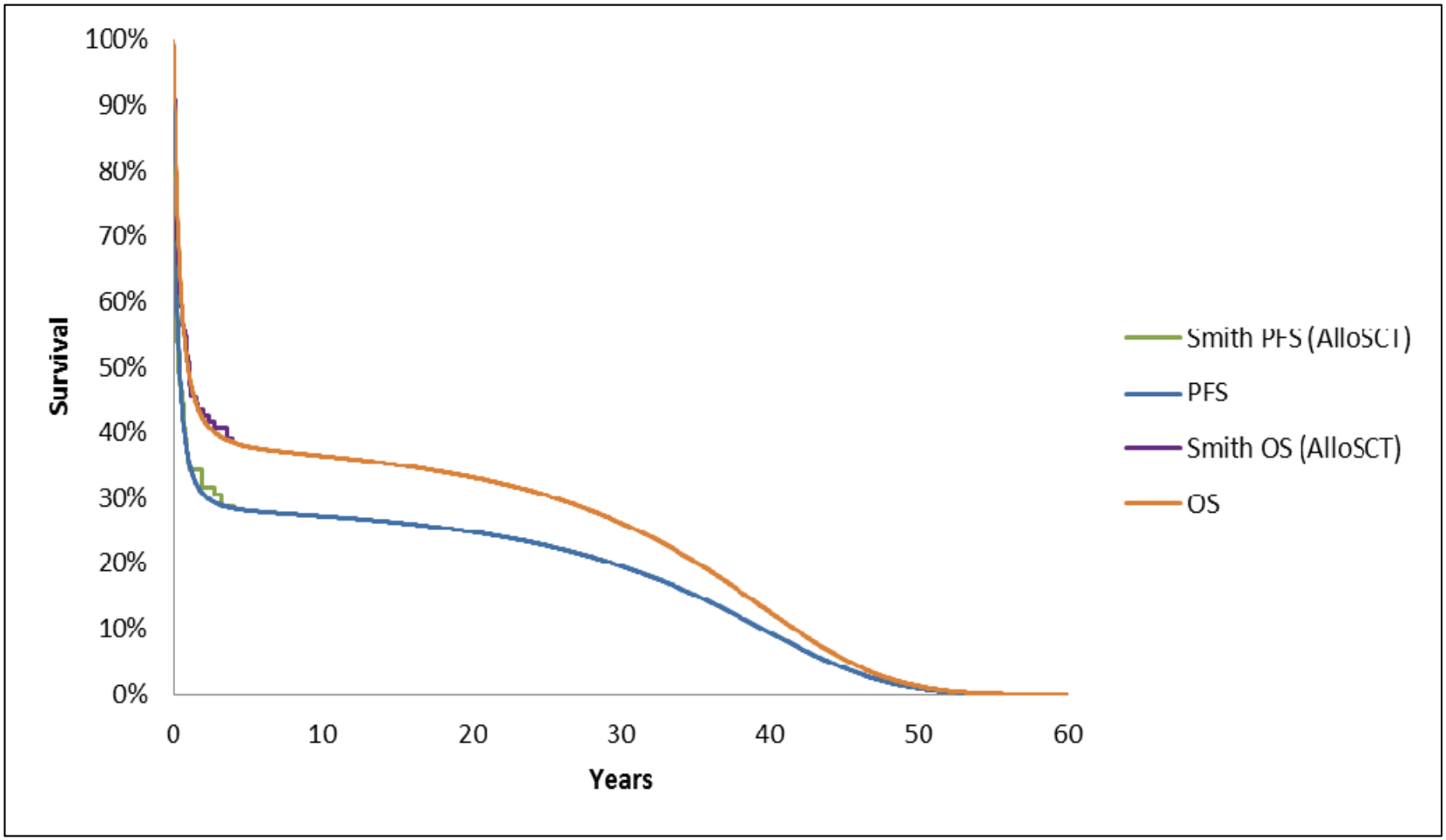
# PFS and OS: ASCT

## Kaplan-Meier curves and extrapolation



# PFS and OS: allo-SCT

## Kaplan-Meier curves and extrapolation



# Excess mortality risk

- Plateaus in the Kaplan Meier curves which informed PFS and OS reflected mortality rate equating to the expected rate in the general population (indicative of long term survival or cure)
- To address the uncertainty in the mortality rate for patients who were long term survivors compared with the general population, general population mortality risk based on UK life tables were applied irrespective of estimated cure fraction or type of model
- Excess mortality was applied to all data apart from those sourced directly from the Kaplan Meier curves to ensure clinical plausibility for the full duration of the model
- Based on the advice of one clinical expert, the following risks were added to the base case

| Cohort | Excess mortality risk |
|---|---|
| Brentuximab vedotin (no SCT) | 5% |
| Brentuximab vedotin (SCT) | 10% |
| Chemotherapy (no SCT) | 7% |
| Chemotherapy (SCT) | 10% |

# ERG's critique
# Excess mortality risk

- The ERG's clinical advice confirmed that applying an excess mortality risk was appropriate
- The ERG was concerned about the values used as there is little evidence to support assumption that long term excess mortality for brentuximab vedotin should be less than for chemotherapy.
- The ERG noted that the excess mortality risks were applied to both OS and PFS in the brentuximab vedotin arm but not to PFS in the chemotherapy arm in the model. The ERG commented that this had a minor impact on the ICER and created a minor bias against brentuximab vedotin in terms of modelling PFS

# Utility values
# No 'SCT' cohorts

- The company used utility values obtained from Swinburn et al. The study reported utility values for both R/R Hodgkin Lymphoma and sALCL.
- Patients achieving a CR were assigned the utility value of 0.91, based on the general population norm for mean age 38 from Swinburn et al. To reflect a decrement of utility for CR compared with the general population, a further 5% decrement was applied.
- Patients who did not progress by an assumed cure time point (5 years in the base case analysis) were assumed to follow age adjusted population norm utility values
- Patients  who experienced PD were assumed to receive the appropriate decrement from Swinburn et al.

| State | Mean | Decrement |
|---|---|---|
| Base | 0.95 | Not applicable |
| CR | 0.91 | 0.05 |
| PR | 0.79 | 0.16 |
| SD | 0.71 | 0.24 |
| PD | 0.38 | 0.57 |

# Utility values: SCT cohorts
# Time from initiation of salvage therapy to SCT

- For initiation of salvage therapy to SCT, utility values were modelled as per the approach for the 'no SCT' cohort
- Response rates for brentuximab vedotin were based on the 8 and 9 patients who received ASCT and allo-SCT in SG035-0004. Response rates for chemotherapy were based on Smith et al. 2013
- The time from initiation of salvage therapy to SCT was based on data from SG035-0004, corresponding median times were 29.7 weeks and 49.7 weeks respectively for ASCT and allo-SCT

**Weighted response rates and utility values for salvage therapies prior to SCT for PFS**

| Response | Brentuximab Rates *Source: SG035-0004* | | Chemotherapy Rates *Source: Smith et al.* | | Utility applied *Source: Swinburn et al.* | |
|---|---|---|---|---|---|---|
| | ASCT | allo-SCT | ASCT | allo-SCT | Mean | Decrement |
| Base | | | | | **0.95** | **N/A** |
| CR | 100% | 89% | 52% | 40% | 0.91 | -0.05 |
| PR | 0% | 11% | 37% | 42% | 0.79 | -0.16 |
| SD | 0% | 0% | 11% | 18% | 0.71 | -0.24 |

# Utility values: SCT cohorts
# Time from SCT to progression or cure (1)

- The company was informed by clinical experts that because of the nature of each type of SCT, patients would experience a quality of life decrement following ASCT or allo-SCT
- As there was no data available in the literature, the company asked 4 clinical experts to provide an estimate of these decrements
- The decrements were applied as the average of the 4 clinical expert's opinion as follows:
  - 0 to 6 months post SCT: Decrements for CR compared with the general population were 32% (ASCT) AND 50% (allo-SCT)
  - 6 months to cure point: Decrements for CR compared with the general population were 10% (ASCT) and 28% (allo-SCT)
- For CR these decrements were applied multiplicatively to the base base value of 0.95 (that is, Swinburn et al. CR, adjusted to 5% decrement from general population)
- For PD, the additional decrements were applied to the Swinburn et al. reported values for PD (0.38)

# Utility values: SCT cohorts
# Time from SCT to progression or cure (2)

Utility decrements for patients post ASCT and post allo-SCT

| SCT type | Response | 0-6 months post SCT | | 6 months post SCT to cure point | |
|---|---|---|---|---|---|
| | | Mean | Decrement | Mean | Decrement |
| **Base** | | **0.95** | **N/A** | **0.95** | **N/A** |
| **ASCT** | CR | 0.65 | 0.30 | 0.86 | 0.10 |
| | PR | 0.54 | 0.41 | 0.74 | 0.21 |
| | SD | 0.45 | 0.50 | 0.66 | 0.29 |
| | PD | 0.26 | 0.69 | 0.34 | 0.61 |
| **Allo-SCT** | CR | 0.48 | 0.48 | 0.68 | 0.27 |
| | PR | 0.36 | 0.59 | 0.57 | 0.38 |
| | SD | 0.28 | 0.67 | 0.49 | 0.47 |
| | PD | 0.19 | 0.76 | 0.27 | 0.68 |

# Utility values: SCT cohort
# Time from cure to death and adverse event dis-utilities

**Time from cure to death:**

- Utility values in the PFS state after the cured time point reverts to the general population norms with a 5% excess utility decrement applied as in the 'no SCT' cohorts. The cure-time point was adjusted to reflect the time from salvage therapy to SCT. Beyond 60 months post-SCT, the utility value for PD was calculated as the PD decrement from Swinburn et al., subtracted from age adjusted population norms.

**Adverse events**

- QALY decrements for adverse events (grade 1-2 [≥10%] and 3-4 [≥5%]) based on estimated durations of events, proportion of patients experiencing the event in each cohort and the associated utility decrement for each event from Swinburn et al., other published literature and previous NICE STAs

# Resource use and costs – Brentuximab vedotin

| **Brentuximab vedotin acquisition costs** | | | | |
|---|---|---|---|---|
| Dose:<br>1.8 mg/kg every 3 weeks | Dose per cycle | Cost (50 m vial)<br>List price | Cost (50 m vial)<br>CAA price* | Cost per cycle* |
| | 180 mg | £2,500 | | Non SCT*<br>SCT* |
| **Mean number of cycles** | | | | |
| SCT : 8.8 | | | No SCT : 8.0 | |
| **Brentuximab vedotin administration costs** | | | | |
| Costed as outpatient treatment | | | Concomitant | |
| £198 per 3 week treatment cycle<br>Total cost for 8 treatment cycles over 24 weeks=£1,584 | | | Dexamethasone (12 mg daily dose=£4.68 per treatment cycle, £37 over 24 weeks | |
| *Source: NHS reference costs 2015-16* | | | | |
| **TOTAL COSTS PER CYCLE** | | | | |
| Initial | | | Subsequent | |
| No SCT*<br>SCT* | | | No SCT*<br>SCT* | |

# Resource use and costs: Others

**Chemotherapy**

- Company used a weighted average cost based on the proportion of patients assumed to receive each treatment. Required dosing and time on treatment based on sources identified in NCCN guidelines on non-Hodgkin lymphomas which are no longer current. Undiscounted drug acquisition cost of chemotherapy is £5,275 (no SCT cohort) and £5,180 (SCT cohorts)

**SCT**

- Cost of SCT included cost of donation, BEAM conditioning, transplant and follow-up care for both ASCT and allo-SCT.
- Costs sourced from the BMT Unit at the Beatson West of Scotland Cancer Centre (WoSCC). Base case analysis assumed a total cost of £53,790 and £108,241 for ASCT and allo-SCT respectively
- In both casesthe company provided an alternative sensitivity analysis, based on the national unit costs for key components of the transplant process

# Resource use and costs
# Post-progression therapies

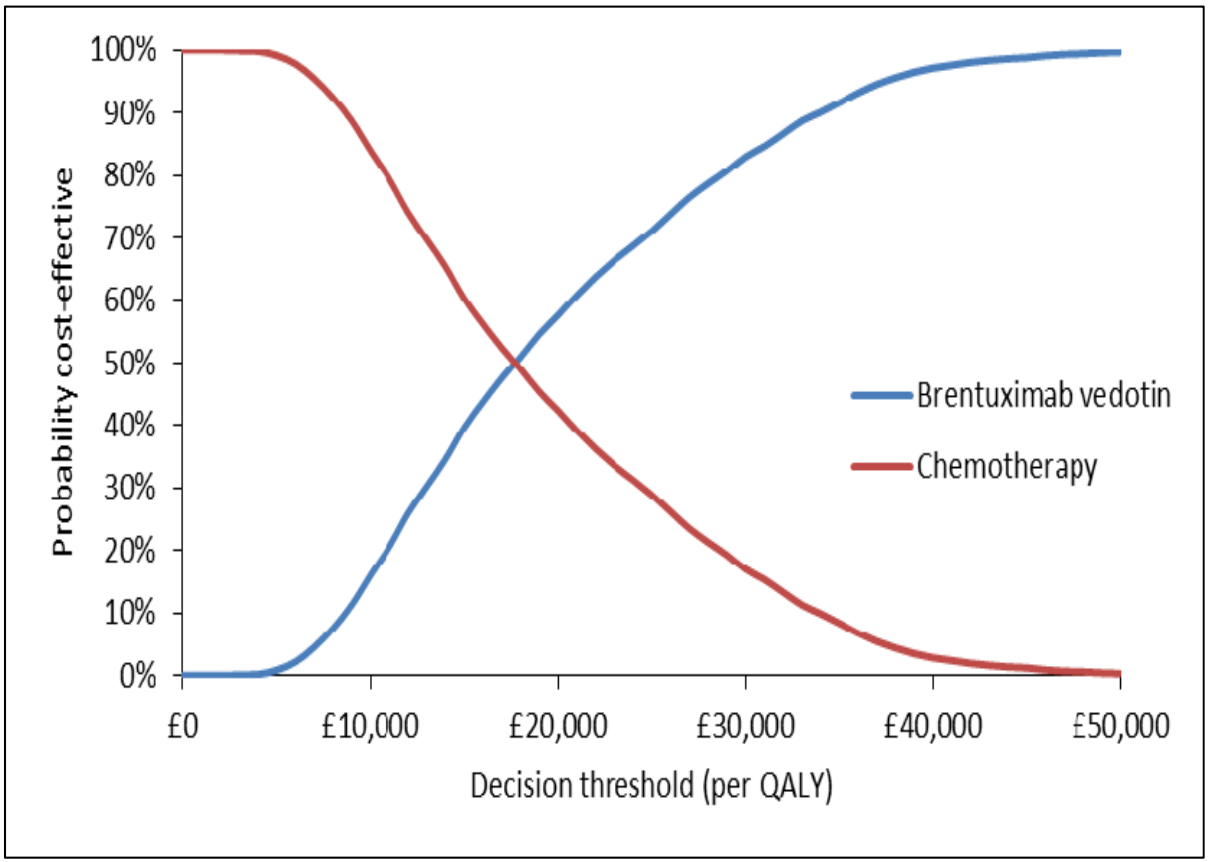
- In the company's original model, 100% of patients were assumed to receive a further line of treatment following progression. 80% of patients with PD following chemotherapy were modelled to receive brentuximab vedotin. The ERG considered this to be inappropriate as it was not in-line with the final scope issued by NICE
- In response to clarification, the company provided a revised economic model incorporating 2 alternative distributions of post-progression therapy
  - The trial based distribution included the distribution of treatments according to the studies used to obtain OS data
  - The clinical expert based distribution was developed after further contact with clinical expert advisors.
- The company suggested that the 'clinical expert distribution' should form the base case analysis given that non-licenced treatments were used in the SG035-0004 trial following progression. However, the ERG noted that these unlicensed treatments were replaced with multi-agent chemotherapy in the company's 'trial based distribution'
- The ERG preferred the use of the 'trial based distribution' (to be in keeping with modelled effects) and used this as its preferred version of the company's base case.

# Company's deterministic base case (with CAA*): Revised base case after clarification

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| ***Trial based post-progression therapy distribution (ERG preferred analysis)*** | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £19,470 |
| ***Post-progression therapy based on clinical expert*** | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £12,873 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

# Revised probabilistic analyses (with CAA*)

The ERG re-ran the probabilistic analyses using the revised company mode'




- Probabilistic ICER for the 'trial based' post-progression therapy distribution was £19,034 per QALY gained, similar to the deterministic analysis (£19,470).
- Probability of brentuximab vedotin being cost-effective at the thresholds of £20,000, £30,000 and £50,000 per QALY gain was 59%, 83% and 100% respectively,

# ERG's base case (with CAA*)

- The ERG corrected 2 errors in the company's model (error in discounting of post-progression therapy costs and an error in the probabilistic sensitivity analysis)
- The ERG's preferred base case incorporated the following 3 scenarios:
  - trial based distribution of post-progression therapy costs
  - removing the costs of brentuximab vedotin from the chemotherapy comparator
  - data from Mak et al. for both PFS and OS
- The ERG's deterministic ICER was £21,267 per QALY gained. Probabilistic results are shown below

| Comparator | Costs | QALYs | ICER | P (C/E) @ £20k | P (C/E) @ £30k | P (C/E) @ £50k |
|---|---|---|---|---|---|---|
| **Brentuximab vedotin** | XXXXXX | XXXX | | | | |
| **Chemotherapy** | XXXXXX | XXXX | | | | |
| **Incremental** | XXXXXX | XXXX | £20,667 | 53% | 77% | 99% |

# ERG's deterministic scenario analyses: key results

| | | BV | | Chemo | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analysis** | **Description** | **Cost** | **QALY** | **Cost** | **QALY** | **Inc. Cost** | **Inc. QALY** | **ICER** |
| 6 | No. treatment cycles on brentuximab vedotin (No SCT) =4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £13,09 |
| 7 | No. treatment cycles on brentuximab vedotin (No SCT) =16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,32 |
| 24 | PFS & OS hazard (-25%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,12 |
| 25 | PFS & OS hazard (-50%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £31,53 |
| 27 | BV PFS based on IRF data | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,29 |
| 30 | Chemo PFS (KM data from Mak et al PS<2) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,26 |
| 31 | Chemo OS (KM data from Mak et al) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,72 |
| 32 | Combined scenarios 27 to 31 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £38,78 |
| 33 | Equal rates of SCT progression in both arms | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,44 |
| 34 | Combined scenarios 32 & 33 (worst case for BV) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £49,99 |

# ERG's scenario analyses: summary

- ICER most sensitive to:
  - Rate of SCT following brentuximab vedotin or chemotherapy
  - Time horizon and discount rates
  - Cost of brentuximab vedotin (that is, the number of cycles of treatment).
  - Assumptions regarding the relative treatment effectiveness (PFS and OS) for brentuximab vedotin (no SCT) relative to chemotherapy (no SCT)
- The ERG noted a plausible but conservative estimate of the ICER using IRF data for PFS and standard parametric models for both PFS and OS for brentuximab vedotin, together with Mak et al. data (PTCL subgroup, performance status<2, n=47) for chemotherapy (OS and PFS). The ICER increased to £38,783 per QALY gained (see scenario 32)
- The ERG's worst case scenario for brentuximab vedotin involved combining the above analysis with assumption of equal rates of progression to SCT for both chemotherapy and brentuximab vedotin. Deterministic ICER increased to £49,994 per QALY gained (probabilistic ICER £54,082 per QALY gained) (see scenario 34).

# End of life

- Based on the company's cost effectiveness results, the company view was that it did not need to make a case for brentuximab vedotin to be considered for NICE's End of Life criteria

| **NICE End of life Criterion** | **Data available from cost-effectiveness analysis** |
|---|---|
| The treatment is indicated for patients with a short life-expectancy, *normally* less than 24 months | Company's original submission: Mean OS 4.6 years*<br>Company's 'Trial based post progression therapy distribution': Discounted Life Years 3.35 years |
| There is sufficient evidence to indicate that the treatment offers an extension to life, *normally* of at least an additional 3 months, compared with current NHS treatment | Company's original submission: Mean OS 16.31 years*. Represents an extension in mean OS of 11.7 years<br>Company's 'Trial based post progression therapy distribution': Discounted Life Years 9.53 years |

* Company's original submission: Table 5.71 page 188

# Innovation: Company's comments

- Brentuximab vedotin is the first new medicine to be approved for the treatment of sALCL in more than 30 years, and is currently the only treatment approved by the European Medicines Agency for patients with R/R sALCL. Medicine meets a high unmet need.
- Conditional marketing authorisation for brentuximab vedotin for sALCL granted, based on only Phase II data.
- Offers targeted therapy and has shown unprecedented single-agent activity in the treatment of relapsed or refractory sALCL; viewed as a 'step-change' in the management of relapsed or refractory sALCL
- Improved tolerability and a more convenient schedule than chemotherapy.
- Additional treatment option where otherwise only best supportive care.
- Potential to act as bridge to allo-SCT

# Equality considerations

- No equality issues raised by patient or professional groups
- Company stated:
  - Brentuximab vedotin has become established “standard of care” for patients with R/R sALCL because of its availability through the CDF. There would be a significant adverse impact on patients if brentuximab vedotin is not recommended by NICE and becomes unavailable to patients after the old CDF closes.
  - Potential equity issues could arise because patients with R/R sALCL in England who would previously have been able to access brentuximab vedotin through the CDF would be unable to, based purely on the timing of their relapse in relation to the NICE decision and the closure of the old CDF.
  - Within a UK context there could also potentially be an inequity of access if patients in Scotland and Wales are able to receive brentuximab vedotin through individual patient funding mechanisms while patients in England are not in the event of a negative NICE decision.

# Authors

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  Technical Lead
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  Technical Adviser
- with input from the Lead Team (Iain Miller, Robert Walton, Judith Wardle)

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma

## Final scope

### Final remit/appraisal objective

To appraise the clinical and cost effectiveness of brentuximab vedotin within its marketing authorisation for treating relapsed or refractory systemic anaplastic large cell lymphoma.

### Background

Anaplastic large cell lymphoma is a peripheral T-cell non-Hodgkin's lymphoma. It belongs to the group of CD30-positive lymphoproliferative disorders, which affect lymph nodes and extranodal sites. Anaplastic large cell lymphoma can appear in the skin, in lymph nodes, or in organs throughout the body. Symptoms may include a painless swelling in the neck, armpit or groin; loss of appetite; tiredness; night sweats; high temperatures; weight loss; and cough. There are 2 forms of anaplastic large cell lymphoma, systemic and cutaneous, with different outcomes and treatment options. There are 2 subtypes of systemic anaplastic large cell lymphoma: anaplastic lymphoma kinase (ALK)-positive, and ALK-negative. The latter subtype is generally associated with a less favourable prognosis.

In 2013, 11,392 people were diagnosed with non-Hodgkin's lymphoma in England.[1] It is reported that 3% of people with non-Hodgkin's lymphoma have systemic anaplastic large cell lymphoma.[2] The cancer occurs most commonly in children and young people. It is more common in males than females. Approximately 40–65% of people with anaplastic large cell lymphoma develop recurrent disease after initial therapy.[3]

CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone), with or without etoposide, is a commonly used first-line regimen for people with systemic anaplastic large cell lymphoma. If the cancer relapses, people who are eligible for transplant can be treated with second-line chemotherapy before transplant. Consolidation therapy with high-dose therapy followed by autologous stem cell transplantation can then be given to people who have a complete or partial response. People who are not eligible for transplant may be treated with second-line chemotherapy regimens or palliative radiotherapy, although there is no standard of care in this clinical setting.

### The technology

Brentuximab vedotin (Adcetris, Takeda UK) is an antibody–drug conjugate comprising an anti-CD30 monoclonal antibody attached by an enzyme-

cleavable linker to a potent chemotherapeutic agent, monomethyl auristatin E (MMAE). The antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells. It is administered by intravenous infusion.

Brentuximab vedotin has a marketing authorisation in the UK for treating adults with relapsed or refractory systemic anaplastic large cell lymphoma. Brentuximab vedotin is funded by the Cancer Drugs Fund for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma.

| | |
|---|---|
| **Intervention(s)** | Brentuximab vedotin |
| **Population(s)** | People with relapsed or refractory systemic anaplastic large cell lymphoma. |
| **Comparators** | Established clinical management without brentuximab vedotin. |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• objective response rate<br>• complete response rate<br>• rate of stem cell transplantation (autologous and allogeneic)<br>• adverse effects of treatment<br>• health-related quality of life. |
| **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.<br>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.<br>Costs will be considered from an NHS and Personal Social Services perspective. |

| | |
|---|---|
| **Other considerations** | If the evidence allows, the economic analysis should model stem cell transplantation further down the treatment pathway.<br><br>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations and NICE Pathways** | Appraisals in development (including suspended appraisals)<br><br>'Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma' NICE technology appraisals guidance [ID722]. Publication expected January 2017. |
| **Related National Policy** | NHS England, National Cancer Drugs Fund List, November 2016.<br><br>NHS England, Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (all ages): Revised, Jan 2015.<br><br>Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf |

## References

[1] Cancer Research UK (2013) Non-Hodgkin lymphoma incidence statistics. Accessed July 2016.

[2]Skarbnik APZ and Smith MR (2012) Brentuximab vedotin in anaplastic large cell lymphoma. Expert opinion in biological therapy 12(5): 633–639.

[3]Pro B et al. (2012) Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. Journal of Clinical Oncology 30: 2190–2196.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal STA

## Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

## Matrix of consultees and commentators

| Consultees | Commentators (no right to submit or appeal) |
|---|---|
| Company<br>Takeda (brentuximab vedotin)<br><br>Patient/carer groups<br>• African Caribbean Leukaemia Trust<br>• Anthony Nolan<br>• Black Health Agency<br>• Bloodwise<br>• Cancer Black Care<br>• Cancer Equality<br>• Cancer52<br>• Delete Blood Cancer<br>• HAWC<br>• Helen Rollason Cancer Charity<br>• Independent Cancer Patients Voice<br>• Leukaemia Cancer Society<br>• Leukaemia CARE<br>• Lymphoma Association<br>• Macmillan Cancer Support<br>• Maggie's Centres<br>• Marie Curie<br>• Muslim Council of Britain<br>• Rarer Cancers Foundation<br>• South Asian Health Foundation<br>• Specialised Healthcare Alliance<br>• Tenovus Cancer Care<br><br>Professional groups<br>• Association of Cancer Physicians<br>• British Committee for Standards in Haematology<br>• British Geriatrics Society<br>• British Institute of Radiology<br>• British Psychosocial Oncology Society | General<br>• Allied Health Professionals Federation<br>• Board of Community Health Councils in Wales<br>• British National Formulary<br>• Care Quality Commission<br>• Department of Health, Social Services and Public Safety for Northern Ireland<br>• Healthcare Improvement Scotland<br>• Medicines and Healthcare Products Regulatory Agency<br>• National Association for Primary Care<br>• National Pharmacy Association<br>• NHS Alliance<br>• NHS Commercial Medicines Unit<br>• NHS Confederation<br>• Scottish Medicines Consortium<br><br>Comparator companies<br>• None<br><br>Relevant research groups<br>• Cochrane Haematological Malignancies Group<br>• Institute of Cancer Research<br>• Leuka<br>• Leukaemia Busters<br>• Lymphoma Research Trust<br>• MRC Clinical Trials Unit<br>• National Cancer Research Institute<br>• National Cancer Research Network |

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| • British Society for Haematology<br>• Cancer Research UK<br>• Royal College of General Practitioners<br>• Royal College of Nursing<br>• Royal College of Pathologists<br>• Royal College of Physicians<br>• Royal College of Radiologists<br>• Royal Pharmaceutical Society<br>• Royal Society of Medicine<br>• Society and College of Radiology<br>• UK Clinical Pharmacy Association<br>• UK Health Forum<br>• UK Oncology Nursing Society<br><br><u>Others</u><br>• Department of Health<br>• NHS Blackburn with Darwen CCG<br>• NHS England<br>• NHS Wyre Forest CCG<br>• Welsh Government | • National Institute for Health Research<br><br><u>Associated Public Health Groups</u><br>• Public Health England<br>• Public Health Wales |

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

***PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS***

**Definitions:**

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Single technology appraisal

# Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

## Submission by Takeda UK Ltd

**3rd February 2017**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| | | Yes/no | |

# Table of Contents

# List of Tables

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# List of Abbreviations

| | |
|---|---|
| ADC | antibody-drug conjugate |
| AE | Adverse event |
| AITL | Angioimmunoblastic T-cell lymphoma |
| ALK | Anaplastic lymphoma kinase |
| ALK- | Anaplastic lymphoma kinase-negative |
| ALK+ | Anaplastic lymphoma kinase-positive |
| Allo-SCT | Allogeneic stem cell transplant |
| ASCT | Autologous stem cell transplant |
| ASH | American Society of Haematology |
| ATLL | Adult T-cell leukaemia /lymphoma |
| AWMSG | All Wales Medicines Strategy Group |
| BV | Brentuximab vedotin |
| CDF | Cancer Drugs Fund |
| CHOP | Cyclophosphamide, Hydroxydaunomycin, Oncovin®, Prednisolone |
| CI | Confidence interval |
| CR | Complete remission |
| CRF | Case report form |
| DLBCL | Diffuse large B-cell lymphoma |
| DOR | Duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | Event-free survival |
| EMA | European Medicines Agency |
| EOS | End of study |
| EOT | End of treatment |
| GCP | Good clinical practice |
| GvHD | Graft versus host disease |
| HL | Hodgkin lymphoma |
| HRQoL | Health-related quality of life |
| ICML | International Conference on Malignant Lymphoma |
| IFR | Individual funding requests |
| IPTR | Individual Patient Treatment Requests |
| IRF | Independent review facility |
| LYs | Life years |
| MMAE | Monomethyl auristatin E |
| NE | Not estimable |
| NHL | Non-Hodgkin lymphoma |
| NPM | Nucleophosmin |
| NPP | Named Patient Programme |

| | |
|---|---|
| ORR | Objective response rate |
| OS | Overall survival |
| PACE | Patient And Clinician Engagement |
| PD | Progressive disease |
| PET-CT | Positron emission tomography–computed tomography |
| PFS | Progression-free survival |
| PICOS | Patients, Interventions, Comparators, Outcome and Study design |
| PPS | Post-progression survival |
| PR | Partial remission |
| PSS | Personal Social Services |
| PTCL | Peripheral T-Cell Lymphoma |
| QALY | Quality-adjusted life year |
| RCT | Randomised controlled trial |
| RIC | Reduced intensity conditioning |
| R/R or r/r | Relapsed or refractory |
| SAE | Serious adverse event |
| sALCL | Systemic anaplastic large cell lymphoma |
| SD | Stable disease |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SmPC | Summary of Product Characteristics |
| SPD | Sum of the product of diameters |
| TEAE | Treatment-emergent adverse event |
| VAPEC-B | Vincristine, doxorubicin (Adriamycin), Prednisone, Etoposide, Cyclophosphamide, Bleomycin |

# 1. Executive summary

## 1.1 Statement of decision problem

### 1.1.1 Remit/appraisal objective

The remit/appraisal objective, as defined in the final NICE scope, is to appraise the clinical effectiveness and cost effectiveness of brentuximab vedotin within its marketing authorisation for relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL).

On October 25th 2012, the European Commission granted conditional marketing authorisation for Adcetris® (brentuximab vedotin) for the treatment of adult patients with R/R sALCL.[1]

Clinical evidence regarding brentuximab vedotin is from the SG035-0004 study which is a Phase II, multinational, open-label, single-arm trial, examining the efficacy and safety of brentuximab vedotin in patients who had a diagnosis of R/R sALCL after treatment failure of at least one prior therapy with curative intent.[2]

### 1.1.2 Background to relapsed, refractory systemic anaplastic large cell lymphoma

Systemic anaplastic large cell lymphoma (sALCL) is an aggressive CD30+ non-Hodgkin lymphoma of T-cell origin. The disease is classed as orphan (rare), defined in the EU as a prevalence not exceeding 5 in 10,000 people. Anaplastic lymphoma kinase –positive (ALK+) ALCL is associated with the NPM-ALK t(2;5) translocation, which is highly correlated with the identification of the ALK protein by immunohistochemistry. ALK+ ALCL typically occurs in younger patients and has a more favourable prognosis with 5-year survival rates of 70% to 90% in comparison with 40% to 60% for ALK-negative (ALK-) ALCL.[3]

Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the standard chemotherapy for aggressive lymphomas, including ALCL.[4] High-dose chemotherapy and autologous stem cell transplantation (ASCT) represent the standard of care for relapsed ALCL if chemo-sensitivity is demonstrated. In R/R ALCL patients ineligible for transplantation, or for whom second-line salvage therapy has failed, the outcome has historically been poor. The British Columbia Cancer Agency evaluated the survival of PTCL patients following first relapse or progression who had received chemotherapy, and the median overall survival (OS) and progression-free survival (PFS) were only 3.0 months and 1.8 months, respectively, for patients with ALCL, which supports a role for novel therapies and clinical trials for this poor prognosis group.[3]

There have been a number of trials evaluating novel therapies in relapsed/ refractory peripheral T-Cell lymphomas (PTCLs). Most have included all PTCL subtypes, but there has been a minority specifically in sALCL. Brentuximab vedotin is the most widely studied agent in sALCL. The pivotal Phase II study in relapsed/ refractory ALCL (42 ALK -ve, 16 ALK +ve)

demonstrated an overall response rate (ORR) of 86% and a complete response (CR) rate of 59%.[2] The estimated median PFS was 14.3 months, and for those who achieved a CR, it was 14.5 months (see Section 4.11.10.1 for further details).[1,5] A final analysis of patients observed for almost 5 years demonstrated a median duration of response for CR patients who did not receive an SCT as consolidation of 39.4 months, and 16 (42%) of 38 remained in remission. [6]

A health economic model has been developed for the evaluation of the cost-effectiveness of brentuximab vedotin in R/R sALCL. There is a high unmet medical need for patients in England and Wales with R/R sALCL as without brentuximab vedotin the only option available is a range of chemotherapy treatments that are offered as salvage therapy, and the prognosis of patients with ALK-negative disease is poor with a five-year failure free survival after treatment of only 36%.[7] Clinical expert opinion in the UK has supported the high clinical need for brentuximab vedotin for the treatment of sALCL in patients who have relapsed or who are refractory following at least one multi-agent chemotherapy regimen, and it has become the standard of care in these patients since receiving marketing authorisation in October 2012 (with access through an initial Named Patient Programme [NPP] and, since April 2013, through the national Cancer Drug Fund [CDF] in England).

### 1.1.3 Decision problem and NICE scope

The NICE scope[8] issued in November 2016 has specified the comparator (established clinical management without brentuximab vedotin) based on line of therapy to reflect clinical practice, i.e. for patients who have received at least one therapy: multi-agent chemotherapy regimen (e.g. CHOP) with or without ASCT, depending if chemo-sensitivity is demonstrated, in ALK-negative disease. Allogeneic transplantation (allo-SCT) may be an effective procedure for ALK-positive ALCL, but its value in the treatment of ALK-negative disease remains to be defined.[9]

One of the considerations in the NICE scope[8] was that if the evidence allows, the economic analysis should model stem cell transplantation further down the treatment pathway. In line with the treatment pathway for sALCL, and the place of brentuximab vedotin within it, the economic analysis will include the following five cohorts based on the addition of ASCT or allo-SCT to either brentuximab vedotin or chemotherapy:

- Brentuximab vedotin + ASCT
- Brentuximab vedotin + allo-SCT
- Chemotherapy
- Chemotherapy + ASCT
- Chemotherapy + allo-SCT

The final scope issued by NICE in November 2016 and the decision problem addressed in this submission is shown in Table 1.1.

## Table 1.1: 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 relapsed or refractory systemic anaplastic large cell lymphoma | Patients with relapsed or refractory systemic anaplastic large cell lymphoma who have received at least one prior regimen with curative intent:<br>• ALK-positive<br>• ALK-negative | None |
| **Intervention** | Brentuximab vedotin | Brentuximab vedotin | None |
| **Comparator (s)** | Established clinical management without brentuximab vedotin | Established clinical management without brentuximab vedotin | None |
| **Outcomes** | • Overall survival<br>• Progression-free survival<br>• Objective response rate<br>• Complete response rate<br>• Rate of stem cell transplantation (autologous and allogeneic)<br>• Adverse effects of treatment<br>• Health-related quality of life | • Overall survival<br>• Progression-free survival<br>• Objective response rate<br>• Complete response rate<br>• Rate of stem cell transplantation (autologous and allogeneic)<br>• Adverse effects of treatment<br>• Health-related quality of life | None |
| **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.<br>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.<br>Costs will be considered from an NHS and Personal Social Services (PSS) perspective. | The analysis performed is in line with the NICE reference case, and Guide to the Methods of Technology Appraisal (2013).<br>The main output of the economic analysis is the cost per QALY gained. | Using cost per QALY gained as per decision problem, but from the perspective of the NHS. No PSS costs have been considered |
| **Subgroups to be considered** | Not applicable | Not applicable | Not applicable |

| | Final Scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE Scope |
|---|---|---|---|
| **Special considerations including issues related to equity or equality** | If the evidence allows, the economic analysis should model stem cell transplantation further down the treatment pathway.<br>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator | The economic analysis includes modelling the following cohorts:<br>• Brentuximab vedotin + ASCT<br>• Brentuximab vedotin + allo-SCT<br>• Chemotherapy<br>• Chemotherapy + ASCT<br>• Chemotherapy + allo-SCT | None |
| Abbreviations: ALK = Anaplastic lymphoma kinase; PSS = Personal Social Services; QALY = Quality-adjusted life year; ASCT = autologous stem cell transplant; allo-SCT = allogeneic stem cell transplant | | | |

## 1.2 Description of the technology being appraised

### 1.2.1 Description of the technology

Brentuximab vedotin is an antibody drug conjugate which is composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). It delivers an antineoplastic agent to CD30-expressing tumour cells resulting in selective apoptotic cell death. CD30 is a cell membrane protein which is highly expressed on certain tumours including systemic anaplastic large cell lymphoma (sALCL) and Hodgkin lymphoma (HL).[7] Details of the licensed indication are presented in Table 1.2 (see also Section 2.1 and 2.2 of the submission).

**Table 1.2: Technology being appraised: Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma**

| | |
|---|---|
| **UK approved name and brand name** | Brentuximab vedotin (Adcetris®) |
| **Marketing authorisation/CE mark status** | On 25 October 2012, Takeda Pharma A/S was granted a conditional marketing authorisation* for brentuximab vedotin by the European Commission, valid throughout the European Union, reference EU/1/12/794/001.[1]<br><br>Adcetris® was designated as an orphan medicinal product (EU/3/08/596 and EU/3/08/595) on 15 January 2009. Adcetris® was designated as an orphan medicinal product in the following indications: Treatment of Anaplastic Large Cell Lymphoma (sALCL) (EU/3/08/595) and Treatment of Hodgkin lymphoma (HL) (EU/3/08/596).[7] In September 2012, the Committee for Orphan Medicinal Products (COMP) reviewed brentuximab vedotin's orphan designation and recommended that it be maintained for both sALCL and HL.[10,11] |
| **Indications and any restriction(s) as described in the summary of product characteristics** | Adcetris® is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).<br><br>Adcetris® is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):<br><br>1. following autologous stem cell transplant (ASCT) or<br><br>2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.<br><br>Adcetris® is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.[1] |
| **Method of administration and** | The recommended dose of brentuximab vedotin is 1.8 mg/kg administered as an intravenous infusion over 30 minutes |

| | |
|---|---|
| **dosage** | every 3 weeks.<br><br>The recommended starting dose for the retreatment of patients with relapsed or refractory sALCL or HL who have previously responded to treatment with brentuximab vedotin is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose.<br><br>Brentuximab vedotin must not be administered as an intravenous push or bolus. Brentuximab vedotin should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products.[1] |
| Abbreviations: HL = Hodgkin lymphoma, sALCL = systemic anaplastic large cell lymphoma; ASCT = autologous stem cell transplant; COMP = Committee for Orphan Medicinal Products | |

# 1.3 Summary of the clinical effectiveness analysis

## 1.3.1 Summary of efficacy evidence for brentuximab vedotin

Brentuximab vedotin has been shown to have unprecedented single agent efficacy in relapsed or refractory (R/R) systemic anaplastic large cell lymphoma (sALCL). The available clinical evidence indicates that brentuximab vedotin has fulfilled a major unmet medical need in R/R sALCL. The key evidence comes from a Phase II study in 58 heavily pre-treated patients with sALCL who had relapsed following at least one prior therapy with curative intent, the most common being a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The final 5-year data cut has shown an objective response rate (ORR) of 86%, with 66% of patients achieving complete remission (CR). Furthermore, of the 66% of patients who achieved CR, 16 patients (42%) were still in remission at study closure without the start of new anticancer therapy, other than stem cell transplantation (SCT).[6] Based on the strength of this data, brentuximab vedotin is viewed by clinical experts as a real 'step-change' in the management of R/R sALCL and, over the past 4 years via the CDF, it has become established as the standard of care in England for these patients. Section 4.11 presents the full efficacy and safety evidence for brentuximab vedotin.

***Efficacy in R/R sALCL – Study SG035-0004***

The following results were seen in a Phase II, open-label, single-arm, multi-centre study in which brentuximab vedotin was given to 58 heavily pre-treated patients (median age 52 years) with sALCL who had relapsed following multi-agent chemotherapy (62% of patients were primary refractory to front-line treatment, 22% had not achieved an objective response to any prior therapy, and 26% of patients experienced treatment failure with an ASCT before study enrolment).[2]

- Objective response rate (ORR) was 86% (n=50/58)
- 66% of patients (38/58) achieved CR (34/58; 59% by IRF)
- Of the 38 CR patients, 16 underwent consolidative SCT (8 allogeneic, 8 autologous) as the next therapy after brentuximab vedotin.

The final, end of study results from this trial, following a median observation time from first dose of 71.4 months (range 0.8 to 82.4 months) showed:[6]

- 16 of the 38 patients who achieved CR (42%) were still on study, alive, and in remission at study closure
- The estimated 5-year OS rate was 60% (95% CI: 47, 73), and the median OS was not estimable (95% CI: 21.3,-; range 0.8 to 82.4+ months) (Figure 4.7)
- The median PFS was 20.0 months (95% CI: 9.4,-) (Figure 4.8). The median PFS in patients who achieved a CR has not been reached
- Of the 58 enrolled patients, 42 (72%) had ALK-negative disease: The estimated 5-year OS was 61% (95% CI: 47%, 76%) for ALK-negative and 56% (95% CI: 32%, 81%) for ALK-positive patients. The median PFS for ALK-negative and ALK-positive ALCL was 20 months (95% CI 6.7,-) and 25.5 months (95% CI 8.0,-) respectively, with the median OS not reached for either.

### 1.3.2 Summary of safety evidence for brentuximab vedotin

Brentuximab vedotin has been shown to have a manageable safety profile across the clinical trial programme in 261 patients with CD30+ haematologic malignancies (including sALCL) that received brentuximab vedotin at the approved dose of 1.8 mg/kg every 3 weeks. A summary is provided below and Section 4.12 presents the full safety evidence for brentuximab vedotin.

***Safety in R/R sALCL – Study SG035-0004***

In a Phase II, open-label, single-arm, multi-centre study in which brentuximab vedotin was given to 58 pre-treated patients with sALCL which had relapsed quickly following at least one multi-agent chemotherapy regimen:[2]

- Median number of cycles administered per patient was 7 (range 1 to 16)
- AEs that occurred in ≥20% of patients included peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhoea (29%), rash (24%), constipation (22%), and neutropenia (21%)
- Most AEs were managed through standard supportive care, and the most common events were grade 1 or 2
- 14 (24%) of patients experienced an AE that resulted in treatment discontinuation
- Doses of brentuximab vedotin were delayed because of adverse events in 40% of patients; however, only 10% of doses were delayed delayed overall.

### 1.3.3 Strength and limitations of the evidence in R/R sALCL

***Strengths:***

Brentuximab vedotin received an expedited, conditional licence approval for R/R sALCL in Europe and the US on the basis of a single Phase II trial in 58 patients (SG035-0004) which demonstrated unprecedented activity and emphasised the great unmet medical need that exists in this patient group.

In this pre-treated population the median number of prior therapies received was 2 (range 1-6), 50% of patients experienced relapse, and 50% were considered refractory relative to their most recent therapy; 62% of patients were primary refractory to front-line treatment; 22% had not achieved an objective response to any prior therapy; and 26% of patients experienced treatment failure with an ASCT before study enrolment, representing a population with a historically poor prognosis, particularly as 72% of patients in the SG035-0004 trial were ALK-negative.[2]

Following the administration of single agent brentuximab vedotin, 97% of patients achieved some reduction in their tumour size, with 86% achieving an objective response and 59% achieving a CR (by IRF).[1] These results compare very favourably with those seen in historical patient cohorts before the availability of brentuximab vedotin.

At study closure, following a median observation time from first dose of 71.4 months, the estimated 5-year OS rate was 60% (95% CI: 47, 73), and the median OS was not estimable (95% CI: 21.3,-; range 0.8 to 82.4+ months).[6] The median PFS was 20.0 months (95% CI: 9.4,-), demonstrating that the majority of patients achieved clinically significant durable remissions. The median PFS in patients who achieved a CR had not been reached. Of the 38 patients who achieved a CR, 16 (42%) were still alive and in remission at study closure. [6]

These end-of-study results demonstrate that single agent brentuximab vedotin can induce durable remissions and long-term survival in heavily pre-treated patients with R/R sALCL. Indeed, the authors of the recently presented 5-year follow up data concluded that a subset of patients with R/R sALCL may potentially have been cured with single-agent brentuximab vedotin.[6]

Outpatient therapy with brentuximab vedotin was also associated with manageable toxicities. Observed peripheral neuropathy was predominantly low grade, sensory in nature and largely reversible.[2]

Based on the strength of the above data, brentuximab vedotin is viewed by clinical experts as a real ‘step-change’ in the management of R/R sALCL and over the past 4 years (via the CDF) it has become established as the standard of care in England for these patients.

***Limitations:***

The clinical evidence for brentuximab vedotin in R/R sALCL comes from a single-arm, open label Phase II trial in 58 patients.[2] Although this is a relatively limited evidence base, a number of important factors need to be taken into account:

- R/R sALCL is a very rare cancer (ultra-orphan indication)
- This is the largest prospective trial ever conducted in patients with R/R sALCL
- The results seen in this trial are unprecedented in R/R sALCL
- In light of the large unmet medical need, brentuximab vedotin received expedited regulatory review and the evidence from this single trial was sufficiently impressive for EMA to grant a conditional marketing authorisation

Hence, despite the apparent limitations of its evidence base, brentuximab vedotin rapidly become established as the standard of care for R/R sALCL within months of its UK launch in November 2012.

A Phase III, randomised comparator trial was not considered feasible in the setting of R/R sALCL, due to the rarity of the disease which, prior to the introduction of brentuximab vedotin, also lacked any licensed therapies and consistent standards of care. Protocol Assistance was received from both the EMA and the FDA who both acknowledged that there was no standard treatment to which brentuximab vedotin could be compared. Indeed, no randomised controlled trials of any therapeutic intervention have been reported at this stage of sALCL.

## 1.4 Summary of the cost-effectiveness analysis

In line with the SG035-0004 study population, the economic model assesses the cost-effectiveness of brentuximab vedotin compared to established clinical management without brentuximab vedotin for the treatment of patients with R/R sALCL, consisting of the use of a range of different chemotherapy regimens.

The economic model includes three health states commonly used in cancer modelling (PFS, post-progression and death). A partitioned survival approach is used to estimate health state occupancy. The model uses a lifetime horizon and adopted a NHS and PSS perspective.

To align with the clinical pathway of care (Section 3.3), the model estimates long-term costs and outcomes associated with ASCT and allo-SCT in addition to brentuximab vedotin (no SCT) and chemotherapy (no SCT). These are assigned to a proportion of patients in both the brentuximab vedotin and chemotherapy arms.

PFS and OS data for brentuximab vedotin (no SCT) were taken from the 5 year follow-up data from SG035-0004 for the subset of 41 patients who did not receive SCT. PFS data for chemotherapy (no SCT) were based on a self-control dataset of 39 patients in SG035-0004 whose most recent therapy was for R/R disease. OS data for chemotherapy (no SCT) were

taken from Mak et al., (2013).[12] PFS and OS for ASCT and allo-SCT were taken from Smith et al., (2013).[13]

The cost-effectiveness model predicted that patients who receive brentuximab vedotin (no SCT) experience the second longest mean OS and an additional 8.5 years mean PFS compared to chemotherapy (no SCT). Brentuximab vedotin was predicted to enable a greater proportion of patients to receive ASCT or allo-SCT, and mean PFS and OS were significantly greater than for conventional chemotherapy, thus yielding a large incremental QALY gain of 3.56 with brentuximab vedotin. This is driven primarily by the superior PFS and OS for brentuximab vedotin (no SCT) compared to conventional chemotherapy (no SCT), and also the superior response profile of brentuximab vedotin.

Based on the strength of its clinical evidence, brentuximab vedotin is highly cost-effective at decision thresholds of £20,000 and £30,000 per QALY, with a base case ICER (with PAS) of only £8,829 per QALY, which is very low for an orphan (indeed ultra-orphan) medicine (see Table 1.3). The application of a significant PAS contributes to the low ICER, although brentuximab vedotin for the treatment of patients with R/R sALCL would remain cost-effective even without the PAS. The corresponding probabilities that brentuximab vedotin is cost-effective were 99% and 100% at £20,000 and £30,000 per QALY thresholds. Moreover, a variety of deterministic sensitivity analyses were conducted in order to explore uncertainty relating to structural assumptions (including the self-control and unanchored indirect comparisons of PFS and OS respectively) and aspects of the model that were largely informed by clinical expert opinion. None of these sensitivity analyses yielded ICERs that were above the £20,000 per QALY decision threshold, reflecting the fact that the incremental QALY gains with brentuximab vedotin remain large even in scenarios that adopt more pessimistic assumptions.

In conclusion, this analysis has shown that brentuximab vedotin is a highly cost-effective treatment for patients with R/R sALCL. Sensitivity analyses indicate that the cost-effectiveness results are robust and this provides added reassurance that brentuximab vedotin represents a cost-effective use of NHS resources. The existence of a significant PAS further enhances its cost-effectiveness and helps to mitigate any remaining uncertainty.

### 1.4.1 Incremental cost-effectiveness results

**Table 1.3: Incremental cost-effectiveness results (with PAS)**

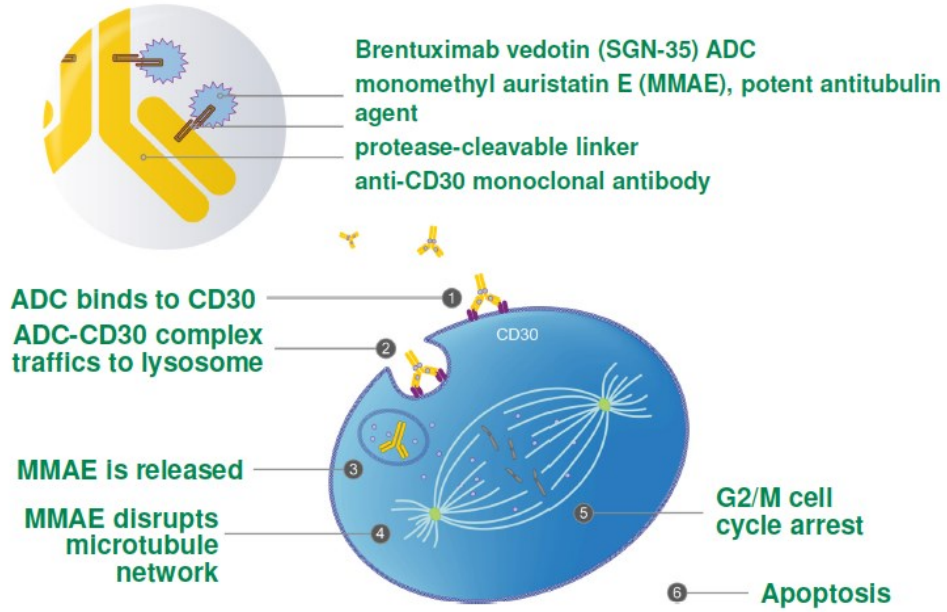
| Technology (and comparators) | Total costs | Total life years | Total QALYs | Incremental costs | Incremental life years | Incremental QALYs | ICER vs. chemotherapy |
|---|---|---|---|---|---|---|---|
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £8,829 |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | | | |

# 2. The technology

## 2.1 Description of the technology

| | |
|---|---|
| Brand Name: | Adcetris® |
| UK approved name: | Brentuximab vedotin |
| Therapeutic class: | Antineoplastics: Lymphomas |
| Mechanism of action: | Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of a CD30-directed monoclonal antibody that is covalently linked to the anti-microtubule agent monomethyl auristatin E (MMAE). It that delivers and anti-neoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Non-clinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE (monomethyl auristatin E) is released from the ADC via proteolytic cleavage of the peptide linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell (see Figure 2.1 below).[1]<br><br>Classical HL and sALCL express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention. Because of the CD30-targeted mechanism of action, brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. The CD30-targeted mechanism of action of brentuximab vedotin, the consistent expression of CD30 throughout the classical HL and sALCL disease and therapeutic spectrums, and clinical evidence in two CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL and sALCL with or without prior ASCT, Contributions to the mechanism of action by other antibody associated functions have not been excluded.[1] |

**Figure 2.1: Brentuximab vedotin mechanism of action schematic**




## 2.2 Marketing authorisation/CE marking and health technology assessment

### 2.2.1 Marketing authorisation and regulatory status

Adcetris® (brentuximab vedotin) is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Adcetris® is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem cell transplant (ASCT) or
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option

Adcetris® is also indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.[1]

On 25 October 2012, Takeda Pharma A/S was granted a conditional marketing authorisation for brentuximab vedotin by the European Commission, valid throughout the European Union (reference EU/1/12/794/001).[1] A conditional licence is granted when a medicinal product fulfils an unmet medical need and the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required.

Adcetris® was designated as an orphan medicinal product (EU/3/08/596 and EU/3/08/595) on 15 January 2009. Adcetris was designated as an orphan medicinal product in the following indications: Treatment of Anaplastic Large Cell Lymphoma (sALCL) (EU/3/08/595). and Treatment of Hodgkin lymphoma (HL) (EU/3/08/596).[7] In September 2012, the Committee for Orphan Medicinal Products (COMP) reviewed brentuximab vedotin's orphan designation and recommended that it be maintained for both sALCL and HL.[10,11]

The SmPC for brentuximab vedotin[1] is included as Appendix 1.

### 2.2.2 Health technology Assessment performed in the UK

Within the UK, brentuximab vedotin has been subject to prior HTAs in Scotland by the Scottish Medicines Consortium (SMC), and in Wales by the All Wales Medicines Strategy Group (AWMSG). The outcome of these HTAs were that brentuximab vedotin is accepted for restricted use within its licensed indications at the time of the guidance issued in September 2014 and June 2015 by SMC[14] and AWMSG,[15] respectively (restricted to treatment of R/R CD30+ HL patients following ASCT, or following two or more therapies when ASCT or multi-agent chemotherapy is not an option).

It has not been accepted by SMC and AWMSG for use in the treatment of adult patients with R/R systemic anaplastic large cell lymphoma (sALCL) because Takeda did not make a submission for this indication due to the very small number of patients affected in Scotland and Wales. However, despite this, eligible patients with R/R sALCL in both Scotland and Wales are able to access it via individual patient treatment requests (IPTRs) or individual funding requests (IFRs), based on their high level of unmet medical need and the undoubted efficacy of brentuximab vedotin in this setting.

## 2.3 Administration and costs of the technology

The recommended dose of brentuximab vedotin is 1.8 mg/kg administered as a single agent intravenous infusion over 30 minutes every 3 weeks under the supervision of a physician experienced in the use of anti-cancer agents. If the patient's weight is more than 100kg, the dose calculation should use 100kg. Hence, the maximal recommended dose is 180mg. Patients should be monitored during and after infusion. Treatment should be continued until disease progression or unacceptable toxicity. Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year).[1]

**Table 2.1: Costs of the technology being appraised**

| | Details | Source |
|---|---|---|
| **Pharmaceutical formulation** | Each vial contains 50mg powder for concentrate for solution for IV infusion. | |
| **Acquisition cost (excluding VAT)** | NHS list price is £2,500 per vial (ex VAT).<br>There is an approved simple Patient Access Scheme (PAS) which offers a confidential net price of £[redacted] per 50mg vial (a [redacted]% discount from the NHS List price). | BNF 72, 2016 [16] |
| **Method of administration** | IV infusion over 30 minutes | SmPC[1] |
| **Doses** | The recommended dose regimen is 1.8 mg/kg<br>If weight >100kg, then 100kg is assumed (i.e. max dose per cycle = 180mg) | SmPC[1] |
| **Dosing frequency** | every 21 days | SmPC[1] |
| **Average length of a course of treatment** | **R/R sALCL**<br>Median of 7 cycles in trial 0004 – see Section 1.3.2<br>Mean of 8.2 cycles received by ITT population in SG035-0004.<br>• Mean of 8.8 cycles received by patients who received SCT as the first therapy after discontinuing brentuximab vedotin in remission in SG035-0004 (Section 5.5).<br>• Mean of 8 cycles received by patients who did not receive SCT as the first therapy after discontinuing brentuximab vedotin in remission in SG035-0004 (Section 5.5).<br>Number of cycles used in clinical practice likely to be less than in the 0004 trial. SmPC states a minimum of 8 cycles.[1] | SG035-0004 trial;[2] EPAR for brentuximab vedotin[7] |
| **Average cost of a course of treatment (drug acquisition costs)** | **R/R sALCL**<br>Mean of 8.2 cycles received by ITT population in SG035-0004.<br>• The estimated cost per course for patients who received SCT as the first therapy after discontinuing brentuximab vedotin in remission in SG035-0004 is £[redacted] (based on PAS price, see Section 5.5)<br>The estimated cost per course for patients who did not receive SCT as the first therapy after discontinuing brentuximab vedotin in remission in SG035-0004 is £[redacted] (based on PAS price, see Section 5.5) | |
| **Anticipated average** | N/A | |

| | Details | Source |
|---|---|---|
| **interval between courses of treatments** | | |
| **Anticipated number of repeat courses of treatments** | N/A | |
| **Dose adjustments** | Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment.<br>Brentuximab vedotin dosing should be permanently discontinued if a diagnosis of PML is confirmed, or pancreatic cancer, | SmPC[1] |
| **Anticipated care setting** | Hospital | |
| * Expected to be fewer number of cycles in actual clinical practice for this patient population | | |

## 2.4 Changes in service provision and management

Brentuximab vedotin has been available in the UK since November 2012 for the treatment of relapsed or refractory (R/R) systemic anaplastic large cell lymphoma (sALCL). It has been included in the national Cancer Drugs Fund (CDF) in England for this indication since April 2013 and has become the established standard of care across the UK for the very small number of patients with R/R sALCL. Hence, any changes in service provision and management will have already taken place to accommodate its use. Some key features are as follows:

- Brentuximab vedotin has an IV formulation, and is weight based dosing - it is to be administered in a hospital setting, but as standard chemotherapy and radiotherapy is also administered in a hospital setting this has not had a particular service provision impact. Indeed, as no one therapy had previously represented standard of care, the launch of brentuximab vedotin may have simplified service provision by displacing a range of salvage therapies of limited effectiveness, with an effective agent that is simple and convenient to administer. Brentuximab vedotin is a single agent, administered as a short 30-minute intravenous infusion once every three weeks on an out-patient basis. Comparator chemotherapy options at this stage of sALCL involve multi-agent chemotherapy regimens, many of which are much more complex to administer. The simple administration schedule for brentuximab vedotin and the fact it can be given on an out-patient basis means that it has less impact on patients' lives and simplifies service provision.

- Relapsed/refractory sALCL is a very rare condition which affects only a very small number of patients each year in the UK. Due to the inclusion of brentuximab vedotin in the national CDF since April 2013, we have reliable data on the extent of its use in real world clinical practice in England. The data from the CDF shows that the use of brentuximab vedotin in sALCL is stable and amounts to only about 45 patients per

year in the whole of England. Given this very small number of patients, who are treated in specialist centres, any impact on service provision is minor and has already taken place due to its inclusion in the CDF for almost 4 years.

- Brentuximab vedotin is the first new medicine to be approved for the treatment of sALCL in more than 30 years, and is currently the only treatment with European Medicines Agency (EMA) approval for patients with R/R sALCL. Based on its unprecedented single agent activity and the impressive survival data seen in the pivotal trial, it is considered a 'step-change' in the management of CD30-positive R/R sALCL.

## 2.5 Innovation

Brentuximab vedotin is a targeted and highly innovative therapy that has shown unprecedented single-agent activity in the treatment R/R sALCL. It has a unique mechanism of action and published data outcomes for efficacy and safety, thus providing an opportunity to make a significant and substantial impact on health-related benefits and address an otherwise significant unmet medical need. Brentuximab vedotin is the first new medicine to be approved for the treatment of sALCL in more than 30 years, and is currently the only treatment with EMA approval for patients with R/R sALCL. Based on its unprecedented single agent activity and the impressive long-term survival data seen in the pivotal trial, brentuximab vedotin is viewed by physicians and patient interest groups as a real 'step-change' in the management R/R sALCL.

In approximately 50%-80% of sALCL cases, the t(2;5)(p23;q35) chromosome translocation, prompting the anaplastic lymphoma kinase (ALK) gene on chromosome 2 to fuse with the nucleophosmin (NPM) gene on chromosome 5 (ALK-positive), is detected. ALK-positive patients are younger and have a better prognosis than patients who are ALK-negative. Although 75-85% of patients achieve an objective response (either a complete or partial response) with front-line anthracycline based therapy, the 5-year failure-free survival after treatment was 60% in ALK-positive compared with 36% in ALK-negative patients. The 5-year overall survival rate was 70% in those with ALK-positive and 49% in those with ALK-negative ALCL.[17,18] For patients that are refractory to or who relapse following anthracycline based therapy, the prognosis is poor with only a minority of patients surviving beyond 2 years.

There has been a significant unmet need for new treatments for patients with R/R sALCL. Specifically, there are unmet needs for new therapies that demonstrate a favourable safety profile, as well as improved efficacy on key endpoints such as overall survival, progression free survival and objective response rate. It is for these reasons that the EMA granted a conditional marketing authorisation to brentuximab vedotin for sALCL, based on only Phase II data. A conditional licence is granted when a medicinal product fulfils an unmet medical need and the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required.

Further, during the appraisal of brentuximab vedotin for patients with R/R CD30+ HL by the SMC, a patient and clinician engagement (PACE) meeting with patient group representatives

and clinical specialists was held to consider the 'added value' of brentuximab vedotin, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland. The PACE process in Scotland takes account of the views of clinicians and patients to determine other factors than those accounted for within the QALY. The key non-QALY benefits of brentuximab vedotin were identified as follows,[14] (and we believe many of these will also apply to the R/R sALCL indication):

- It offers a convenient administration schedule compared to standard multi-agent chemotherapy, with improved tolerability which helps maintain dignity and allows patients to live as normal a life as possible during treatment.[14] This dignity and HRQoL benefit of brentuximab vedotin over standard therapy is not adequately captured in the economic model by the utility and QALY assessment.

- The potential for brentuximab to be a bridge to curative transplant in some patients was recognised in the PACE process as highly important due to the young age of many of the r/r post ASCT patients and so could have a 'profound positive impact on the physical and psychological health of the patient and offer substantial life year gains (in the order of 20-30 years)."[14] This benefit maybe partly captured by the QALY assessment in the economic model, although due to limitations in the data available the full HRQoL benefit associated with being able to bridge to allo-SCT has not been possible to capture.

The Lymphoma Association also highlighted that brentuximab vedotin may also provide rapid relief of symptoms, and its speed of treatment delivery enables people to spend more time at home with family and friends.[14] Some patients have reported fewer side effects than with chemotherapy. From the patients' perspective, the above benefits should be captured through QALY estimation in the economic model. However, the economic evaluation has not taken into account the impact of brentuximab vedotin on caregivers and family members HRQoL.

# 3. Health condition and position of the technology in the treatment pathway

## 3.1 Relapsed or refractory systemic anaplastic large cell lymphoma

### 3.1.1 Overview

Peripheral T-cell lymphoma (PTCL), a subset of non-Hodgkin lymphoma (NHL), comprises a spectrum of rare and aggressive T-cell lymphomas with a generally poor prognosis. The 2008 World Health Organisation classification system contains 22 biologically and clinically different T-cell lymphoma subgroups, which are distinct with respect to pathology, clinical presentation, response to therapy, prognosis and expression of surface markers. The most common subgroups are PTCL-not otherwise specified (PTCL-NOS; 25.9%), angioimmunoblastic T-cell lymphoma (AITL; 18.5%), adult T-cell leukaemia/lymphoma (ATLL; 9.6%), and anaplastic large-cell lymphoma (ALCL; 12.1%). PTCLs are characterised by frequent relapses, and primary refractory disease is not uncommon.[12]

ALCL occurs most commonly in children and young adults with the estimated incidence being around 5,000 adults per year, and 20,000 children per year in Europe,[19] and is more common in males than females. It can appear in the skin, in lymph nodes, or in organs throughout the body.[20]

It has two distinct forms, systemic ALCL (sALCL) and a primarily cutaneous form. There are two subtypes of sALCL, defined by the presence or absence of anaplastic lymphoma kinase (ALK) protein expression. ALK +ve ALCL is clinically distinctive with patients presenting at a younger age and having a prognosis that is superior to those with ALK -ve ALCL. ALK –ve ALCL can be more difficult to diagnose and the prognosis may be similar to that of PTCL-NOS. Relapsed/refractory sALCL is a very rare condition which easily meets the definition of an ultra-orphan indication. CD30 is invariably expressed on the surface of ALCL cells.

### 3.1.2 Treatment of sALCL in the UK

CHOP-based chemotherapy (cyclophosphamide, hydroxydaunomycin, vincristine [[Oncovin®], and prednisolone) is generally considered the standard first-line treatment for sALCL,[9] and is effective in approximately 60% of ALK +ve patients.[18,21,22] Consolidation with high-dose chemotherapy and autologous stem cell transplant is not recommended for those ALK +ve patients who achieve complete remission.[9] In ALK -ve disease, chemotherapy is effective in approximately 40% of patients and, due to their adverse prognosis, it is recommended that ALK –ve patients are consolidated in 1st remission with an ASCT. Approximately 40% to 65% of patients with sALCL develop recurrent disease after front-line therapy.[9,18] Allogeneic stem cell transplantation (allo-SCT) may be an effective procedure for R/R ALK +ve ALCL, but its value in the treatment of ALK –ve disease remains to be defined.[9] Thus, without brentuximab vedotin, R/R sALCL remains a clinical challenge, associated with poor outcomes and there is no standard therapy.[18,21,23-25]

The UK PTCL clinical guideline states *'the most exciting development in the treatment of relapsed ALCL has been the introduction of the anti-CD30 antibody drug conjugate brentuximab vedotin'*.[25] The UK guidelines recommend that at relapse patients should receive platinum–based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemo-sensitive disease should be considered for transplant (ASCT if not received in the front-line, or allo-SCT).[25]

Brentuximab vedotin is currently the only treatment with European Medicines Agency (EMA) approval for patients with R/R sALCL. Recognising that R/R sALCL represents an unmet medical need, the EMA granted a conditional marketing authorisation to brentuximab vedotin based on a single Phase II, open-label study comprising 58 patients.[2] Indeed, this study represents the largest prospective trial ever conducted in patients with R/R sALCL. A Phase III, randomised comparator trial was not considered feasible in the setting of R/R sALCL, due to the rarity of the disease which, prior to the introduction of brentuximab vedotin, also lacked any licensed therapies and consistent standards of care. Protocol Assistance was received from both the EMA and the FDA who both acknowledged that there was no standard treatment to which brentuximab vedotin could be compared. No randomised controlled trials of any therapeutic intervention have been reported at this stage of sALCL. Due to the unprecedented efficacy seen in the Phase II pivotal trial, brentuximab vedotin has, since its launch in November 2012, rapidly become the standard of care for UK patients with R/R sALCL.

## 3.2 Impact of the condition on patients and society and the role of brentuximab vedotin

While ALK +ve ALCL usually affects children and young adults, ALK -ve ALCL is more common in patients over the age of 55 years.[26] The majority (72%) of patients included in the pivotal Phase II trial of brentuximab vedotin (SG035-0004) were mainly middle-aged, with a median age of 52 years.[2]

The outlook for a significant proportion of patients with sALCL who relapse following front-line therapy is extremely poor, with a median overall survival (OS) of only 3.0 months in patients treated with chemotherapy alone.[12] In the 0004 study of brentuximab vedotin, 62% of patients were primary refractory to front-line treatment, and 22% had not achieved an objective response to any prior therapy,[2] and these patients are the primary target for the use of brentuximab vedotin in UK clinical practice.

Because of the rarity of the disease, there are currently no randomised controlled trials (RCTs) to guide treatment decisions in ALCL. The majority of evidence describing outcomes for adult patients with systemic ALCL and the impact of various treatment regimens comes from retrospective studies or subgroup analyses of completed prospective studies in aggressive lymphomas or PTCLs. Although retrospective in nature, there have been numerous studies evaluating the efficacy of ASCT in relapsed PTCLs that report 3- and 5-year EFS (event-free survival) rates ranging from 25% to 75%,[27] with some studies demonstrating salvage rates comparable to those seen in diffuse large B-cell lymphoma (DLBCL), especially for patients with ALCL.[3,22,28-30]

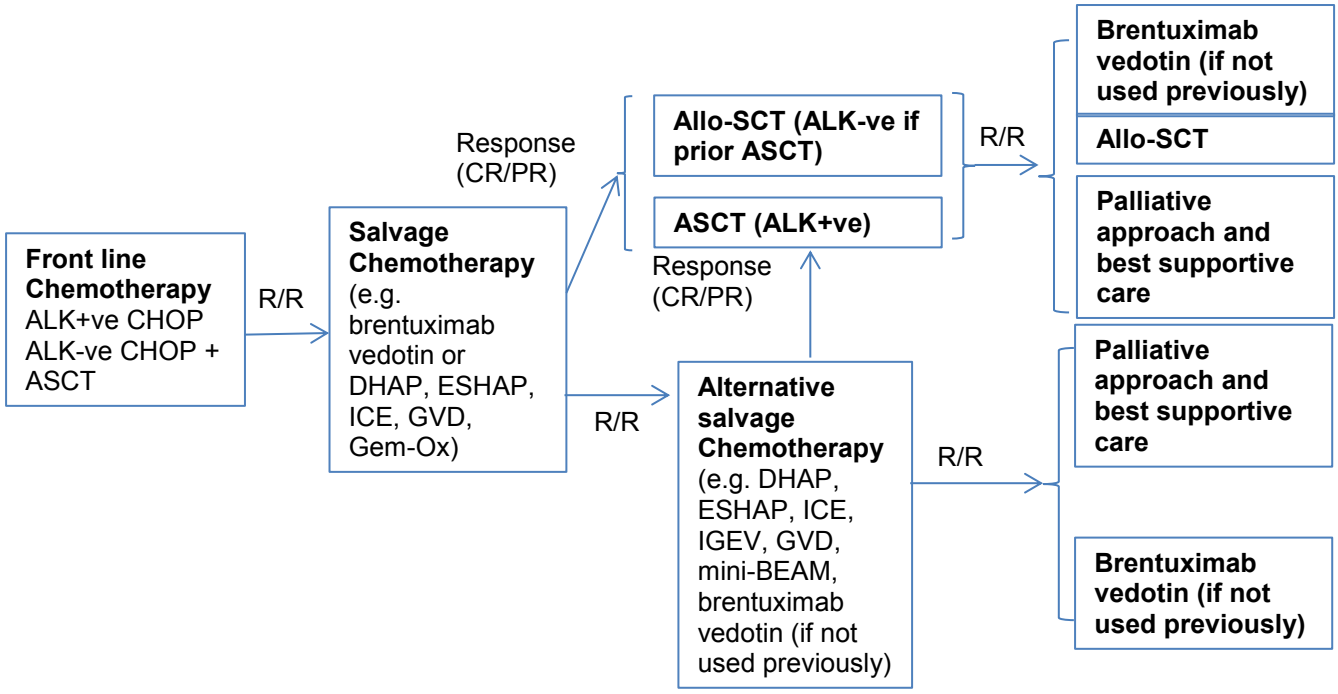
Information is more limited on the role of allo-SCT in R/R ALCL, and many studies pool all PTCL subtypes. Taken together, myeloablative allo-SCT in this setting results in approximately 30% of patients remaining alive and disease-free at 3 to 5 years with full myeloablative transplantation; however, treatment-related mortality rates are also ~30%, and very few studies have reported results for ALCL.[13,27,31,32] The Centre for International Blood and Bone Marrow Transplant Research study demonstrated that ASCT was associated with a better PFS (55% vs. 35%; P = 0.0319) and OS (68% vs. 41%; P = 0.0034) compared with allo-SCT if all ALCL patients were considered.[13]

In R/R ALCL patients ineligible for transplantation or for whom second-line salvage therapy has failed, the outcome has historically been poor. The British Columbia Cancer Agency (BCCA) evaluated the survival of PTCL patients following first relapse or progression who had received chemotherapy, and the median OS and PFS were only 3.0 months and 1.8 months, respectively, for patients with ALCL, which supports a role for novel therapies and clinical trials for this poor prognosis group.[3]

## 3.3 Treatment pathway for sALCL and the place of brentuximab vedotin in the pathway

A simplified treatment pathway for sALCL, illustrating where brentuximab vedotin is currently licensed for use (and funded by the CDF), is shown in Figure 3.1.

**Figure 3.1: Simplified treatment pathway in sALCL, showing where brentuximab vedotin is licensed for use**




Standard front-line therapy for sALCL is multi-agent CHOP chemotherapy (+ a consolidative ASCT at first remission in ALK –ve patients); an approach that can provide long-term

remission in up to 60% and 40% of ALK +ve and ALK -ve newly diagnosed patients, respectively.[18,21,25,33] Prior to the introduction of brentuximab vedotin, no consensus had been reached regarding the treatment of relapsed or refractory disease. A second complete remission with standard salvage chemotherapy can be achieved in 30%-40% of patients.[17,34] Allogeneic transplantation may be an effective procedure for R/R ALK +ve ALCL, but it's value in the treatment of ALK -ve disease remains to be defined.[9,33] Generally, ALK -ve patients have a poorer prognosis than the ALK +ve patients in the first-line setting.

Brentuximab vedotin is the most widely studied agent in sALCL. The pivotal Phase II study in relapsed/ refractory ALCL (42 ALK -ve, 16 ALK +ve)[2] demonstrated an overall response rate (ORR) of 86% and CR of 59%. The estimated median PFS was 14.3 months, and for those who achieved a CR, it was 14.5 months. [1,5] A final analysis of patients observed for almost 5 years demonstrated a median duration of response for CR patients who did not receive an SCT as consolidation of 39.4 months, and 16 (42%) of 38 remained in remission.[6]

Hence, brentuximab vedotin is a novel, targeted treatment for a small group of R/R sALCL patients who lack other effective treatment options. It offers the potential for long-term survival in many patients and may also be used as a potential bridge to allogeneic stem cell transplant (allo-SCT) in some patients. The value of brentuximab vedotin has been clearly illustrated by its adoption as the standard of care for R/R sALCL patients in the UK, with access via the national CDF in England since April 2013 (and regional cancer drug funds prior to this), and via individual funding requests in Scotland and Wales.

## 3.4 Clinical Guidelines

UK Guidelines for the management of sALCL, including R/R sALCL, have been developed by the British Committee for Standards in Haematology (BCSH):[25] "Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma), Updated 2013." These guidelines recommend the following for ALCL patients: "*At relapse, patients should receive platinum-based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemo-sensitive disease should be considered for transplant."* These guidelines state that *"the most exciting development in the treatment of relapsed ALCL has been the introduction of the anti-CD30 antibody drug conjugate brentuximab vedotin."*

In the US, the National Comprehensive Cancer Network (NCCN) guidelines[24] were updated in 2014 and include brentuximab vedotin as an option for patients who have failed front-line therapy with a multi-agent chemotherapy regimen (e.g. CHOP), regardless of their eligibility for autologous or allogeneic stem cell transplant.[24]

## 3.5 Current patient numbers and clinical practice

Based on the stage of disease (R/R sALCL) under review, brentuximab vedotin meets the definition of an ultra-orphan medicine (a prevalence of less than 1 in 50,000 persons).

In 2013, the National Cancer Drugs Fund (CDF) approved the use of brentuximab vedotin for:

- *R/R ALCL when no other salvage treatment is available.*

ALCL patients in England meeting the above criteria were able to access brentuximab vedotin via the CDF. Brentuximab vedotin was also included on the CDF list in England for *"the treatment of relapsed or refractory CD30+ Hodgkin lymphoma where the following criteria are met:*

1. *Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.*

2. *Relapsed or refractory CD30+ Hodgkin lymphoma.*

3. *a) Following autologous stem cell transplant (ASCT), OR*
   *b) Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

Between April 2013 to March 2014, a total of 44 patients in England with R/R sALCL received brentuximab vedotin via the CDF. In the following year, April 2014 to March 2015, 45 patients in England received brentuximab vedotin via the CDF for R/R sALCL. In the latest available data from CDF notifications, capturing patient claims for the first six months of fiscal year 2015 (April 2015 to September 2015), 22 patients in England received brentuximab vedotin for R/R sALCL. This figure is consistent with half-year figures from fiscal years 2013 and 2014. Hence, the use of brentuximab vedotin for R/R sALCL via the CDF has already reached steady-state and, as such, the number of patients forecast to receive it is expected to remain constant over the next five years at approximately forty-five patients per year, in line with the CDF experience. See Section 6 for more details of patient numbers.

## 3.6 End of life criteria

Based on compelling cost effectiveness results (see Section 5) which show that brentuximab vedotin easily meets NICE's conventional cost-effectiveness threshold (i.e. £20,000 - £30,000 per QALY), Takeda does not wish for the medicine to be considered at this time for the application of NICE's End of Life criteria.

## 3.7 Equality issues

There are no major equality issues concerning the use of brentuximab vedotin. However, given that it has been on the national Cancer Drugs Fund (CDF) in England for almost four years and has become established as the standard of care for patients with R/R sALCL, there would be a significant adverse impact on patients if it is not recommended by NICE and thus becomes unavailable to patients after the old CDF closes. There would be equity issues arising from this because patients with R/R sALCL in England who would previously

have been able to access brentuximab vedotin via the CDF would then be unable to benefit from the medicine, based purely on the timing of their relapse in relation to the NICE decision and the closure of the old CDF. Thus, a situation would arise whereby patients presenting on one day are able to access brentuximab vedotin (via the CDF), while patients presenting a day later are unable to (because the CDF had closed to new patients).

Within a UK context there could also be inequity of access if patients in Scotland and Wales are able to receive brentuximab vedotin via individual patient funding mechanisms while patients in England are not in the event of a negative NICE decision.

# 4. Clinical effectiveness

## 4.1 Identification and selection of relevant studies

A systematic literature review (SLR) of the clinical evidence relating directly to the appraisal decision problem in Section 1.1 was performed. The primary objective of the SLR was to address the following decision problem:

> "What is the clinical efficacy and safety of brentuximab vedotin or established clinical management for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL)?"

In line with this, data on the clinical efficacy and safety of brentuximab vedotin or comparator was obtained by a systematic search and review of published research evidence and conference abstracts (with supporting poster presentations), supplemented by unpublished trial data for brentuximab vedotin supplied by Takeda UK.

The search terms were developed specifically for each database. Searches took into account non-proprietary and other product names including variations in different countries. Specific search filters for randomised controlled trials were used to retrieve studies of clinical effectiveness. Each abstract was assessed by two independent reviewers.

The search strategy used is reported in Appendix 2. In the systematic review, the search strategies were executed on the 18th January 2011 and repeated firstly on the 18th June 2012, secondly on the 13th July 2015, and then more recently on the 17th November 2016 to update the search and fill in gaps in the evidence from the first systematic search in the following databases:

- Ovid MEDLINE® Daily Update and Ovid MEDLINE® (OVID SP)
- MEDLINE® In-Process & Other Non-Indexed Citations
- EMBASE (OVID SP)
- CENTRAL (The Cochrane Central Register of Controlled Trials)
- PubMed (for E-publications ahead of print)

Search strategies combined free-text and controlled vocabulary terms (MeSH terms in MEDLINE® and CENTRAL and EMTREE terms in EMBASE) for sALCL. In addition, manual searches of the following conferences were performed to identify relevant abstracts, not yet available as full publications:

- American Society of Haematology (ASH)
- European Haematology Association (EHA)
- International Conference on Malignant Lymphoma (ICML)

### 4.1.1 Eligibility criteria

The following eligibility criteria were used to determine articles to be included in the systematic review. Eligibility criteria are specified in the table below in terms of patients, interventions, comparators, outcome and study design (PICOS). The same criteria were applied for the 2012, 2015 and 2016 updates as for the original search carried out in 2011.

**Table 4.1: Eligibility criteria for search strategies conducted in 2011, 2012, 2015, and 2016**

| | |
|---|---|
| **Patients** | Patients with R/R sALCL |
| **Interventions/ Comparators** | No restrictions by intervention were imposed |
| **Outcome** | Response, overall survival, progression-free survival, adverse events |
| **Study design** | All study designs were considered with the exception of study protocols or conference abstracts (unless they were identified from the conference proceeding search):<br>• RCTs<br>• Non-randomised studies: prospective interventional, prospective observational studies, or retrospective studies<br>Studies must have included 20 or more patients with R/R sALCL<br>Only studies in the English language were included |

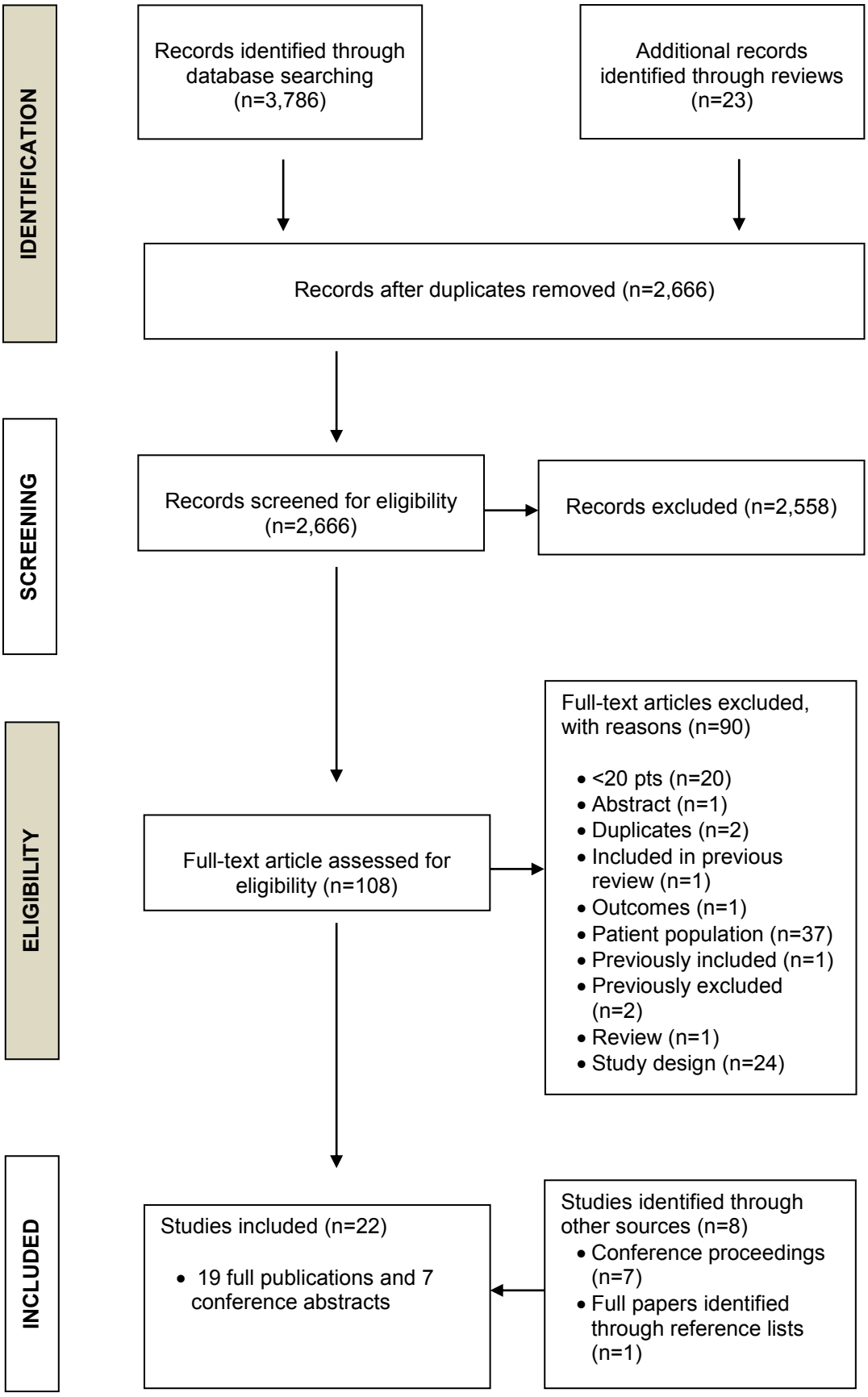
### 4.1.2 Study selection

Due to the limited availability of randomised evidence for the R/R sALCL indication, non-randomised study designs such as prospective interventional studies, prospective observational studies, as well as retrospective studies were considered in this systematic review.

All abstracts were reviewed by two experienced systematic reviewers according to the eligibility criteria outlined in Section 4.1.1; any difference in opinion regarding eligibility was resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full papers.

A PRISMA flow diagram indicating the number of studies included and excluded at each stage of the review for the R/R sALCL indication is provided below (Figure 4.1). The PRISMA flow diagram includes combined results from the original systematic review (2011) and updates in 2012, 2015, and 2016.

**Figure 4.1: PRISMA flow diagram of the study selection process for R/R sALCL patients**



### 4.1.3 Results

An updated systematic review of electronic databases was conducted on the 17th November 2016 following an original search carried out in 2011, and previous updates in 2012, and 2015. The search strategies used for each database are described in Appendix 2. References were downloaded into dedicated Reference Manager® databases. After de-duplication a total of 613 articles were identified. These abstracts were double reviewed for eligibility and six full-text articles were ordered for assessment. Following full paper review, one full text articles was identified for inclusion.

The 2016 update identified two new studies, all reporting brentuximab vedotin usage, in two conference proceedings (Chihara et al., ASH 2015, and Pellegrini et al., ASH 2016).[35,36] In addition, the 5-year brentuximab vedotin final data reported at ASH in December 2016 [6] was included and one full publication[37] reporting a different data cut of the French Named Patient Programme (NPP) from the previously included abstract from the same author [38] was also included here.

Three identified conference abstracts (Pro et al., ASH 2013,[39] Pro et al., ASH 2014,[40] and Pro et al., ASH 2016)[6] were linked to the already included full publication of the pivotal Phase II trial for brentuximab vedotin (SG035-0004).[2] All abstracts were included in the review as they provided 3-, 4-, and 5-year survival data.

No RCTs were identified in the systematic review. From the non-RCT evidence, the majority of studies were prospective, interventional studies and retrospective case series.

For a complete list of all the non-RCTs that were identified during the systematic review, including contributing data sources, please see the updated systematic review report.[41]

## 4.2 List of relevant randomised controlled trials

No randomised controlled trials (RCTs) were identified and all studies took the form of either prospective, interventional studies or retrospective case/ cohort studies. This is typical for this aggressive disease.

From the systematic search, one non-RCT study for brentuximab vedotin considered to be relevant to the decision problem was identified.[2] Details of this study will be presented in Section 4.11 (non-randomised and non-controlled evidence). In addition, five retrospective, case series[35,42] (including two Named Patient Programmes in France and Italy[36-38] were identified. Details of these studies will be presented in Section 4.1.1 (non-randomised and non-controlled evidence).

## 4.3 Summary of methodology of the relevant randomised controlled trials

Not applicable.

## 4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Not applicable.

## 4.5 Participant flow in the relevant randomised controlled trials

Not applicable.

## 4.6 Quality assessment of the relevant randomised controlled trials

Not applicable.

## 4.7 Clinical effectiveness results of the relevant randomised controlled trials

Not applicable.

## 4.8 Subgroup analysis

Not applicable.

## 4.9 Meta-analysis

No formal meta-analysis was performed for brentuximab vedotin compared with established clinical management for patients with R/R sALCL as the data was from an open-label, single-arm trial.,[2] retrospective studies,[35,42] and Named Patient Programme (NPP) data.[36-38,43]

## 4.10 Indirect and mixed treatment comparisons

No formal indirect or mixed-treatment comparison was performed for patients with R/R sALCL for the reason outlined in Section 4.9 above.

## 4.11 Non-randomised and non-controlled evidence

### 4.11.1 Overview of non-RCT evidence

The clinical effectiveness of brentuximab vedotin in the treatment of patients with R/R sALCL was demonstrated in one pivotal Phase II, multinational, open-label study (SG035-0004),[2] two retrospective case series,[35,42] and data from three NPPs (including the UK)[36-38,43] (Table 4.2).

**Table 4.2: List of relevant non-randomised and non-controlled evidence**

| Study ID | Objective | Population | Intervention | Comparator | Primary study reference(s) | Justification for inclusion |
|---|---|---|---|---|---|---|
| **Prospective, interventional study** | | | | | | |
| SG035-0004 | To evaluate the efficacy and safety of brentuximab vedotin in patients with R/R sALCL | Patients with R/R sALCL after ≥1 prior therapy | Brentuximab vedotin 1.8 mg/kg every 3 weeks (n=58) | Not applicable, single-arm study | Pro et al., 2012 [2] | Pivotal, multinational trial based on the absence of a definitive optimal therapy for patients with R/R sALCL |
| **Retrospective studies** | | | | | | |
| Retrospective case series | To evaluate the safety and efficacy of brentuximab vedotin in adults<60 to ≥60 years with relapsed CD30-positive lymphomas | Patients with R/R CD30-positive lymphomas from previous clinical trials | Brentuximab vedotin (≥1.2 mg/kg, q3wk; ≥0.6 mg/kg q1wk)<br>Total patients age <60 (n= 326); ALCL (n=52)<br>Total patients age ≥60 (n=40); ALCL (n=22) | Not applicable, single-arm studies | Gopal et al., 2014 [42] | Includes patients with R/R sALCL |
| Retrospective case series | To evaluate the impact of BV, and survival outcome of patients with ALCL who experienced progression after BV | Patients with R/R ALCL | Dose of BV not reported<br>Total ALCL patients (n=176): ALK- (n=102); ALK+ (n=74)<br>30 patients received treatment with BV | Not applicable, single-arm study | Chihara et al., 2015 [35] | Patients with ALCL |
| **Named Patient Programmes (NPP)** | | | | | | |
| NPP | To evaluate the use of BV in a real-world setting | Patients with CD30+ T-cell lymphomas | Brentuximab vedotin 1.8 mg/kg every 3 weeks<br>Total patients (n=24) | Not applicable, NPP (UK) | Gibb et al., 2013 [43] | Includes patients with R/R sALCL in a real-world context |

| Study ID | Objective | Population | Intervention | Comparator | Primary study reference(s) | Justification for inclusion |
|---|---|---|---|---|---|---|
| | | refractory to ≥2 lines of chemotherapy or autotransplant with a positive PET-CT scan (from 2010-2011) | ALCL patient s (n=5): ALK- (n=2); ALK unknown (n=3) | | | |
| NPP | To conduct a retrospective multicentre study on a cohort or R/R PTCL patients treated with BV during the NPP in France | Patients with R/R PTCL from a compassionate patient programme in France (from March 2011 to January 2014) | Brentuximab vedotin 1.8 mg/kg every 3 weeks<br>Total patients (n=56)<br>sALCL (n=24): ALK- (n=15); ALK+ (n=9)<br>Total patients (n=65); ALCL (n=24): ALK- (n=14); ALK+ (n=10) | Not applicable, NPP (France) | Lamarque et al., 2016 [37]<br>Lamarque et al., 2014 [38] | Includes patients with R/R sALCL in a real-world context |
| NPP | To evaluate the use of BV in everyday clinical practice to confirm clinical trial results in a real-life context | Patients with relapsed sALCL (from November 2012 to July 2014) | Brentuximab vedotin 1.8 mg/kg every 3 weeks<br>Total patients (n=40): ALK- (n=18); ALK+ (n=22) | Not applicable, NPP (Italy) | Pellegrini et al., 2015 [36] | Includes patients with relapsed sALCL in a real-world context |
| Abbreviations: R/R sALCL = relapsed or refractory systemic anaplastic large cell lymphoma; q3wk = every 3 weeks; q1wk = every week; PTCL = peripheral T-cell lymphoma; ALK- = Anaplastic lymphoma kinase-negative; ALK+ = Anaplastic lymphoma kinase-positive; BV = brentuximab vedotin; NPP = Named Patient Programme; PET-CT = Positron emission tomography–computed tomography | | | | | | |

### 4.11.2 Excluded trials

No trials were excluded from the list of studies presented in Table 4.2.

### 4.11.3 Methodology of the non-randomised and non-controlled evidence

The methodology of the relevant single-arm studies is summarised in Table 4.3.

**Table 4.3: Comparative summary of methodology of brentuximab vedotin single-arm studies and NPP's (non-RCT evidence)**

| Study characteristics | Study SG035-0004 | Retrospective case series | Named Patient Programmes (NPP's) |
|---|---|---|---|
| Patient population (n=) | Patients with R/R sALCL after ≥1 prior therapy (n=58) | Patients with R/R CD30+ lymphoma/ R/R PTCL (including ALCL):<br>• sALCL (n= 74) [42]<br>• sALCL (n=176)* [35] | Patients with CD30+ T-cell lymphoma (including ALCL)<br>• ALCL (n=5) UK centre [43]<br>• ALCL (n=24) French centre,[38] [37]<br>• ALCL (n=40) Italian centre [36] |
| Study design | Phase II, open-label, single-arm, multicentre study | Retrospective studies (including from previous clinical trials) | Compassionate use via a Named Patient Programme |
| Location | 22 centres in the US, Canada, and Europe (including the UK) | Multicentre including the US, Canada, and Europe (including the UK) | UK, France, and Italy |
| Duration of study | • Maximum 16 cycles of brentuximab vedotin (approximately 1 year)<br>• Median number of cycles 7<br>• Among patients with an objective response, median number of cycles was 8 | Maximum 16 cycles of brentuximab vedotin (approximately 1 year) | • UK centre – patients received a median of 5.5 cycles (range 1-13) of BV [43]<br>• French centre - patients received a median of 6 cycles (range 1-16) [37]<br>• Italian centre – Best response was observed after a median of 4 cycles in 31 patients Pellegrini 2015 [36] |
| Intervention | Brentuximab vedotin 1.8 mg/kg every 3 weeks | Brentuximab vedotin 1.8 mg/kg every 3 weeks, or<br>Brentuximab vedotin 0.6 to 1.4 mg/kg q1wk | Brentuximab vedotin 1.8 mg/kg every 3 weeks |
| Primary efficacy outcome(s) | ORR per independent review | • Response assessments [42]<br>• PFS and OS [35] | • UK centre – Authors describe ORR, subsequent allo-SCT rate, PFS and OS of patients enrolled onto the programme [43] |

| Study characteristics | Study SG035-0004 | Retrospective case series | Named Patient Programmes (NPP's) |
|---|---|---|---|
| | | | • French centre – ORR and PFS,[38] [37]<br>• Italian centre - ORR and PFS [36] |
| Secondary efficacy outcome(s) | • DOR by independent review<br>• CR by independent review<br>• PFS by independent review<br>• OS | Not reported | Not reported |
| Safety outcomes | Incidence and severity of AEs | Recording of AEs, physical examination findings, vital signs and routine laboratory tests Gopal 2014 [42] | Incidence of AEs |
| Duration of follow-up | Final five-year data was presented at ASH 2016 [6] | Median follow-up of 64 months[35] | • UK centre – NPP ongoing. Now with a total of n=33 patients; ALCL (n=8)[44]<br>• French centre – median follow-up of 13.4 months (range 0.4 to 28.9)[37,38]<br>• Italian centre – NPP ongoing |

Abbreviations: R/R sALCL = relapsed or refractory systemic anaplastic large cell lymphoma; ORR = objective response rate; DOR = duration of response; CR = complete remission; PFS = progression-free survival; OS = overall survival; AEs = adverse events; PTCL = peripheral T-cell lymphoma; q1wk = once weekly for each 3-week cycle; BV = brentuximab vedotin; NPP = Named Patient Programme

* Only 30 patients received brentuximab vedotin

### 4.11.4 Statistical analysis of the non-randomised and non-controlled evidence

The statistical methodology used in the brentuximab vedotin non-RCT clinical trial (SG035-0004)[2] is summarised in Table 4.4.

**Table 4.4: Summary of statistical analyses in the non-RCT trial SG035-0004**

| **Study ID** |
|---|
| SG035-0004 |
| **Hypothesis objective** |
| To determine the antitumour efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate (ORR) in patients with R/R sALCL following frontline chemotherapy (CHOP or equivalent) |
| **Statistical analysis** |
| The ORR per independent review (IRF) and its two-sided 95% exact confidence interval (CI) were calculated. Duration of response per IRF, PFS per IRF, and OS were estimated using Kaplan-Meier methodology. The median duration of response, PFS, OS and their two-sided 95% CIs were calculated. |
| **Sample size, power calculation** |
| Approximately 55 patients were to be enrolled in this study. With a sample size of 55, observing 18 (33%) objective responses (CR or PR) would allow us to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 50%, the study would have over 95% power. |
| **Data management, patient withdrawals** |
| Sponsor personnel conducted initiation visits with the Investigators and ancillary staff before the start of the study. These initiation visits included review and explanation of the protocol, CRFs (Case report forms), adverse event reporting procedures, and discussion of the responsibilities of the Investigator for record keeping, drug accountability, and good clinical practice. Sponsor personnel or delegates made periodic site visits to review study progress and source documentation. Data in the CRFs were source data verified, deviations from the protocol were noted, and incoming data were monitored to detect and resolve discrepancies or inconsistencies. A total of 3 clinical site audits were conducted to assess compliance to the protocol and Good Clinical Practice.<br><br>A patient may have been discontinued from the study (during treatment cycle or follow-up) for any of the following reasons:<br>• Death.<br>• The patient withdrew consent for further follow-up.<br>• Lost to follow-up.<br>• Study termination by Seattle Genetics, Inc. |
| Abbreviations: ORR = objective response rate; R/R s ALCL = relapsed or refractory systemic anaplastic large cell lymphoma; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin®, prednisolone; IRF = independent review facility; CI = confidence interval; PFS = progression-free survival; OS = overall survival; CR = complete remission; PR = partial remission; CRF = case report form |

### 4.11.5 Participant flow in the SG035-0004 study

***Study design***

Brentuximab vedotin is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL).[1] The pivotal data supporting this indication comes from a Phase II, open-label, single-arm, multi-centre study in 58 patients with R/R sALCL (Study SG035-0004, the "0004" trial).[2] This was designed as a single-arm study based on the absence of a definitive optimal treatment option for patients with R/R sALCL. Because of disease rarity, there are currently no RCTs to guide treatment decisions in sALCL. The majority of evidence describing outcomes for adult patients with sALCL and the impact of various treatment regimens comes from retrospective studies or subgroup analyses of completed prospective studies in a broader group of aggressive lymphomas or PTCLs.[3]

***Patient eligibility***

Inclusion for this study included a diagnosis of R/R sALCL after treatment failure of at least one prior therapy with curative intent, the most common being a combination of CHOP chemotherapy.[a] CD30-positive disease and histology were documented by central pathology review. Patients had measurable disease (> 1.5cm) by CT and fluorodeoxyglucose-avid disease by PET. Age ≥12 years and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were required. Amongst other criteria, patients could not previously have received an allogeneic stem cell transplant (allo-SCT).[2]

***Patient characteristics***

Key baseline patient and disease characteristics are shown in Table 4.5. In summary, this was a cohort of middle-aged (median age 52 years), mostly White (83%) with predominantly ALK-negative and chemo-refractory disease patients (72%). Relative to their most recent therapy, 50% were considered refractory, and 50% experienced relapse; 62% of patients were primary refractory to front-line treatment (i.e. no complete remission (CR) or relapse within three months of front-line therapy); and 22% had not achieved an objective response to any prior therapy. The median number of prior chemotherapy regimens excluding autologous stem cell transplant (ASCT) was two (range one to six regimens; and 26% of patients experienced treatment failure with an ASCT before study enrolment. The most recent therapy before study enrolment was ASCT or multi-agent chemotherapy for 91% of patients (Table 4.5).[2]

[a] CHOP chemotherapy is named after the initials of the drugs used, which are: **c**yclophosphamide, doxorubicin (**h**ydroxyaunomycin), vincristine (**O**ncovin®), **p**rednisolone

**Table 4.5: Summary of Baseline Patient and Disease Characteristics**

| **Patient Characteristics** | **N = 58** |
|---|---|
| Median age, years (range) | 52 (14-76) |
| Gender | 33M (57%)/ 25F (43%) |
| Race | |
| Asian | 1 (2%) |
| Black or African American | 7 (12%) |
| White | 48 (83%) |
| Other | 2 (3%) |
| ECOG performance status* | |
| 0 | 19 (33%) |
| 1 | 38 (66%) |
| 2† | 1 (2%) |
| Anaplastic lymphoma kinase status | |
| Negative | 42 (72%) |
| Positive | 16 (28%) |
| **Disease Characteristics** | |
| Baseline B symptoms | 17 (29%) |
| Primary refractory to front-line treatment§ | 72 (71%) |
| Disease status relative to most recent treatment | |
| Refractory‖ | 29 (50%) |
| Relapsed¶ | 29 (50%) |
| Patients who had not achieved a response to any prior treatment | 13 (22%) |
| No. of prior chemotherapy regimens | |
| Median | 2 |
| Range | 1-6 |
| Prior autologous SCT | 15 (26%) |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ASCT = autologous stem cell transplant; PFS = progression-free survival; CI = confidence interval

* ECOG performance status defined as follows: 0, able to perform daily activities with no restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; and 2, ambulatory and capable of self-care but unable to carry out work activities

† ECOG status of 2 was prohibited per protocol; patient was enrolled in violation

§ No complete remission or relapse within 3 months of front-line therapy

‖ Best response of partial remission, stable disease, or progressive disease if a patient had only one prior therapy, or a best response of stable disease or progressive disease to the most recent therapy if a patient had more than one prior therapy

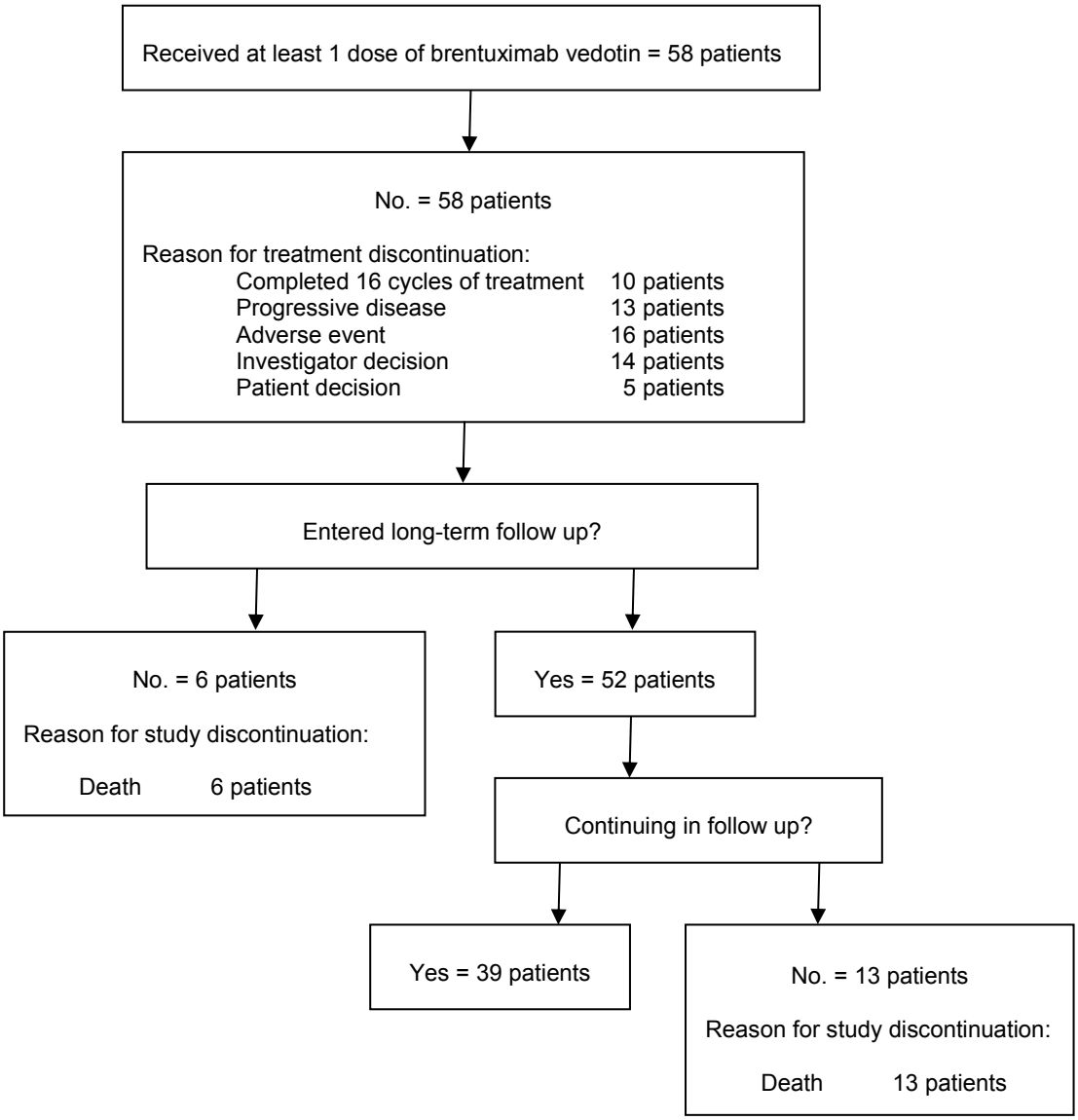
¶ Best response of complete remission if a patient had only one prior therapy, or a best response of complete or partial remission to most recent therapy if a patient had more than one prior therapy

Source: Pro et al., (2012)[2]

### *Patient disposition*

A total of 77 patients were screened for this study; of these, 58 patients were enrolled at 22 study centres; 15 sites in the United States, 3 sites in France, 2 sites in Canada, and 1 site each in Belgium and the United Kingdom. Of the 19 patients who were screened but not subsequently enrolled in the study, the majority of patients were not enrolled because they did not meet at least one of the eligibility criteria. Of the patients screened, 58 patients were enrolled and received at least one dose of brentuximab vedotin.[5] Patient disposition is presented in Figure 4.2.

**Figure 4.2: Patient disposition in the SG035-0004 trial**




Source: CSR SG035-0004 [5]

### *Treatment*

Brentuximab vedotin was given as a single agent at a dose of 1.8mg/kg administered intravenously on Day 1 of each 21-day cycle once every 3 weeks over 30 minutes on an out-patient basis for up to 16 total doses. Dosing for each patient was calculated based on baseline weight; however, doses were to be adjusted for patients who experienced a ≥10% change in weight during the study. Actual weight was to be used except for patients weighing greater than 100 kg; doses for these patients were to be based on a weight of 100 kg. Intra-patient dose reductions to 1.2 mg/kg were allowed depending on the type and severity of toxicity.

## *Efficacy assessment*

The primary efficacy variable was the overall objective response rate (ORR) per an independent review facility (IRF). Treatment response was assessed by spiral CT of chest, neck, abdomen, pelvis and PET scans. Determination of antitumour efficacy was based on objective response assessments made according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).[45] Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) was to be determined at each assessment. Responses were determined by an independent review facility (IRF) and treatment decisions were made based on investigator assessment of response. [2]

Secondary endpoints included duration of response (DOR) by IRF, complete remission (CR) by IRF, and progression-free survival (PFS) by IRF, as well as overall survival (OS) to further assess clinical benefit. For the secondary efficacy endpoints, PFS was defined as the time from start of study treatment to first documentation of objective tumour progression or to death due to any cause whichever came first. OS was defined as the time from the start of study treatment to the date of death due to any cause. The median PFS and OS were estimated using the Kaplan-Meier method.[5]

Other efficacy parameters included event –free survival (EFS), defined as the time from start of study treatment to any treatment failure including toxicity, patient preference, initiation of a new treatment other than stem cell transplant without documented progression, disease progression, or death; and 'B' symptom resolution rate. 'B' symptom resolution was defined as the proportion of patients with lymphoma-related 'B' symptom(s) at baseline who achieve resolution of all 'B' symptoms at any time during the treatment period. 'B' symptoms were defined as fever, night sweats, or weight loss >10%.[5]

Patients had an End of Treatment (EOT) assessment 30 ± 7 days after receiving their final dose of study drug. Long-term follow-up assessments (including survival and disease status information) are performed every 12 weeks until either patient death or study closure, whichever occurs first. Patients who discontinued study treatment with stable disease or better had CT scans done every 12 weeks until disease progression.

## *Patient follow-up*

Follow-up of patients included in this trial was up to 5 years, the survival results of which have been presented after 3 years,[39] 4 years,[40] and 5 years[6] at the ASH annual meetings.

The original publication by Pro et al., (2012)[2] presented the primary endpoint data (ORR by IRF) and the secondary endpoint data (PFS, DOR, OS) following a median observation time from first dose of 16.8 months.[1] Data updates for up to five-years follow-up were presented at the American Society of Haematology (ASH) Annual Meeting in December 2012 (median observation time of 22.8 months);[46] at the ASH 2013 Annual Meeting (median observation of 33.4 months);[39] at the ASH 2014 Annual Meeting (median observation of 46.3 months);[40] and at the recent ASH 2016 Annual Meeting (median observation of 71.4 months).[6]

### 4.11.6 Quality assessment of the relevant non-randomised and non-controlled evidence

***Validity of results***

In the absence of RCT evidence, non-randomised, prospective trials are considered the next best level of evidence. The results of the pivotal Phase II SG035-0004 study were assessed to be both internally and externally valid as the study was representative of the target population (the inclusion criteria of the trial specified that only patients with R/R sALCL was allowed), and the primary and secondary outcomes are standard, validated measures, and the trial was performed in accordance with GCP. In R/R sALCL patients already treated with at least one prior therapy with curative intent, treatment with brentuximab vedotin led to 86% ORR with 59% of patients achieving CR, and 28% achieving PR.[1] Obtaining CR is an important advantageous 'interim' outcome for further curative treatment options, i.e. stem cell transplantation. Furthermore, 97% of patients achieved tumour reduction, and the majority had resolution of disease-related signs and symptoms whenever these were present at baseline. These improvements were independent of ALK status or number of prior therapies, suggesting that responses observed with brentuximab vedotin are not limited to a specific subgroup of patients. Furthermore, patients with poor prognostic factors, such as primary refractory patients or patients with advanced disease (i.e. Stage III/IV at initial diagnosis), were also able to achieve CR with brentuximab vedotin treatment as shown in Table 4.7 below supporting strong efficacy for the treatment irrespective of patient risk profile.

### 4.11.7 Assessing risk of bias in the brentuximab vedotin non-RCT studies

The risk of bias was limited in the pivotal Phase II SG035-0004 study as the primary endpoint of ORR was by IRF (independent review facility) rather than assessed by the investigator. Secondary end points included duration of response by IRF, complete remission (CR) rate by IRF, and progression-free survival (PFS) by IRF. In addition to independent review, assessment of efficacy by the study investigators was collected as a protocol-defined exploratory analysis. A $\kappa$ coefficient was calculated to characterise the concordance in objective response and best response assessments between IRF and investigator.

### 4.11.8 Summary of responses to the critical appraisal questions

A summary of responses to the critical appraisal questions is presented in Table 4.6.

**Table 4.6: Quality assessment of brentuximab vedotin non-RCTs and NPP's**

| Critical appraisal | Brentuximab vedotin non-RCTs and NPP's | | |
|---|---|---|---|
| | SG035-0004 [2] | Retrospective case series [35,42] | NPP'S (UK, France and Italy)[36-38,43] |
| Do the selected patients represent the eligible population for the intervention? | Yes | Yes | Yes |
| Was selection bias minimised? | Yes | Yes | Yes |
| Were all participants accounted for at study conclusion? | Yes | Yes | Yes |
| Did the setting reflect UK practice? | Yes | Yes | Yes |
| Were outcome measures reliable? Were all clinically relevant outcome measures assessed? | Yes | Yes | Yes |
| Did the analysis include an intention-to-treat analysis? | Yes | Yes | No* |
| Are the study results internally valid? | Yes | Yes | Yes |
| Are the findings externally valid? | Yes | Yes | Yes |
| * There was no ITT dataset as these were Named Patient Programmes and not clinical trials | | | |

## 4.11.9 Complete quality assessment of the relevant non-randomised and non-controlled evidence

A complete quality assessment for each non-randomised study and NPP can be found in Appendix 3.

### *4.11.9.1 Efficacy in patients with R/R sALCL: Retrospective case series*

Data to support the efficacy of single-agent brentuximab vedotin in R/R sALCL patients from the pivotal Phase II clinical trial (SG035-0004)[2] Pro 2012 comes from two retrospective case series presented by Gopal et al., (2014)[42] and Chihara et al., (2015).[35]

Systemic ALCL is associated with a worse prognosis in patients 60 years of age and above, largely due to the association between ALK-negative status and older age.[18,47] A retrospective analysis was conducted in patients at least 60 years of age with relapsed or refractory CD30-+ lymphomas (primarily sALCL and HL), treated on one or more of seven clinical studies, to better define the safety and efficacy of single-agent brentuximab vedotin in this population. Demographics, baseline disease characteristics and safety data were compared with data from younger patients (Table 4.7).[42]

**Table 4.7: Demographics and baseline characteristics (Gopal et al., 2014)**

| Characteristic | Age ≥60 (n=40) | Age <60 (n=326) | P-value* |
|---|---|---|---|
| Age (years) | | | |
| Median | 66.0 | 32.0 | <0.0001 |
| Min, max | 60, 82 | 12, 59 | |
| Gender, n (%) | | | |
| Female | 14 (35) | 152 (47) | 0.1811 |
| Male | 26 (65) | 174 (53) | |
| ECOG status, n (%) | | | |
| 0 | 13 (33) | 159 (49) | 0.0665 |
| 1 | 25 (63) | 161 (49) | |
| 2 | 2 (5) | 6 (2) | |
| Disease diagnosis, n (%) | | | |
| **ALCL** | **22 (55)** | **52 (16)** | **<0.0001** |
| HL | 16 (40) | 272(83) | |
| Other CD30+ lymphoma subtypes | 2 (5)† | 2 (<1)§ | |
| Prior cancer-related systemic therapies | | | |
| n¶ | 34 | 264 | 0.0030 |
| Median | 2.0 | 3.0 | |
| Min, max | 1, 6 | 1, 13 | |
| Prior stem cell transplants, n (%) | | | |
| n¶ | 34 | 262 | <0.0001 |
| 0 | 22 (65) | 56 (21) | |
| 1+ | 12 (35) | 206 (79) | |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ALCL = anaplastic large cell lymphoma; HL =Hodgkin lymphoma; PTCL = peripheral T-cell lymphoma

* P-value from Fisher exact test for gender, ECOG status, disease diagnosis and prior stem cell transplants and from t-test for all other variables

† Both patients were diagnosed with PTCL not otherwise specified (PTCL-NOS)

§ One patient was diagnosed with PTCL-NOS and one patient was diagnosed with gray-zone lymphoma

¶ Number of treatment courses for which data are available

Source: Adapted from Gopal et al., (2014)[42]

Patients in the analysis set were enrolled in one or more of seven brentuximab vedotin clinical trials between 2006 and 2012. These trials included all studies of single-agent brentuximab vedotin in the treatment of R/R CD30+ lymphomas for which data were available at the time of analysis. These studies included two Phase I dose-escalation trial (SG035-0001/ 0002), two pivotal Phase II trials (SG035-0003/ 0004), one Phase II study of patients who had participated in a previous brentuximab vedotin study (SG035-006), one Phase I brentuximab vedotin cardiovascular electrophysiology study (SG035-007), and one Phase I brentuximab vedotin pharmacokinetics study (SG035-008). Patients received at least one dose of single-agent brentuximab vedotin (≥1.2 mg/kg, q3wk; ≥0.6 mg/kg q1wk) up

to a maximum of 16 cycles Response assessments were performed according to the Revised, Response Criteria for Malignant Lymphoma.[45]

### *4.11.9.2 Efficacy in patients with refractory CD30+ lymphomas treated in a UK Named Patient Programme*

#### *Design and methods*

During December 2010 and August 2011, twenty-four patients presenting with either ALCL, HL or CD30+ T-cell lymphoma refractory to ≥2 lines of chemotherapy or ASCT, a positive PET-CT scan and deemed suitable for systemic therapy were considered for the single-centre UK NPP. This included patients with poor performance status due to progressive disease. Exclusion criteria included previous allo-SCT. All patients considered for the NPP received at least one dose of brentuximab vedotin dosed at 1.8 mg/kg every 3 weeks. Response was assessed using PET-CT after 4 (PET4) and 8 (PET8) cycles.[43]

Eligibility for allo-SCT was assessed according to institutional guidelines (including age under 66 years). Allotransplants were performed utilising a reduced intensity conditioning (RIC) regimen. [43]

#### *Patient demographics*

Demographics of the 24 patients are detailed in Table 4.8.

**Table 4.8: Demographics, histology and prior therapies of patients in the brentuximab vedotin UK NPP**

| Characteristic | Brentuximab vedotin (N=24) |
|---|---|
| Median age (range) | 41.5 (21-78) |
| Female, n (%) | 13 (54) |
| Histology (and initial stage at diagnosis) | |
| HL | 18 (2A-4XB) |
| **ALCL** | **5 (4A-4XB, ALK neg 2; ALK-1 unknown,3)** |
| CD30+ TCL | 1 (2A) |
| Median number of prior regimens (range) | 3 (2-8) |
| Prior auto-transplant, n (%) | 8 (33) |
| Previous radiotherapy, n (%) | 10 (42) |
| No response to most recent treatment, n (%) | 17 (71) |
| Potentially eligible for Allo-SCT at baseline, n (%) | 22 (92%) |
| HL = Hodgkin lymphoma; ALCL = anaplastic large cell lymphoma; TCL = T-cell lymphoma<br>X signifies presence of bulk disease | |

Source: Gibb et al., (2013)[43]

Brentuximab vedotin has also been made available for patients with R/R sALCL via Named Patient Programmes in other European countries, including France[37,38] and Italy.[36]

### 4.11.10 Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

#### *4.11.10.1 Results for patients with R/R sALCL in the SG035-0004 trial*

The results presented below and in Table 4.9 are based primarily on those considered by the European Medicines Agency (EMA) and reported in the pivotal publication and SmPC.[1,2]

- The ORR was 86% (n=50/58)
- 59% of patients achieved a CR (n=34/58)
- 28% of patients achieved a PR (n=16/58)
- 90% overall disease control rate (CR+PR+SD; n=52/58)
- 82% of patients with 'B' symptoms at baseline achieved resolution (n=14/58)
- Tumour reduction was achieved in the majority of patients (97%)
- 70% of patients alive 1 year after the initiation of treatment (n=41/58)

Importantly, the improvements achieved were independent of ALK status or number of prior therapies, suggesting that responses observed with brentuximab vedotin are not limited to a specific subgroup of patients. Furthermore, the responses achieved with brentuximab vedotin were durable: following a median follow-up time from first dose of 16.8 months.

At the time of the pivotal analysis and publication, the median Duration of Response (DOR) for all patients with an objective response was 13.2 months (95% CI 5.7 months to not estimable [NE]), whilst the median DOR for patients who achieved a CR had not been reached [CI 95% (13.0 months, -)].[1,5]

**Table 4.9: Key efficacy results per IRF assessment in R/R sALCL patients treated with 1.8mg/kg of brentuximab vedotin every 3 weeks (median follow-up time from first dose = 16.8 months)**

| **Best clinical response (N=58)** | **IRF N (%)** | **95% CI** |
|---|---|---|
| Objective response rate (CR + PR) | 50 (86) | 74.6, 93.9 |
| Complete remission (CR) | 34 (59) | 44.9, 71.4 |
| Partial remission (PR) | 16 (28) | NA |
| Disease control rate (CR+PR+SD) | 52 (90) | 78.8, 96.1 |
| **Duration of response** | **Median per IRF** | **95% CI** |
| Objective response rate (CR + PR)* | 13.2 | 5.7, NE |
| Complete remission (CR) | Not reached | 13.0, NE |
| **Overall survival** | **Median** | **95% CI** |
| Median | Not reached** | 21.3, NE |

NE = Not estimable

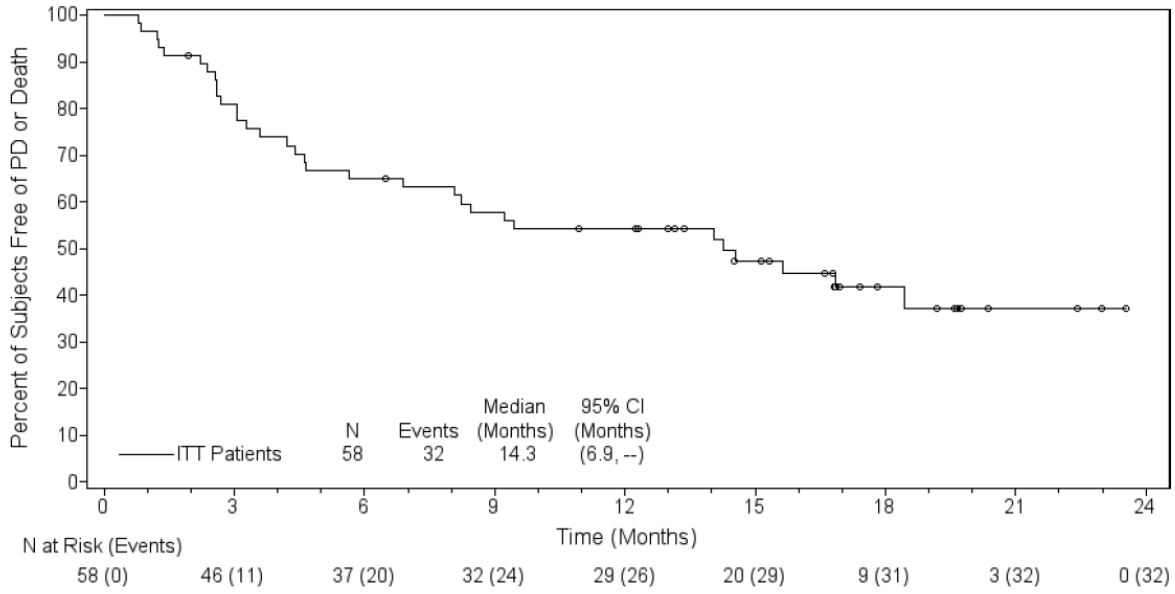
* The range of DOR was 0.1+ months to 21.7+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 11.8 months.

** The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 months

Source: Brentuximab vedotin SmPC (2016)[1]

The estimated median PFS per IRF analysed by Kaplan-Meier methods was 14.3 months (95% CI, 6.9 months to NE; see Figure 4.3). Per investigator assessment, the median PFS with brentuximab vedotin was 14.5 months compared with a median PFS of 5.9 months after the most recent prior therapy, including ASCT. Using a correlated survival analysis for this prespecified comparison, the hazard ratio was 0.44 (brentuximab vedotin to prior systemic therapy), indicating that PFS was significantly prolonged with brentuximab vedotin compared with the most recent prior therapy (P<0.001). Of the most recent therapies, 91% were multi-agent chemotherapy regimens delivered with or without ASCT. [5]

**Figure 4.3: Progression-free survival per IRF (ITT set)**



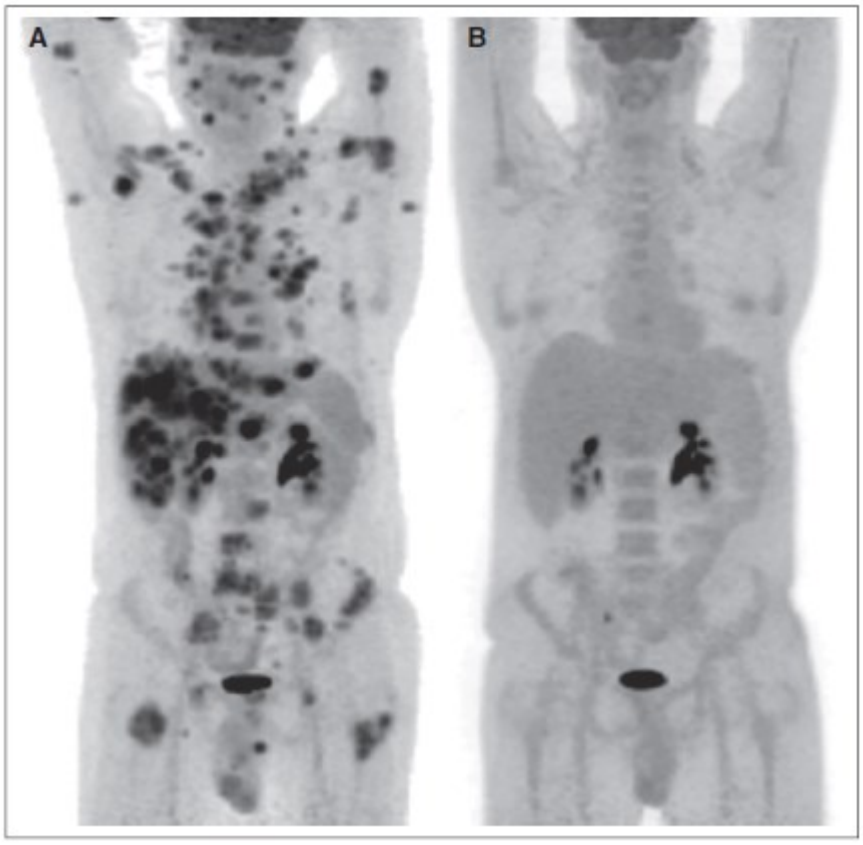

Source: CSR SG035-0004 (2011)[5]

Analyses of efficacy by subgroups did not reveal any subgroup of patients that did not achieve clinically meaningful antitumour activity. ORR was consistent among all groups analysed. Importantly, in the subgroups of patients with ALK-positive and ALK-negative disease, similar proportions of patients achieved objective responses, including CRs in at least half the patients in both subgroups. Achieving a CR rate of 50% is clinically meaningful, especially given the poor prognosis of ALK-negative patients. Additionally, the median PFS among patients with ALK-positive disease was 14.6 months and 14.3 months in patients with ALK-negative disease, indicating that there was no difference in progression rates between the subgroups. At the time of this first analysis, the median OS had not been reached. After achieving a remission with brentuximab vedotin, 8 patients went on to receive an allo-SCT,

and 8 received an ASCT. In patients who achieved a CR, similar outcomes in PFS and duration of response were observed regardless of subsequent transplant. [5]

Due to the rarity of the disease, individual case study data is of interest to show the potential impact of brentuximab vedotin on substantially reducing disease activity. Of particular mention is a 42-year old male patient from the UK with ALK-positive sALCL who was recruited in the SG035-0004 trial with baseline scans showing aggressive disease (Figure 4.4). Prior therapies administered were combination chemotherapy regimens, VAPEC-B and CHOP[b], and an ASCT. The patient experienced tumour lysis syndrome after the first dose of brentuximab vedotin, which resolved following treatment with sodium bicarbonate to adjust the urine pH.[5] Following this, the patient received an additional seven doses of brentuximab vedotin (eight total doses). The patient received an allo-SCT after discontinuing treatment with brentuximab vedotin,[2] returned to work, and remains in complete remission to date (>7 years later) (see Figure 4.5 for before and after treatment with brentuximab vedotin photos).

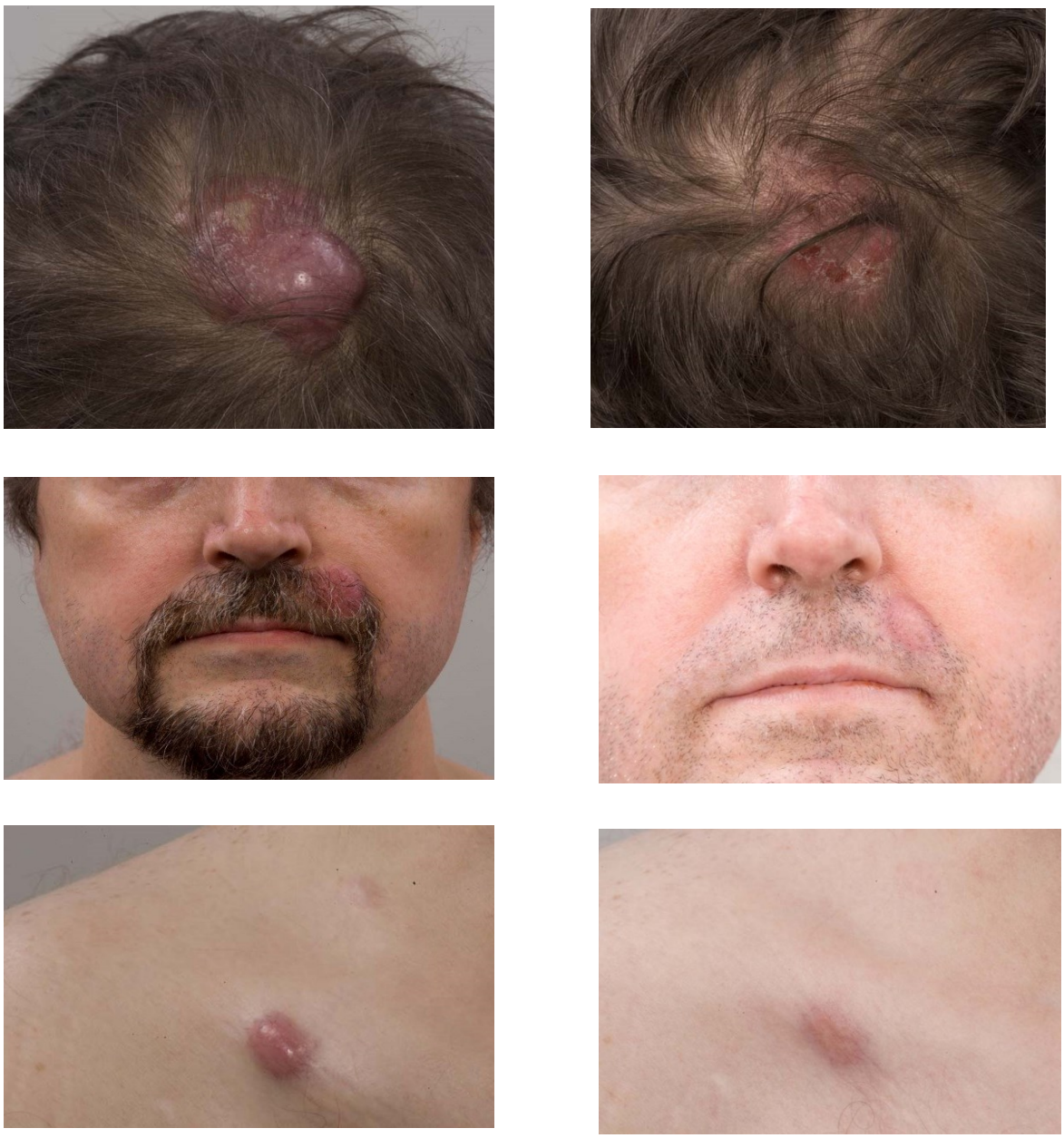
**Figure 4.4: Baseline (A) and post-brentuximab vedotin (B) scans from a male patient diagnosed with sALCL and enrolled on the SG035-0004 trial**




Source: Pro et al., (2012)[2]

[b] VAPEC-B chemotherapy regimen = **v**incristine, doxorubicin (**A**driamycin), **p**rednisone, **e**toposide, **c**yclophosphamide, **bl**eomycin
CHOP chemotherapy regimen = **c**yclophosphamide, **h**ydroxydaunorubicin (doxorubicin), vincristine (**O**ncovin®), **p**rednisone;

**Figure 4.5: Cutaneous lesions at entry to SG035-0004 study, and Day 8 after treatment with one cycle of brentuximab vedotin**



Images provided with permission from Professor Tim Illidge, Christie Hospital, Manchester

Long-term survival results up to five years (study end), presented at the American Society of Haematology (ASH) Annual Meeting in December 2016, confirm the durability of clinical benefits with brentuximab vedotin therapy (see Section 4.11.10.3 below).

### *4.11.10.2 Long-term survival data*

In this section, response and survival outcomes data from the pivotal Phase II trial described above is presented.[2] This is based on a median observation period of 71.4 months and this data was recently presented as an abstract and Poster at the ASH Annual meeting in December 2016.[6]

During the long-term follow-up period, all patients were followed for survival/ disease status every three months during years 1 and 2, every six months during years 3 to 5, and annually thereafter. Long-term data was first presented at ASH after a median observation time from first dose of 22.8 months,[46] and then subsequently after 33.4 months,[39] after 46.3 months,[40] and finally after 71.4 months at the end of the study.[6] For the purpose of this submission, we will present the final, end of study results (five-year data from the SG035-0004 trial.

***Efficacy assessments***

The first patient in the study was enrolled in June 2009. All patients completed treatment in June 2011 and were followed for progression and survival until the end of the study.

The primary endpoint of the trial was objective response rate (ORR) by independent review facility (IRF). Secondary endpoints included DOR, CR rate, and PFS, all by IRF, and OS as previously described above in Section 4.11.3, Table 4.3.[2]

The analysis by Pro et al., (2016)[6] represents a median of approximately 5 years of observation time for all patients. In the section below, we present long-term OS results as well as investigator assessments of response duration and PFS, which were both pre-specified additional analyses in the study's statistical analysis plan.

***Results***

<u>Duration of response</u>

Following a median observation time from first dose of 71.4 months (range 0.8 to 82.4 months), results according to the investigator were as follows:

- The ORR was 86% (n=50/58)
- 66% of patients (38/58) achieved CR (34/58; 59% by IRF)
- Median duration of response for the 38 patients who achieved a CR was not reached (95% CI: 20.0, -) and ranged from 0.9 to 79.7+ months
- Of the 38 CR patients, 16 underwent consolidative SCT (8 allogeneic, 8 autologous) as the next therapy after brentuximab vedotin. Median OS and PFS were not reached in these patients who underwent subsequent SCT
- In the 22 patients with CR who did not receive SCT as consolidation, the median OS was not reached , and the median PFS was 39.4 months (95% CI: 14.3, -)
- Of the 38 patients who achieved CR, 16 patients (42%) were still on study and in remission at study closure without the start of new anticancer therapy, other than SCT (Figure 4.6)

- The median observation time for the 16 patients still on study and in remission was 75.4 months (range 69 to 82.4).

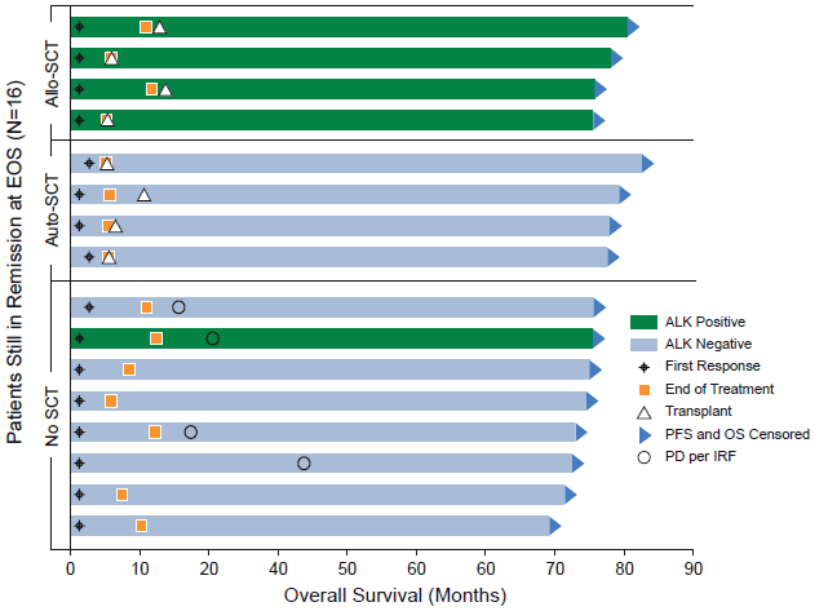
Patients who obtained a best response of CR had the following baseline characteristics as shown in Table 4.10 below.

**Table 4.10: Baseline characteristics of patients with best response of complete remission**

| | CR and in remission at EOS (N=16) | All other CR (N=22) |
|---|---|---|
| Median age in years (range) | 56 (14, 76) | 50 (17, 74) |
| Female, n (%) | 4 (25) | 13 (59) |
| ECOG status, n (%) | | |
| 0 | 4 (25) | 11 (50) |
| 1 | 12 (75) | 11 (50) |
| ALK-negative, n (%) | 11 (69) | 17 (77) |
| Median time from initial diagnosis, months (range) | 22 (6.2, 113.2) | 20 (4.4, 186.5) |
| Stage III/IV at initial diagnosis, n (%) | 6 (37) | 1 (46) |
| Refractory to front-line therapy, n (%) | 7 (44) | 16 (73) |
| Refractory to most recent treatment, n (%) | 5 (31) | 11 (50) |
| Median baseline SPD, $cm^2$ (range) | 14 (3.2, 76.8) | 12 (2.0, 51.3) |
| Baseline bone marrow involvement, n (%) | 0 (0) | 2 (9) |
| Abbreviations: ECOG = Eastern Cooperative Oncology Group; ALK = anaplastic lymphoma kinase; SPD = sum of the product of diameters; EOS = end of study; CR = complete remission | | |

Source: Pro et al., (2016)[6]

**Figure 4.6: Patients who remain in remission per the investigator following treatment with brentuximab vedotin**



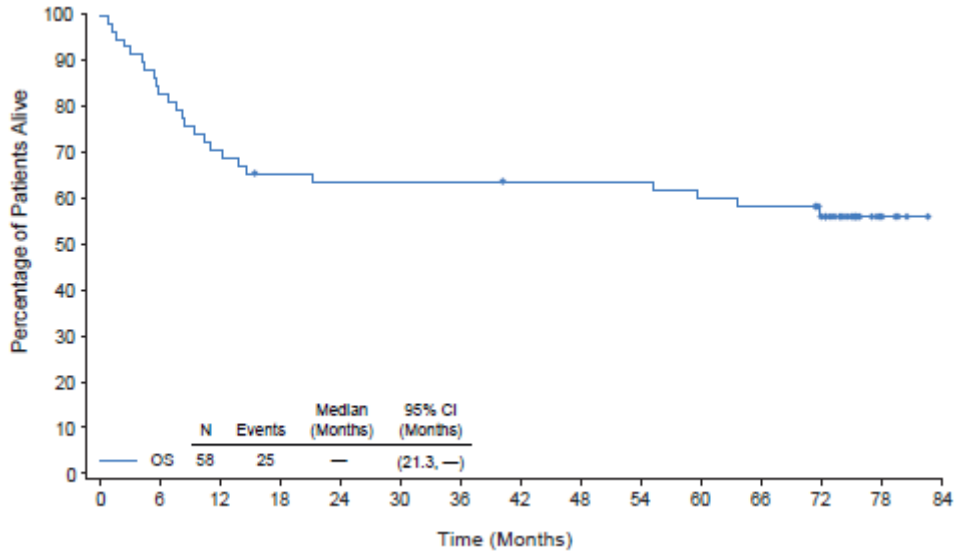

Source: Pro et al., (2016)[6]

OS and PFS per investigator

After a median follow-up of approximately 5 years for all enrolled patients:

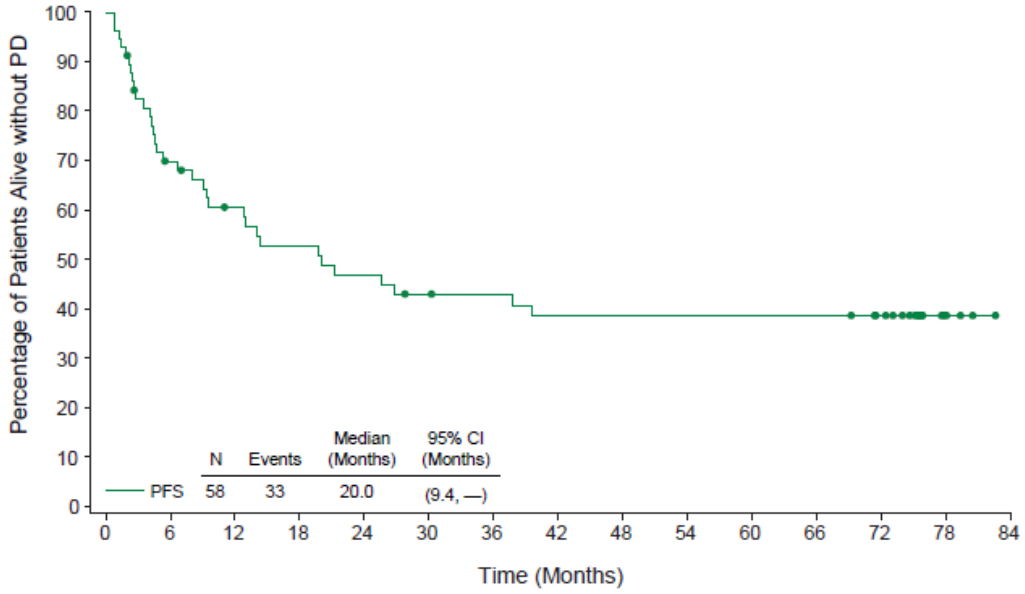
- 16 of the 38 patients who achieved CR (42%) were still on study, alive, and in remission at study closure
- The estimated 5-year OS rate was 60% (95% CI: 47, 73), and the median OS was not estimable (95% CI: 21.3,-; range 0.8 to 82.4+ months) (Figure 4.7)
- The median PFS was 20.0 months (95% CI: 9.4,-) (Figure 4.8). The median PFS in patients who achieved a CR has not been reached
- Of the 58 enrolled patients, 42 (72%) had ALK-negative disease: The estimated 5-year OS was 61% (95% CI: 47%, 76%) for ALK-negative and 56% (95% CI: 32%, 81%) for ALK-positive patients. The median PFS for ALK-negative and ALK-positive ALCL was 20 months (95% CI 6.7,-) and 25.5 months (95% CI 8.0,-) respectively, with the median OS not reached for either.

**Figure 4.7: OS following treatment with brentuximab vedotin**




Source: Pro et al., (2016)[6]

**Figure 4.8: PFS following treatment with brentuximab vedotin**



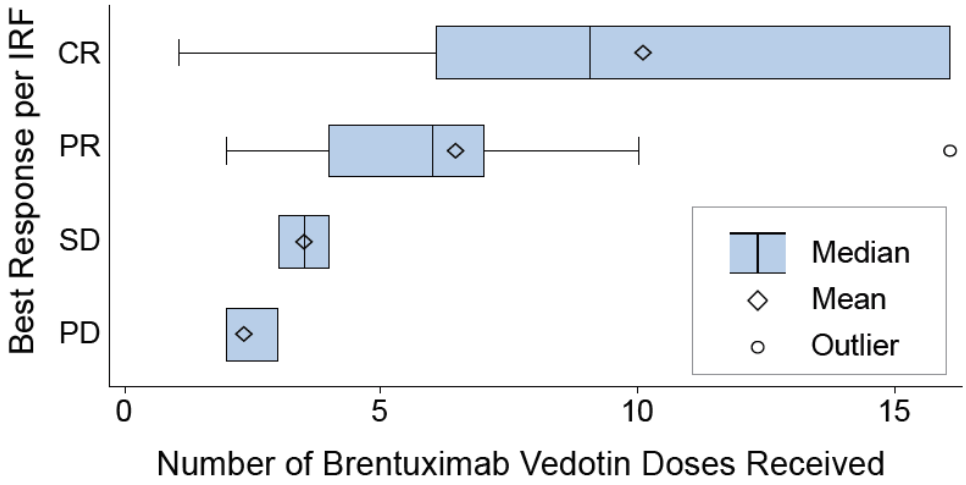

Source: Pro et al., (2016)[6]

### *4.11.10.3 Number of cycles*

The median number of brentuximab vedotin cycles administered to patients in the SG035-0004 trial was 7 (range 1-16) with a mean of 8.2.[2,39,46]Patients who achieved an objective response received more cycles of therapy as shown in Figure 4.9.[39] Patients with CR received a median of 9 cycles (range 1 to 16). Patients who received a subsequent

allogeneic or autologous SCT both received a median of 8 cycles.[46] Only10 patients (17%) in the trial received the full course of 16 cycles of brentuximab vedotin.[1]

**Figure 4.9: Number of cycles by best response (range and interquartile range)**




Source: Pro et al., (2013)[39]

Based on the SG035-0004 trial protocol, the SmPC recommends that patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles of brentuximab vedotin.[1] There is evidence to show that the number of cycles of brentuximab vedotin used in everyday clinical practice is significantly less than that used in the SG035-0004 trial. This evidence comes from the real-world experience with brentuximab vedotin via the UK Named Patient Programme (NPP) where patients received a median of only 5.5 cycles (range 1-13), as discussed further in Section 4.11.10.5. Further evidence comes from the fact that brentuximab vedotin has been available in England via the national CDF for almost 4 years and, according to clinicians, the number of cycles of the drug being used in real world practice are similar to that in the NPP.

### *4.11.10.4 Results of sALCL patients from other non-RCTs: Retrospective analysis*

Across the seven clinical trials, 40 patients were identified ≥60 years of age with either sALCL (n=22), HL (n=16), or PTCL-NOS (n=2). Eighteen of the 19 older patients with sALCL with a known ALK status were confirmed to be ALK-negative. Older patients received a median of 7.5 cycles (range 1-22) of brentuximab vedotin.

Results from this retrospective study showed that in patients with R/R sALCL ≥60 years, clinically meaningful responses can be achieved as evidenced by an objective response rate of 100% and a complete remission (CR) rate of 50% after a median of 7.5 cycles of brentuximab vedotin, suggesting that the use of brentuximab vedotin as a single agent in sALCL [and HL] in elderly patients is a feasible option, even as initial treatment (Table 4.11).[42]

**Table 4.11: Best clinical response by diagnosis in patients ≥60 years of age**

| | Diagnosis | | | |
|---|---|---|---|---|
| | **sALCL (n=22)** | **HL (n=16)** | **PTCL-NOS (n=2)** | **Total (n=40)** |
| Objective response | **22 (100)** | 9 (56) | 2 (100) | 33 (83) |
| Complete remission | **11 (50)** | 6 (38) | 1 (50) | 18 (45) |
| Partial remission | **11 (50)** | 3 (19) | 1 (50) | 15 (38) |
| Stable disease | **0 (0)** | 3 (19) | 0 (0) | 3 (8) |
| Progressive disease | **0 (0)** | 3 (19) | 0 (0) | 3 (8) |
| Not evaluable | **0 (0)** | 1 (6) | 0 (0) | 1 (3) |
| Abbreviations: sALCL = systemic anaplastic large cell lymphoma; HL = Hodgkin lymphoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified | | | | |

Source: Gopal et al., (2014)[42]

The median duration of the objective response for patients ≥60 years of age with sALCL was 13 months (95% CI: 3.0, -). PFS data was available for 34/ 40 of these patients. PFS in these patients with sALCL had a median duration of 15.6 months (95% CI: 4.2, -; range 0.0+ to 22.4+ months) and a median duration of 9.0 months (95% CI: 1.9, -; range 1.9 to 23.3+ months). Across diagnoses, the median PFS in patients ≥60 years who had achieved a best response of CR or PR was 18.5 months and 8.5 months, respectively.[42]

Long-term survival data were available for 34 of 40 older patients. The median OS of patients with sALCL had not been reached (range 1.2 to 32.7+ months). The estimated 2-year OS rate was 76% and 48% for patients ≥60 years with sALCL and HL, respectively. Following brentuximab vedotin treatment, two patients each went on to receive autologous or allogeneic stem cell transplants, and at the time of analysis, all four of these patients were still alive.[42]

### *4.11.10.5 Results – patients receiving brentuximab vedotin in NPP's*

***Results from a UK NPP (real world evidence)*** Gibb 2013 [43]

Following a median follow-up of 12.9 months (as of April 2012):

- 18 patients with a diagnosis of HL, 5 patients with sALCL and 1 patient with CD30+ T-cell lymphoma
- 71% of patients had had no response to their most recent treatment
- Patients received a median of 5.5 cycles of brentuximab vedotin (range 1-13)
- The overall response rate for sALCL patients was 60% (3/5 patients) all of whom achieved a CR or 67% for all patients (Table 4.12)
- Median PFS for all patients is 5.1 months (Figure 4.10)

- No significant differences in response between patients who had previously received auto-transplant (n=8) and those who had not (n=16), with a CR rate of 35% in both groups
- 16/24 (67%) patients are alive
- 6/22 (27%) eligible patients (2 with sALCL and 5 with HL) have undergone allo-SCT

**Table 4.12: Responses at PET4 by histology and transplant history of patients in the brentuximab vedotin Named Patient Programme**

| Transplant history | Histology | Response at PET4 | | | | |
|---|---|---|---|---|---|---|
| | | CR | PR | SD | PD | Not done |
| **Prior auto SCT** | | | | | | |
| All cases | 8 | 2 (1) | 5 (2) | | | 1 |
| HL | 6 | 1 (1) | 5 (2) | | | |
| **ALCL** | **1** | **1*** | | | | |
| CD30+ TCL | 1 | | | | | 1 |
| **No prior auto SCT** | | | | | | |
| All cases | 16 | 4 (3) | 5 | | 4 | 3 |
| HL | 12 | 2 (1) | 5 | | 3 | 2 |
| **ALCL** | **4** | **2 (2)**** | | | **1***** | **1***** |

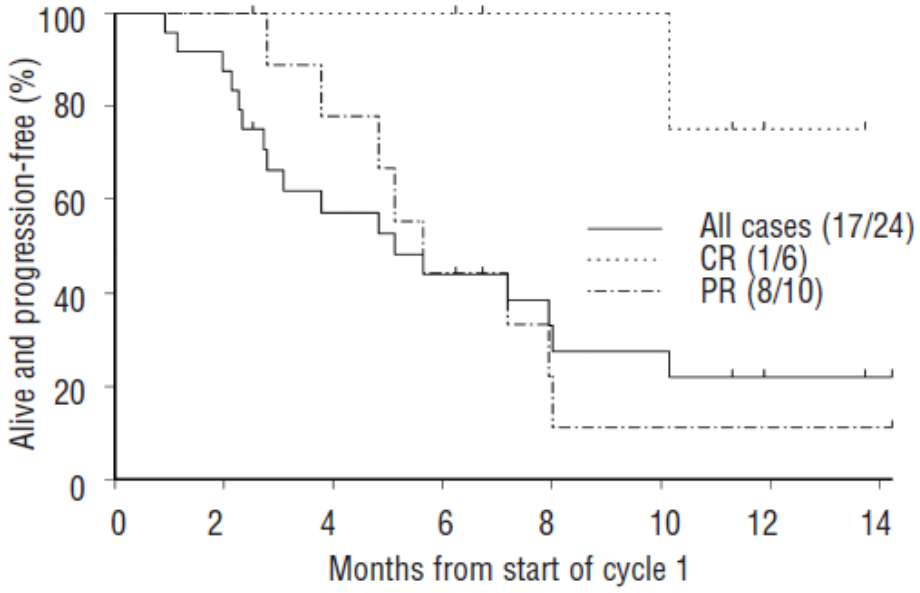
Abbreviations: SCT = stem cell transplant; HL = Hodgkin lymphoma; ALCL = anaplastic large cell lymphoma; TCL = T-cell lymphoma; CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease

( ) Represent patients who subsequently underwent allotransplant

* ALK-1 negative; ** one ALK-1 negative and one ALK-1 status unknown; *** ALK-1 status unknown

Source: Gibb et al., (2013)[43]

**Figure 4.10: Progression-free survival of patients treated in the brentuximab vedotin UK Named Patient Programme**



Source: Gibb et al., (2013)[43]

This data demonstrates that brentuximab vedotin was effective with an ORR of 67% and a median PFS of 5.1 months in a population of heavily pre-treated patients with CD30+ lymphoma managed in a non-trial setting at a single UK centre. The ORR of 60% for patients with sALCL was lower than the 86% reported in the pivotal Phase II SG035-0004 trial.[2] Pro 2012 Due to the very small patient numbers (n=5), it is not possible to draw definitive conclusions about the efficacy of brentuximab vedotin in sALCL from this study.

***Three-years follow-up and data on new patients in the UK NPP***

This section provides an update on the outcomes reported above for 24 patients (Gibb 2013), with more than 3-years of additional follow-up and includes data on 9 new patients.

Patients and methods

Subsequent to brentuximab vedotin being granted conditional marketing authorisation by the EMA on the 25th October 2012,[1] a further 9 patients were added to the series (including a further 3 patients with sALCL, taking the total with sALCL to 8 patients).[44]

Results

- Patients received a median of 5 cycles of brentuximab vedotin (range 1-16)
- The overall response rate (ORR) was 61%: By histology, the ORR was 63% in both ALCL (5/8) and HL (15/24) patients
- Complete response rate was 24% (ALCL n=4, HL n=4); this was higher in the ALCL group (50%, 4/8) than the HL group (17%, 4/24)
- Overall, the best response was seen at PET4 in all but 1 patient with HL who improved to CR at PET8
- Of the 25 patients who were eligible for allo-SCT, 8/25 (32%) proceeded to allo-SCT without further systemic therapy
- 7 patients were assessed for outcomes and toxicity following allo-SCT (n=1 was lost to follow-up after transferring to another centre, and died at an unknown time point of unknown cause)
- After a median follow-up of 25.3 months (range 2.4 to 59.8), 5 patients are still alive
- Acute graft versus host disease (GvHD) was seen in 5 patients (71%). One patient experienced severe GvHD involving skin and gut (initially grade 3) which led to death 25 months after allo-SCT
- Of the patients who did not receive an allo-SCT, 14 had an inadequate response (PD at PET4 or PET8). Three patients declined an allo-SCT; 2 of these have achieved CR and remain alive (1 progression-free) at 23.0 and 56.1 months of follow-up. Four patients proceeded to allo-SCT after additional systemic therapy.

Conclusion

In patients with R/R sALCL and R/R HL treated with brentuximab vedotin outside a clinical trial protocol, response rates and toxicity are broadly comparable with the published Phase II trial data.[2,48] It can be concluded that prolonged survival is possible after brentuximab

vedotin in a proportion of real world patients whose prognosis is conventionally regarded as extremely poor.[44]

## 4.12 Adverse reactions

### 4.12.1 Overview

The regulatory filing for brentuximab vedotin included data from six studies (four Phase I and two Phase II) in which 357 patients with CD30+ haematologic malignancies received at least one dose of brentuximab vedotin.[1] A total of 261 patients received brentuximab vedotin at the approved dose of 1.8mg/kg every 3 weeks.[1]

In addition, further safety data on serious adverse events (SAEs) from ongoing clinical studies (including the Phase III SGN35-005 [AETHERA] RCT) and a Named Patient Programme (NPP) was provided to the regulatory authorities.

### 4.12.2 Summary of safety of brentuximab vedotin based on non-RCT clinical trial data: Study SG035-0004

The safety profile of brentuximab vedotin is based on safety data from 6 studies with 357 patients with CD30+ haematologic malignancies who received at least 1 dose of SGN35 (phase 1 dose escalation studies: SG035-0001 and SG035-0002, phase 1 studies SG035-007 and SG035-008A, pivotal phase 2 studies, SG035-0003 and SG035-0004). The median treatment duration with brentuximab vedotin in study SG035-0004 was 20 weeks (range, 3 to 51); a median of 7 cycles (range, 1 to 16) have been administered per patient and slightly less than 50% of patients received 7 or more cycles. A total of 261 patients received brentuximab vedotin at the proposed dose and schedule of 1.8 mg/kg q3 week.[7]

For the purpose of this submission, we will report on the safety of patients with R/R sALCL from the pivotal, Phase II SG035-0004 trial only.

#### *4.12.2.1 Adverse events*

The safety evaluable set consisted of 58 patients who received brentuximab vedotin. Seven patients (12%) had dose reduction to 1.2 mg/kg at least 1 time in the study. Of 476 doses administered, 23 (5%) were reduced. The greatest number of doses were reduced at Cycle 6 (4 doses) and Cycle 7 (4 doses).[5]

Of 58 patients in the safety evaluable set, 100 (%) experienced at least 1 treatment-emergent AE (

Table 4.13). AEs are treatment emergent unless otherwise noted. Twenty-one patients (36%) had a most severe event of Grade 3, 9 patients (16%) had a most severe event of Grade 4, and 6 patients (10%) had a Grade 5 (fatal) event.[5]

**Table 4.13: Summary of adverse events in the SG035-0004 trial**

| | N=58 n (%) |
|---|---|
| Total number of unique adverse event terms [a b] | 255 |
| Total number of unique serious adverse event terms [c b] | 52 |
| Any adverse event, n (%) [a] | 58 (100) |
| Maximum severity of adverse event, n (%) [a] | |
| Grade 1 | 5 (9) |
| Grade 2 | 17 (29) |
| Grade 3 | 21 (36) |
| Grade 4 | 9 (16) |
| Grade 5 | 6 (10) |
| ≥ Grade 3 | 36 (62) |
| Treatment-related adverse event, n (%) [b] | 53 (91) |
| Any serious adverse event, n (%) [c] | 25 (43) |
| Any treatment-related serious adverse event, n (%) [c] | 11 (19) |
| Discontinued treatment due to an adverse event, n (%) [c] | 16 (28) |

[a] Treatment-emergent event, defined as newly occurring (not present baseline) or worsening after first dose of investigational drug

[b] Related to treatment with brentuximab vedotin as assessed by the investigator

[c] All events, from time of informed consent to the end of the safety reporting period

Source: SG035-0004 CSR[5]

### *4.12.2.2 Treatment-emergent adverse events*

Treatment-emergent adverse events (TEAEs) that occurred in >10% of patients receiving brentuximab vedotin are summarised in descending order of frequency in Table 4.14.

**Table 4.14: Treatment-emergent adverse events occurring in >10% of patients receiving brentuximab vedotin**

| | All grades (n=58) | | Grade 3 (n=58) | | Grade 4 (n=58) | |
|---|---|---|---|---|---|---|
| **Adverse Event*** | **No. of patients** | **%** | **No. of patients** | **%** | **No. of patients** | **%** |
| Peripheral sensory neuropathy | 24 | 41 | 7 | 12 | 0 | 0 |
| Nausea | 23 | 40 | 1 | 2 | 0 | 0 |
| Fatigue | 22 | 38 | 2 | 3 | 1 | 2 |
| Pyrexia | 20 | 34 | 1 | 2 | 0 | 0 |
| Diarrhoea | 17 | 29 | 2 | 3 | 0 | 0 |
| Rash | 14 | 24 | 0 | 0 | 0 | 0 |

| Adverse Event* | All grades (n=58) | | Grade 3 (n=58) | | Grade 4 (n=58) | |
|---|---|---|---|---|---|---|
| | No. of patients | % | No. of patients | % | No. of patients | % |
| Constipation | 13 | 22 | 1 | 2 | 0 | 0 |
| Neutropenia | 12 | 21 | 7 | 12 | 5 | 9 |
| Headache | 11 | 19 | 1 | 2 | 0 | 0 |
| Pruritus | 11 | 19 | 0 | 0 | 0 | 0 |
| Cough | 10 | 17 | 0 | 0 | 0 | 0 |
| Dyspnoea | 10 | 17 | 1 | 2 | 0 | 0 |
| Upper respiratory tract infection | 10 | 17 | 0 | 0 | 0 | 0 |
| Vomiting | 10 | 17 | 2 | 3 | 0 | 0 |
| Decreased appetite | 9 | 16 | 1 | 2 | 0 | 0 |
| Dizziness | 9 | 16 | 0 | 0 | 0 | 0 |
| Insomnia | 9 | 16 | 0 | 0 | 0 | 0 |
| Myalgia | 9 | 16 | 1 | 2 | 0 | 0 |
| Alopecia | 8 | 14 | 0 | 0 | 0 | 0 |
| Chills | 8 | 14 | 0 | 0 | 0 | 0 |
| Muscle spasms | 8 | 14 | 1 | 2 | 0 | 0 |
| Thrombocytopenia | 8 | 14 | 5 | 9 | 3 | 5 |
| Weight decreased | 8 | 14 | 2 | 3 | 0 | 0 |
| Oedema peripheral | 7 | 12 | 0 | 0 | 0 | 0 |
| Pain in extremity | 7 | 12 | 1 | 2 | 1 | 2 |
| * Terms according to Medical Dictionary for Regulatory Activities, Version 13.0 | | | | | | |

Source: Pro et al., (2012)[2]

Treatment-emergent events occurring in ≥20% of patients were peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhoea (29%), rash (24%), constipation (22%), and neutropenia (21%). An AE grade ≥3 occurred in 60% of the patients.[2]

Adverse events resulting in dose reduction occurred in 9% of patients; 2 patients out of the 5 patients had dose reductions for peripheral sensory neuropathy. Adverse events that led to dose delay occurred in 31% of patients; these AEs were neutropenia (12%), peripheral sensory neuropathy (7%), and thrombocytopenia (5%).[5]

### *4.12.2.3 Deaths*

At the time of database lock on 11th August 2010, 19 patients had died. Of these, 13 deaths (22%) were attributed to the disease (i.e. they died after greater than 30 days of the last dose of brentuximab vedotin). For the 6 patients who died within 30 days of the last dose of brentuximab vedotin, an AE with an outcome of death was entered in the database and therefore a primary cause of death was known. None of these deaths were attributed to study drug. Four of the deaths were attributed to disease recurrence, one patient had an

acute myocardial infarction and acute renal failure leading to death, and another patient experienced sudden death related to an obstruction of the patient's tracheal prosthesis.[2]

#### *4.12.2.4 Adverse events leading to treatment discontinuation and dose modifications*

Of the 58 patients in the safety evaluable population, 14 (24%) experienced an AE that resulted in treatment discontinuation. Nervous system disorders were the most common events leading to treatment discontinuation: peripheral sensory neuropathy (six patients), demyelinating polyneuropathy, intracranial haemorrhage, and neuralgia (1 patient each).[2] Renal failure led to treatment discontinuation in 2 patients. Other adverse events leading to treatment discontinuation in a single patient each were retinal vein occlusion, sudden death, transaminases increased, and dermatitis.

Doses of brentuximab vedotin were delayed because of adverse events in 40% of patients; however, only 10% of doses were delayed overall. The most common adverse events leading to dose delays were peripheral sensory neuropathy (14%) and neutropenia (12%). Doses of brentuximab vedotin were prospectively reduced from 1.8 to 1.2 mg/kg in seven patients. Two of the patients with dose reductions eventually discontinued treatment in the study as a result of peripheral sensory neuropathy.[2]

### 4.12.3 Safety of brentuximab vedotin in relation to the decision problem

Brentuximab vedotin was evaluated in the patient population with relapsed or refractory sALCL that had treatment failure of at least one prior therapy. No consensus has been reached regarding the treatment of relapsed or refractory disease. A second complete remission with standard salvage therapy can be achieved in 30-40% of patients.[17]

Within the population of R/R sALCL, brentuximab vedotin 1.8 mg/kg every 3 weeks was shown to be well tolerated with the usual expected AEs for this therapy, in one pivotal, Phase II trial [2], retrospective case series,[35,42] and real-world data from European Named Patient Programmes, including the UK.[36-38,43]In addition, long-term data provides evidence of the safety of brentuximab vedotin for up to 5 years in patients with R/R sALCL.[6]

The most common AEs were nervous system disorders which included peripheral sensory neuropathy (41%), demyelinating polyneuropathy (2%), intracranial haemorrhage (2%), and neuralgia (5%). Peripheral neuropathy is a known class effect of agents such as brentuximab vedotin with an anti-microtubule mechanism of action;[49,50] and the patients in the trial may have been predisposed to peripheral neuropathy after exposure to multiple prior chemotherapy regimens. These AEs were often identified early (the median time to onset of events for peripheral neuropathy was 15 weeks). 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. Dose delays and dose reductions to 1.2 mg/kg were used to manage adverse events. These data demonstrate that peripheral neuropathy events with brentuximab vedotin were generally manageable, with high rates of resolution or improvement.

Overall, the evidence from the pivotal Phase II study, a retrospective case study in patients ≥60 years,[42] and the UK NPP shows brentuximab vedotin to be generally well tolerated with a low rate of treatment-related SAEs, and a low rate of discontinuations due to peripheral neuropathy.

Most importantly, brentuximab vedotin is a treatment that has already seen significant post-marketing use in patients through several Named Patient Programmes, gathering substantial evidence that supports "real-world" general safety and tolerability. Brentuximab vedotin has been widely used in clinical practice in the UK for the last 4 years as it has been available via the Cancer Drugs Fund (CDF)[51] in England, and has been accepted for use in Scotland and Wales for R/R HL (with R/R sALCL patients in Scotland and Wales accessing it via individual patient funding mechanisms. Hence, UK clinicians have gained considerable experience with brentuximab vedotin and it is viewed by clinicians as having a predictable and manageable side effect profile.

## 4.13 Interpretation of clinical effectiveness and safety evidence

### 4.13.1 Overview

Brentuximab vedotin is an antibody-drug conjugate that is specifically targeted against CD30 expressing cancer cells such as those in sALCL or HL. Once brentuximab vedotin has been internalised after binding to CD30 on the surface of cancer cells, the active agent MMAE is released inside the cell and induces apoptosis.

The evidence base to support the use of brentuximab vedotin in patients with sALCL comes from a pivotal, Phase II clinical trial (SG035-0004),[2] retrospective case series,[42] and NPPs.[36-38,43] Continuation of these benefits for up to 5 years is supported by data recently presented at ASH 2016.[6] Subjects were chosen for participation in the pivotal trial based on their need for alternative treatment having failed at least one prior multi-agent chemotherapy regimen and, in some cases, an ASCT. In the largest prospective study ever conducted in relapsed or refractory sALCL, a total of 58 patients were enrolled. ALK-negative ALCL (a marker of poor prognosis) comprised the majority of patients in the study (72%), and the incidence of primary refractory disease and disease refractory to the most recent treatment was high (62% and 50%, respectively). Moreover, 22% of patients had never responded to any prior therapy. These factors combine to make this a difficult-to-treat, chemo-refractory population of patients.[2]

As 40-65% of patients develop recurrent disease after initial CHOP chemotherapy, R/R sALCL remains a clinical challenge and, prior to the availability of brentuximab vedotin, there was no standard therapy.[33] In the absence of brentuximab vedotin, treatment choices range from aggressive regimens that enable allogeneic transplantation (with a risk of treatment related mortality of 15-20% or acute/chronic GvHD) to palliative measures with a goal of maximising a patient's quality of life.

### 4.13.2 Efficacy

Brentuximab vedotin has demonstrated unprecedented, long-term efficacy in patients with R/R sALCL. In a pivotal Phase II clinical trial, brentuximab vedotin demonstrated efficacy in patients with sALCL after failure of prior multi-agent chemotherapy.[2] The results from the pivotal Phase II trial, SG035-0004, and the retrospective study by Gopal (2014)[42] in sALCL patients ≥60 years were similar in terms of demonstrating very high ORRs, in the region of 86-100%, and CRs in the region of 50-59% for brentuximab vedotin at a dose of 1.8 mg/kg every 3 weeks.[2 42] Importantly, the responses achieved with brentuximab vedotin were durable: the median DOR for all R/R sALCL patients in the SG035-0004 trial was 13.2 months.[1] In addition, improvements in median PFS of 20.0 months[6] demonstrate that the majority of patients with sALCL achieved clinically significant durable remissions. The authors of the 5-year follow up data concluded that a subset of patients with R/R sALCL may have been potentially cured with single-agent brentuximab vedotin.[6] The estimated 5-year OS rate was 60% (95% CI: 47, 73), and the median OS was not estimable (95% CI: 21.3,-; range 0.8 to 82.4+ months).[6]

Furthermore, clinical trials[52] and the UK NPP[43] have shown that for patients with sALCL refractory to conventional salvage chemotherapy, yet deemed potentially eligible for stem cell transplantation, brentuximab vedotin can provide a bridge to transplant, thus providing an additional therapeutic route for patients in whom palliation had previously been the only option.[43,52]

Therefore, efficacy analyses from the SG035-0004 clinical trial,[2] the retrospective study in patients ≥60 years,[42] and the Named Patient Programmes[36-38,43] are reinforcing in terms of the overall conclusion that brentuximab vedotin provides unprecedented, long-term efficacy in patients with R/R sALCL. Indeed, the authors of the recently presented 5-year follow up data concluded that a subset of patients with R/R sALCL may potentially have been cured with single-agent brentuximab vedotin.[6] Based on the strength of this data, brentuximab vedotin is viewed by clinical experts as a real ‘step-change’ in the management of R/R sALCL and, over the past 4 years via the CDF, it has become established as the standard of care in England for these patients.

### 4.13.3 Safety

Brentuximab vedotin is generally well tolerated and has an established safety profile which was consistent across the study programme and in actual clinical practice. Nervous system disorders were the most frequent adverse events seen with brentuximab vedotin (primarily peripheral neuropathy), but most peripheral neuropathy adverse events were grade 1 or 2 in intensity, identified early, and in most cases were resolved or improved by ≥1 grade. In the Phase II pivotal study (SG035-0004)[2] peripheral neuropathy led to discontinuation and dose reduction in 10% of patients.[1] The incidence and severity of neuropathy is similar to that observed with other microtubule inhibitor-based chemotherapies (including vinca alkaloids, taxanes, and epothilones). In general, peripheral neuropathy was managed by early recognition, dose delay, and subsequent dose reduction to 1.2 mg/kg; and was reversible, with symptom improvement or resolution in more than 91% of patients who experienced peripheral neuropathy events.[6] Importantly, no grade 4 AE has been reported and peripheral

sensory/motoric neuropathy appeared to resolve at least to a certain extent.[5] UK clinicians have gained considerable real world experience with brentuximab vedotin over the past 4 years and it is viewed by them as having a predictable and manageable side-effect profile.

### 4.13.4 End of life criteria

Based on compelling cost effectiveness results (see Section 5) which show that brentuximab vedotin easily meets NICE's conventional cost-effectiveness threshold (i.e. £20,000 - £30,000 per QALY), Takeda does not wish for the medicine to be considered at this time for the application of NICE's End of Life criteria.

## 4.14 Ongoing studies

There is an ongoing single arm, open-label, multicentre, Phase IV clinical trial (NCT 01909934) to evaluate the efficacy and safety of brentuximab vedotin as a single agent in patients with R/R sALCL. Recruitment into this study is still ongoing (including at investigational sites in the UK).

# 5. Cost effectiveness

## 5.1 Published cost-effectiveness studies

### 5.1.1 Identification of studies

An extensive systematic literature review (SLR) to identify cost-effectiveness and cost and resource use evidence was conducted during November 2016. The details of the search strategy and inclusion/ exclusion criteria are provided in Appendix 11.

The SLR was performed to identify and summarise the relevant economic and cost and resource use evidence for adult patients with relapsed and/ or refractory (R/R) sALCL receiving medical therapy. Separate inclusion and exclusion criteria were applied to the search results to collate economic and cost and resource use evidence separately. The results associated with economic evidence are presented in this Section. The results associated with cost and resource use evidence are presented in Section 5.5.

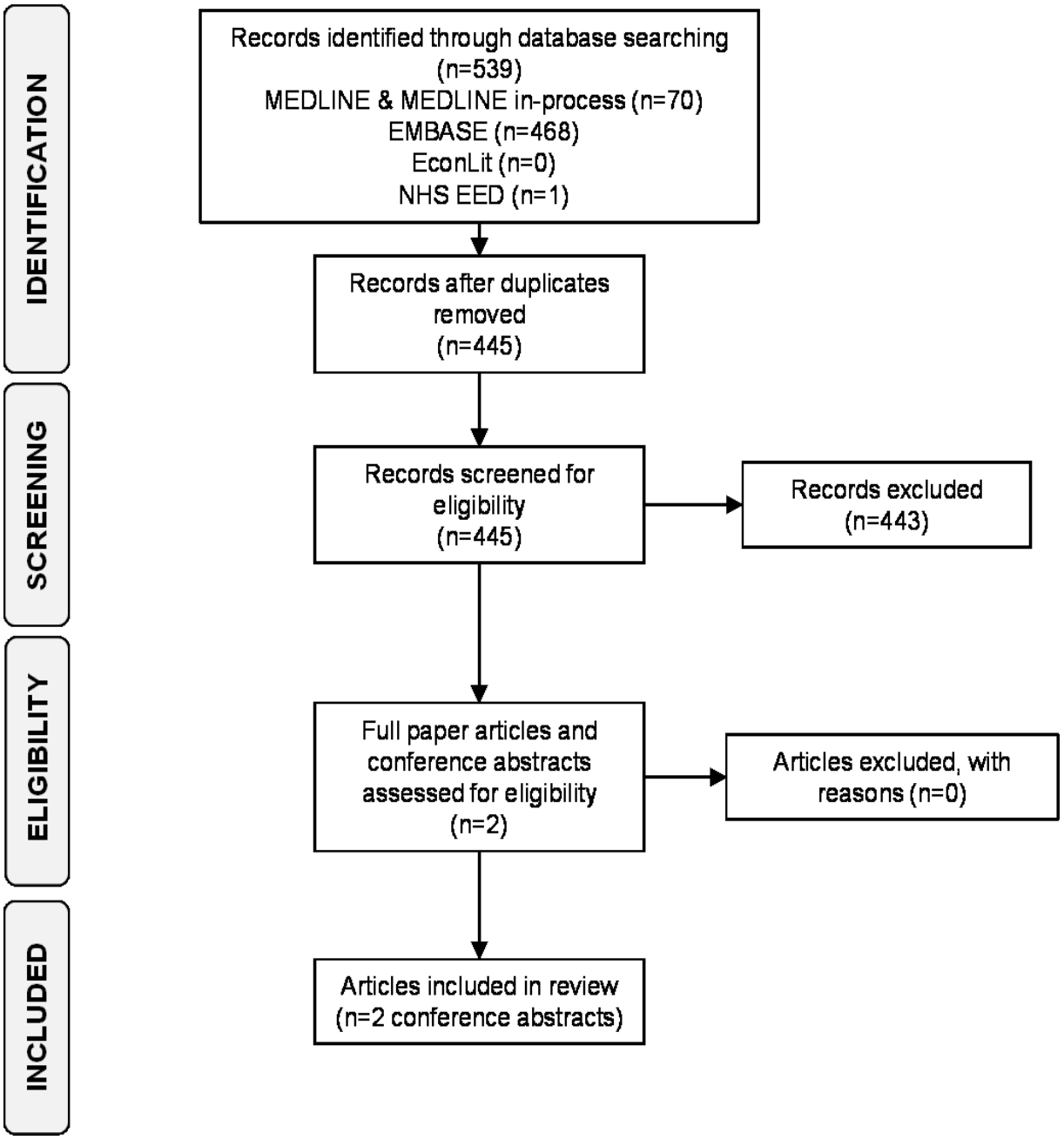
For the economic evidence, studies reporting cost-benefit, cost-minimisation, cost-utility, cost-effectiveness and cost-consequence analyses were included; all other study designs were excluded. Published SLRs were excluded at the screening stage, the reference lists associated with SLRs were screened to ensure all available evidence was included. Due to the rarity of sALCL and the anticipated scarcity of evidence, no restrictions were imposed on interventions, location or date.

Primary screening of abstracts and secondary screening of full-texts were conducted by two independent reviewers. Data extraction from the included full-text of articles was also performed independently by two reviewers to ensure that everything was captured.

### 5.1.2 Description of identified studies

In total, 539 studies were identified from the electronic sources. Following removal of duplicates there were 445 papers eligible for screening. Primary screening of titles and abstracts against the pre-specified inclusion and exclusion criteria for economic evidence (as presented in Appendix 11) excluded 443 studies leaving 2 papers to be reviewed in full. These papers represented abstracts from conference proceedings and satisfied all inclusion and exclusion criteria, as such data were extracted from these sources. The flow diagram of the economic SLR is presented in Figure 5.1.

**Figure 5.1: PRISMA diagram for economic SLR**




Key: EED, Economic Evaluation Database; n, number; NHS, National Health Service; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

There were two studies included in the review, both only available as conference abstracts. These were Hux et al., (2016)[53] and Zou et al., (2016)[54] which consider cost-utility analyses assessing the cost-effectiveness of brentuximab vedotin compared with conventional chemotherapy from a UK and Taiwanese perspective, respectively. The main outcome in both papers was the cost per QALY gained; results were £35,390 and New Taiwan $781,300 (~ £20,000) per QALY gained for brentuximab vedotin compared with conventional chemotherapy reported in Hux et al., (2016) and Zou et al., (2016), respectively. Both consider a partitioned survival model structure with the following health states: pre-progression, post-progression and death. These analyses are summarised in Table 5.1.

These two studies used survival outcomes from the same pivotal phase II single-arm arm brentuximab vedotin trial of 58 R/R sALCL patients with good ECOG performance status after at least one prior therapy; with 40 sALCL patients from a Canadian cancer registry receiving first-line conventional salvage chemotherapy between 1980 and 2010 followed up for 20 years.

Zou et al., (2016)[54] was excluded due to adopting a Taiwanese perspective and being an abstract only. Hux et al., (2016)[53] adopted a UK perspective but was also only available as an abstract. These cost-effectiveness studies identified met the inclusion/exclusion and concluded that brentuximab vedotin may be a cost-effective option but contained limited data, so were unable to be utilised in the model.

**Table 5.1: Economic evaluations identified in economic SLR**

| Study ID | Country | Study design | Patient population | Comparators | Model type | Health states | Model characteristics | Source of treatment effects | Source of HRQL | QALYs | Costs | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hux ASCO 2016 [53] | UK | Cost-utility analysis | R/R sALCL | Brentuximab vedotin vs. conventional chemotherapy | Partitioned survival | Progression-free, post-progression and death | Time horizon: unclear; Cycle length: unclear | Brentuximab: PFS and OS were obtained from the Phase II, single-arm trial of 58 R/R sALCL patients<br><br>Chemotherapy: PFS and OS obtained from a Canadian cancer registry which had data on 40 sALCL patients | Unclear | Unclear | Unclear | £35,390 |
| Zou ISPOR 2016 [54] | Taiwan | Cost-utility analysis | R/R sALCL | Brentuximab vedotin vs. conventional chemotherapy | Partitioned survival | Progression-free, post-progression and death | Time horizon: unclear; Cycle length: unclear | Brentuximab: PFS and OS were obtained from the phase II, single-arm trial of 58 R/R sALCL patients<br><br>Chemotherapy: PFS and OS obtained from a Canadian cancer registry which had data on 40 sALCL patients | Unclear | Unclear | Unclear | $781,300 |

Key: ASCO, American Society of Clinical Oncology; HRQL, health related quality of life; ICER, incremental cost effectiveness ratio; ID, identification; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; R/R, relapsed and/or refractory; sALCL, systemic anaplastic large cell lymphoma; UK, United Kingdom

## 5.2 De novo analysis

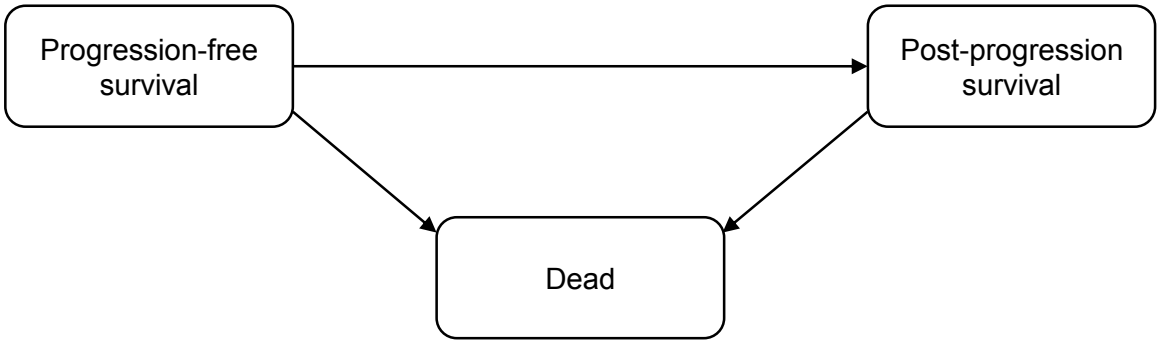
### 5.2.1 Patient population

In line with the SG035-0004 study population, the economic model assesses the cost-effectiveness of brentuximab vedotin compared to established clinical management without brentuximab vedotin for the treatment of patients with R/R sALCL.

### 5.2.2 Model structure

The model includes the following three health states: progression-free survival (PFS); post-progression survival (PPS) and dead (Figure 5.2). This structure is frequently used in economic evaluations of cancer therapies,[55] is consistent with the clinical pathway of care described in Section 3.3 and captures the outcomes listed in the final scope.[8]

**Figure 5.2: Model schematic**




A partitioned survival (area under the curve) approach was used to estimate health state occupancy, whereby the proportion of patients in the PFS state over time is estimated directly from the PFS curves, and the proportion of patients in the PPS state is estimated as the difference between the OS curve and the PFS curve. PFS and OS curves are modelled independently (i.e. using different parametric functions) hence it is possible for the PFS curve to lie above the OS curve, yielding negative numbers of patients in the 'post-progression' health state. This outcome was considered in the process of selecting parametric models, however could still occur in the probabilistic analysis. In such cases the PFS curve was set equal to the OS curve to retain face validity.

Health effects are calculated as both life-years (LYs) and quality-adjusted life-years (QALYs). Costs and QALYs are accrued according to the proportion of patients in the PFS and PPS states over time. A weekly cycle length was used. This is both convenient for the treatment regimens and appropriate given the rate at which relevant clinical events occur in this patient population. A half-cycle correction was applied in all calculations to reduce the potential for bias in the cost-effectiveness estimates.

Costs and health effects are calculated over a 60 year time horizon; this is equivalent to lifetime given the mean starting age (47.7 years) of patients in SG035-0004 and the potential for long term survival in this population.[2]

The model has been developed in Microsoft Excel 2010. Table 5.2 provides a summary of the key structural features of the economic model.

**Table 5.2: Features of the de novo analysis**

| Factor | Chosen values | Justification |
|---|---|---|
| Time horizon | 60 years (lifetime) | Survival is virtually zero in both arms at 60 years and can therefore be considered a lifetime horizon, as is recommended in the Reference Case to capture all relevant differences in costs and outcomes. |
| Were health effects measured in QALYs; if not, what was used? | QALYs | QALY is the outcome measure recommended in the Reference Case. |
| Discount rate of 3.5% for utilities and costs | 3.5% | 3.5% discount rate for costs and benefits is consistent with the Reference Case. |
| Perspective (NHS/PSS) | NHS | The use of Personal Social Services is deemed not to be relevant for the conditions under investigation and therefore only the NHS perspective has been addressed. |
| PSS, personal social services; QALYs, quality-adjusted life years | | |

## 5.2.3 Intervention technology and comparators

### *5.2.3.1 Overview*

In line with the decision problem outlined in the final scope,[8] the model compares brentuximab vedotin with established clinical management without brentuximab vedotin for the treatment of patients with R/R sALCL, consisting of the use of a range of different chemotherapy regimens.

The dose of the intervention was implemented as per its marketing authorisation. The doses of the comparator regimens were implemented in line with the clinical studies referenced in the NCCN guidelines for PTCL.[24]

### *5.2.3.2 Intervention: Brentuximab vedotin*

In line with the marketing authorisation,[1] the model assumes brentuximab vedotin was administered as a single outpatient IV infusion on day 1 of each 21-day cycle at a dose of 1.8 mg/kg.

Also in line with the marketing authorisation, patients in SG035-0004 could have continued on study treatment until disease progression or unacceptable toxicity. Patients who achieved stable disease or better as assessed by investigator were to receive a minimum of 8, but no

more than 16 cycles of study treatment. A mean of 8.2 cycles (range, 1 to 16) were administered per patient in SG035-0004.[5]

In the cost-effectiveness model, acquisition costs are calculated separately for patients who received subsequent SCT and for patients who did not. The corresponding mean numbers of cycles per patient were 8.8 (range, 4 to 16) and 8.0 (range, 0 to 16), respectively.

#### *5.2.3.3 Comparator: Established clinical management*

Aside from brentuximab vedotin, a range of different chemotherapy regimens are used for patients. Therefore, established clinical management (henceforth referred to as chemotherapy) has been included in the model as a composite comparator. This approach was deemed appropriate based on feedback from a clinical expert survey performed (Section 5.3.8 for details of the survey methods) was that the chemotherapy regimens used in practice are not expected to differ with regards to efficacy.

The cost of chemotherapy is calculated as a weighted average of the separate regimens based on their frequency of use in UK clinical practice. Given the lack of definitive guidance regarding the preferred chemotherapy regimens for patients with R/R sALCL,[24] the following regimens were identified based on a survey of UK clinical experts (see Section 5.3.8):

- ICE (ifosfamide, carboplatin and etoposide)
- ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin)
- DHAP (dexamethasone, high-dose cytarabine and cisplatin)
- GDP (gemcitabine, dexamethasone and cisplatin)
- Gem-P (gemcitabine, methylprednisolone and cisplatin)

The frequency of use of these regimens was also based on findings from the survey of UK clinical experts (Section 5.3.8 for details of methods of the survey). Sensitivity analyses are run assuming all patients receive the most and least expensive regimens (GDP and ESHAP respectively) to explore uncertainty in the proportion of patients receiving each regimen. The dosing schedule for each regimen was sourced from the corresponding publications cited in the NCCN guidelines for PTCL.[24]

Table 5.3 presents the proportion of patients receiving each regimen and the associated dosing schedules used in the base case analysis.

**Table 5.3: Chemotherapy regimens, time on treatment and frequency of use**

| Regimen | Drug | Dose (mg) | Unit* | Admins per cycle | Cycle length (days) | Number of cycles¥ | Proportion of patients* | Dosing source |
|---|---|---|---|---|---|---|---|---|
| ICE | Etoposide | 100 | $m^2$ | 3 | 14 | 3 | 25.0% | Zelenetz (2003)[56] |
| | Carboplatin | 800 | N/A | 1 | 14 | | | |
| | Ifosfamide | 5000 | $m^2$ | 1 | 14 | | | |
| ESHAP | Cisplatin | 25 | $m^2$ | 4 | 21 | 7 | 25.0% | Velasquez (1988)[57] |
| | Methylprednisolone | 500 | N/A | 5 | 21 | | | |
| | Etoposide | 40 | $m^2$ | 4 | 21 | | | |
| | Cytarabine | 2000 | $m^2$ | 1 | 21 | | | |
| DHAP | Dexamethasone | 40 | N/A | 4 | 21 | 8 | 25.0% | Velasquez (1994)[58] |
| | Cisplatin | 100 | $m^2$ | 1 | 21 | | | |
| | Cytarabine | 2000 | $m^2$ | 2 | 21 | | | |
| GDP | Gemcitabine | 1250 | $m^2$ | 2 | 21 | 6 | 12.5% | Dong (2013)[59] ɣ |
| | Dexamethasone | 40 | $m^2$ | 4 | 21 | | | |
| | Cisplatin | 25 | $m^2$ | 3 | 21 | | | |
| Gem-P | Gemcitabine | 1000 | $m^2$ | 2 | 28 | 6β | 12.5% | Arkenau (2007)[60] |
| | Cisplatin | 100 | $m^2$ | 3 | 28 | | | |
| | Methylprednisolone | 1000 | N/A | 5 | 28 | | | |

DHAP, dexamethasone, high-dose cytarabine and cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; GDP, gemcitabine, dexamethasone and cisplatin; ICE, ifosfamide, carboplatin and etoposide; *N/A indicates fixed dose; ¥standard error of 10% assumed where uncertainty estimates were not reported; ɣ Dong (2013)[59] selected in preference to Crump (2004)[61] based on date of publication; βmean cycles assumed equivalent to GDP *Estimated by clinical expert survey (Section 5.3.8 for details of methods)

Palliative radiotherapy is discussed in the final NICE scope[8] as part of the treatment pathway. Based on the findings of the survey of UK clinical experts (Section 5.3.8), radiotherapy was assigned to 5% of patients in the chemotherapy (no SCT) cohort. One expert indicated that 40% of patients would receive radiotherapy; this proportion was explored in a scenario analysis.

#### *5.2.3.4 Stem cell transplant*

As cited in the final scope and in the clinical pathway of care described in Section 3.3, treatment for R/R sALCL in UK clinical practice may include ASCT or allo-SCT for a proportion of patients; treatment with brentuximab vedotin or chemotherapy will be used as a bridge to provision of ASCT or allo-SCT in these cases.

The NCCN guidelines for PTCL[24] specify that patients achieving a complete (CR) or partial response (PR) to salvage therapy would be considered for allo-SCT (non-myeloblative or ablative) or high dose therapy (HDT) with ASCT. However, not all patents intended for SCT will ultimately receive SCT for a number of reasons including age (>60 years), comorbidities, lack of an HLA-matched donor, personal choice.[62]

Three approaches were explored to estimate the proportion of patients who receive SCT:

1. Response-based (SG035-0004): 16/38 CRs (42%) and 1/12 PRs (8%) in SG035-0004 received SCT. These proportions reflect patients who were intended for SCT based on their response to salvage, yet who ultimately do not receive SCT.

2. Response-based (clinical expert opinion): Feedback obtained from the survey of UK clinical experts (Section 5.3.8) was that patients who achieve a CR or a 'good' PR would be intended for SCT; it was thus assumed that 100% of CRs and 50% of PRs would be intended for SCT. To account for patients who are intended for but do not ultimately receive SCT, data from Mak et al., (2013)[12] were used; of 55 patients intended for SCT, only 38 went on to receive SCT (69%).

3. Equal rate in both treatment arms (Mak et al., 2013)[12]: Mak et al.,[12] report that of 191 patients with relapsed or refractory PTCL after initial systemic therapy, 55 were intended to undergo HDT followed by SCT (29%). Of 55 patients intended for SCT, only 38 went on to receive SCT (69%).

The proportions of CRs and PRs receiving SCT based on each of the approaches are presented in Table 5.4.

**Table 5.4: Proportions of patients receiving SCT**

| Approach | CR | PR |
|---|---|---|
| Response-based (SG035-0004) | 42% | 8% |
| Response-based (clinical expert opinion) | 69% | 35% |
| Equal rate in both treatment arms (Mak et al., 2013)[12] | 20% | 20% |

To align with the NCCN guidelines[24] and UK clinical practice, the proportion of patients receiving SCT was based on approach 1 in the base case. Approaches 2 and 3 were explored in sensitivity analyses (Section 5.8).

Response rates for brentuximab were based on the ITT population in SG035-0004. Response rates for chemotherapy were based on responses achieved with the most recent cancer-related therapy prior to brentuximab for the subgroup of 39 patients whose most recent therapy was for R/R disease. Despite excluding patients who proceed to SCT, these data were chosen for the base case as they represent a self-control comparison with response for brentuximab. To address the potential bias induced by excluding patients who proceed to SCT, two additional data sources were included.[59,61] These were identified as the only studies reporting response rates of those referenced by the NCCN guidelines and which informed dosing schedules. These data are presented in Table 5.5.

**Table 5.5**: **Response rates used to derive proportions of patients receiving SCT**

| Response | Brentuximab vedotin | Chemotherapy | | |
|---|---|---|---|---|
| | | Self-control cohort | Dong (2013)[59] | Crump (2004)[61] |
| CR | 66% | 31% | 46% | 16% |
| PR | 21% | 13% | 42% | 33% |
| SD | 7% | 10% | 4% | 17% |
| PD | 3% | 36% | 8% | 17% |

The guidelines do not indicate how to identify whether patients should undergo ASCT or allo-SCT. Of the 17 patients who received SCT in SG035-0004, 8 (47%) received ASCT and 9 (53%) received allo-SCT. In relation, findings from the survey of UK clinical experts (Section 5.3.8) indicated that the majority of patients in this setting would receive allo-SCT. As such, the base case analysis utilises the ratio of ASCT to allo-SCT from SG035-0004. As a sensitivity analysis, a ratio of ASCT to allo-SCT of 25%:75% was assumed.

**Table 5.6**: **Ratio of ASCT to allo-SCT**

| Approach | Proportion | |
|---|---|---|
| | ASCT | Allo-SCT |
| SG035-0004 | 47% | 53% |
| Clinical expert opinion | 25% | 75% |

#### *5.2.3.5 Summary of approach for implementing the intervention and comparators*

To align the model with UK clinical practice and to include the costs and outcomes associated with subsequent SCT requested in the final NICE scope,[8] the model estimates costs and health effects for six cohorts:

- Intervention:

    1. Patients who only receive brentuximab vedotin
    2. Patients who receive brentuximab vedotin followed by ASCT
    3. Patients who receive brentuximab vedotin followed by allo-SCT

- Comparator:

    4. Patients who only receive chemotherapy
    5. Patients who receive chemotherapy followed by ASCT
    6. Patients who receive chemotherapy followed by allo-SCT

In order to estimate costs and health effects for brentuximab vedotin, costs and health effects for cohorts 1, 2 and 3 above are weighted according to the proportion of patients in each cohort. Costs and health effects for chemotherapy are estimated using the same approach for cohorts 4, 5 and 6.

The proportion of patients in each cohort was obtained by multiplying the rates of CR and PR (Table 5.5) for each treatment by the corresponding proportion of patients receiving SCT (Table 5.4). The ratio of ASCT to allo-SCT (Table 5.6) was then applied to derive the proportion of patients receiving each type of SCT. The proportion in the 'no SCT' cohort was therefore the residual for each treatment arm. The corresponding proportions applied in the base case are presented as Table 5.7.

**Table 5.7: Modelled cohorts and proportions assumed to be in each cohort**

| Technology | Model cohort | Name | Description | Base case proportion |
|---|---|---|---|---|
| Brentuximab vedotin | 1 | Brentuximab vedotin, no SCT | Patients who only receive brentuximab vedotin | 71% |
| | 2 | Brentuximab vedotin + ASCT | Patients who receive brentuximab vedotin followed by ASCT | 14% |
| | 3 | Brentuximab vedotin + allo-SCT | Patients who receive brentuximab vedotin followed by allo-SCT | 16% |
| Chemotherapy | 4 | Chemotherapy, no SCT | Patients who only receive chemotherapy | 86% |
| | 5 | Chemotherapy + ASCT | Patients who receive chemotherapy followed by ASCT | 7% |
| | 6 | Chemotherapy + allo-SCT | Patients who receive chemotherapy followed by allo-SCT | 7% |
| SCT, stem cell transplant; ASCT, autologous stem cell transplant; allo-SCT, allogeneic stem cell transplant | | | | |

## 5.3 Clinical parameters and variables

### 5.3.1 Patient characteristics

Patient characteristics are provided in Table 5.8. Body weight and body surface area (BSA) were required to calculate the required drug doses. Mean starting age and gender distribution are required to estimate general population mortality and utility. All data were taken from the ITT population of 58 patients in SG035-0004.

**Table 5.8: Patient characteristics**

| Parameter | Mean | SD | Source |
|---|---|---|---|
| Body weight (kg) | 76.35 | 20.385 | SG035-0004, ITT population |
| BSA ($m^2$) | 1.88 | 0.28 | SG035-0004, ITT population |
| Starting age (years) | 47.70 | 16.85 | SG035-0004, ITT population |
| Male | 57% | 7%* | SG035-0004, ITT population |
| *Standard error, derived from proportion and number of patients; BSA, body surface area | | | |

### 5.3.2 Clinical outcomes

#### *5.3.2.1 Brentuximab vedotin – no SCT*

PFS and OS data for brentuximab vedotin (no SCT) were taken from SG035-0004 for the subset of 41 patients who did not receive SCT. Outcomes data from this trial have just become available for 5 years of follow-up and were presented at the 58th American Society

of Haematology (ASH) Annual Meeting in December 2016; the median follow-up was 71.4 months (range, 0.8 to 82.4). These data were used in this analysis.[6]

#### *5.3.2.2 Chemotherapy – no SCT*

Given SG035-0004 is a single arm study, the data sources for chemotherapy (no SCT) were chosen with the objective of minimising the inherent bias associated with unanchored indirect comparisons. As such, PFS achieved with the most recent cancer-related therapy prior to brentuximab vedotin were used for the subgroup of 39 patients in SG035-0004 whose most recent therapy was for R/R disease. Patients whose most recent therapy was frontline therapy were excluded to reflect the final scope.[8]

This self-control comparison of PFS for brentuximab vedotin (no SCT) and chemotherapy (no SCT) adjusts for differences in baseline characteristics given the internal nature of the data set (i.e. a subset of patients from SG035-0004 inform PFS for both brentuximab vedotin (no SCT) and chemotherapy (no SCT)). However, the following potential sources of bias may remain:

- The 39 patients in the self-control subgroup had received one additional line of treatment when receiving brentuximab vedotin; this is likely to bias in favour of chemotherapy.
- Patients achieving long term remission on chemotherapy may not have been captured; this may bias against chemotherapy.
- By nature of study enrollment, PFS from most recent prior therapy did not include any patients who experience death prior to progression following chemotherapy; this is likely to bias in favour of chemotherapy.

Clinical experts consulted as part of the clinical expert survey (see Section 5.3.8) were unable to state which of the above was likely to have the greatest impact. To explore the impact of uncertainty regarding the existence of bias in the relative effect of brentuximab (no SCT) vs. chemotherapy (no SCT), sensitivity analyses were conducted increasing and decreasing the hazard for PFS for chemotherapy (no SCT) by 25%.

Given self-control comparisons cannot be conducted for OS, OS for chemotherapy (no SCT) were taken from Mak et al., (2013).[12] This study was identified by the systematic review of clinical effectiveness (Section 4.1) and reports outcomes for 153 patients (ALK-positive ALCL, *n* = 11; ALK-negative ALCL, *n* = 24; ALK status unknown, *n* = 1) identified in the British Columbia Cancer Agency Lymphoid Cancer database with nodal PTCLs who were R/R after primary therapy. Of these patients, 89 received systemic chemotherapy. The median follow-up was 4 years. None of the patients received SCT; however, 17 patients were felt to be candidates for SCT hence this dataset contains a mix of patients who were not candidates for SCT (*n* = 136) and those who were but did not ultimately receive SCT.

Mak et al., (2013)[12] was selected in preference to Coiffier et al., (2012),[63] the only other non-transplant study identified by the systematic review, as the latter evaluated romidepsin which is not licensed in the UK and had much shorter follow-up (3 years vs. 18 years in Mak et

al.,).[12] Moreover, the chemotherapy regimens administered in Mak et al.,[12] were reflective of those identified by the clinical experts (Section 5.2.3.3) as part of the clinical expert survey and hence align with UK clinical practice. Of the 89 patients who received systemic chemotherapy, 21% received GDP, 25% received other combination chemotherapy regimen such as cyclophosphamide and/or doxorubicin or ICE, and 54% received single-agent chemotherapy (alkylators, etoposide, or gemcitabine).

Given this represents an unanchored indirect comparison of OS for brentuximab vedotin (no SCT) and chemotherapy (no SCT), the existence and extent of bias in the relative effect of brentuximab vedotin (no SCT) vs. chemotherapy (no SCT) is uncertain. An attempt was made to identify heterogeneity in characteristics for patients in SG035-0004 and Mak et al., (2013)[12] which may induce bias; however this was limited by inconsistent reporting of characteristics. Patient characteristics which were reported consistently across both studies were compared and are presented in Table 5.9.

The characteristics presented for SG035-0004 are for the ITT population; these are assumed to be reflective of the no SCT subset which informs the OS curve for brentuximab (no SCT). The characteristics presented for Mak et al., (2013)[12] are for the 89 patients who received conventional chemotherapy in the study; these are assumed to be reflective of the PTCL patients with PS<2 (n=47) and ALCL patient subsets (n=17) which inform OS for chemotherapy (no SCT).

**Table 5.9: Characteristics for patients in SG035-0004 and Mak et al., (2013)**

| Characteristic | Mak et al., (2013)[12] | SG035-0004 [2] |
|---|---|---|
| N | 89 | 58 |
| Age (median, years) | 65 | 52 |
| Age (range, years) | 29-86 | 14-76 |
| Male | 56% | 57% |
| Stage III-IV disease | 89% | 50% |
| Extranodal sites<br>Skin any<br>Skin only<br>Bone marrow<br>GI<br>Liver | <br>19%<br>5%<br>16%<br>10%<br>4.5% | <br>26%<br>NR<br>14%<br>NR<br>NR |
| Performance status ≥2 | 43% | 2% |
| Time elapsed from original pathological diagnosis, months<br><br><=6<br>6-12<br>12-24<br>>24 | <br><br><br>38%<br>28%<br>18%<br>16% | Median: 16.8 months; range: 3.7-186.5<br><br>Mean: 34.74 months; SD: 41.70 |
| Response to primary therapy<br>CR<br>PR/SD<br>PD | <br>51%<br>26%<br>24% | <br>48%<br>29%<br>16% |

Patients in Mak et al, (2013)[12] and SG035-0004 [2] were similar with respect to response to primary therapy (51% vs 48% achieved a CR with primary therapy in both studies respectively). Moreover, a similar proportion of patients in Mak et al., (2013)[12] had bone marrow involvement (16% vs. 14%) compared to SG035-0004.[2]

Heterogeneity is evident for the following characteristics:

- Age
- Stage III-IV disease
- Performance status

The median age of patients in Mak et al., (2013)[12] was 65 years (range: 29-86). In contrast, the median age of patients in SG035-0004 was 52 (range: 14-76),[2] which may bias OS in favour of brentuximab vedotin. Mak et al., (2013)[12] included a higher proportion of patients with Stage III-IV disease (89% vs 50%) compared to SG035-0004,[2] which may also bias OS in favour of brentuximab vedotin.

Moreover, a higher proportion of patients in Mak et al., (2013)[12] had a performance status ≥ 2 compared to patients in SG035-0004 [2] (43% vs 2%). However, the base case analysis uses data from Mak et al. (2013) for the subgroup of PTCL patients with performance status

<2 (n = 47) for OS for conventional chemotherapy (no SCT). As such, any bias induced through differences in performance status has been accounted for.

In an attempt to explore the impact of potential bias in the OS benefit for brentuximab vedotin (no SCT) compared to conventional chemotherapy (no SCT) resulting from both observable heterogeneity (and unobservable heterogeneity), sensitivity analyses were conducted increasing and decreasing the OS hazard by 25% for conventional chemotherapy (no SCT).

#### *5.3.2.3 ASCT*

PFS and OS for ASCT were taken from Smith et al., (2013).[13] This study was identified by the systematic literature review described in Section 4.1 and reports outcomes for 241 patients (ALCL, *n* = 112; PTCL-NOS, *n* = 102; AITL, *n* = 27) reported to the Centre for International Blood and Marrow Transplant Research (CIBMTR) age ≤60 years, of which 115 underwent ASCT between 1996 and 2006.

After excluding studies specifically in paediatric or adolescent patients, the remaining 4 ASCT studies identified by the systematic review (Jagadessh et al., (2014),[64] Nademanee et al., (2011),[65] Smith et al., (2007)[66] and Smith et al., (2013))[13] were compared based on the following criteria:

- Comparability of study population with SG035-0004; to minimise heterogeneity with a particular focus on characteristics which define the trial eligibility criteria.
- Reporting of Kaplan-Meier curves for PFS and OS; to enable individual patient data to be re-estimated and a formal survival analysis to be conducted for both endpoints.
- Patient numbers and follow-up; larger studies with longer follow-up will reduce uncertainty in long term extrapolations.

Jagadessh et al., (2014)[64] and Smith et al. (2007)[66] did not report Kaplan-Meier curves for PFS hence were not considered further. Although Nademanee et al., (2011)[65] provided longer maximum follow-up (18 years vs. 4 years), Smith et al., (2013)[13] was preferred as this was larger (*n* = 115 vs. *n* = 67) and reported Kaplan-Meier curves excluding patients who were transplanted in the frontline setting. Moreover, the Kaplan-Meier curves reported by Smith et al.,[13] had plateaued at approximately 3 years reflecting the cure fraction, hence the longer follow-up reported by Nademanee et al.,[65] was not considered to be important for the long term extrapolations.

Smith et al., (2013)[13] excluded patients who had previously received SCT, whereas 26% of patients in the ITT population of SG035-0004 had received a prior ASCT. However, clinical expert opinion was that outcomes in the R/R setting are independent of prior cancer-related therapy; hence this is not expected to induce bias.

#### *5.3.2.4 Allo-SCT*

PFS and OS for allo-SCT were also taken from Smith et al., (2013),[13] specifically from the remaining 126 patients who underwent allo-SCT.

This and the 2 other studies of allo-SCT in adult patients identified by the systematic review (Aoki et al., (2014)[67] and Le Gouill et al., (2008))[31] were compared using the same process as described for ASCT. Aoki et al., (2014)[67] did not report Kaplan-Meier curves for PFS, or a similar endpoint, hence was not considered further. Similarly, Le Gouill et al., (2008)[31] reported event-free survival (EFS) rather than PFS. In addition, Smith et al., (2013)[13] was larger (*n* = 126 vs. *n* = 77) and reported Kaplan-Meier curves excluding patients who were transplanted in the frontline setting.

### 5.3.3 Summary of clinical effectiveness data sources

A summary of these clinical effectiveness data sources is provided in Table 5.10.

**Table 5.10: Summary of clinical effectiveness data sources used in base case**

| Treatment | Endpoint data source | | Model cohort(s)* |
|---|---|---|---|
| | PFS | OS | |
| Brentuximab vedotin, no SCT | SG035-0004; patients who didn't receive subsequent SCT (*n*=41) | SG035-0004; patients who didn't receive subsequent SCT (*n*=41) | 1 |
| Chemotherapy, no SCT | SG035-0004; self-control patients (*n*=39) | Mak et al., 2013;[12] PTCL patients with PS<2 (*n*=47) | 4 |
| ASCT | Smith et al., 2013;[13] ASCT patients (*n*=115) | Smith et al., 2013;[13] ASCT patients (*n*=115) | 2,3,5,6 |
| Allo-SCT | Smith et al., 2013; [13] allo-SCT patients (*n*=126) | Smith et al., 2013; [13] allo-SCT patients (*n*=126) | 2,3,5,6 |
| PS, performance status; ASCT, autologous stem cell transplant; allo-SCT, allogeneic stem cell transplant; * | | | |

Analyses of time-to-event data from SG035-0004 were conducted using the patient-level data from this study. Analyses of time-to-event data from Mak et al., (2013)[12] and Smith et al., (2013)[13] were conducted using individual patient data which were estimated using the following process:

- The published Kaplan-Meier curves were digitised using TechDig© software to estimate the survival probability at a range of time points, generating a dataset of coordinates for time t and corresponding survival proportion $S(t)$
- An algorithm published by Guyot et al., (2012)[68] was used to estimate the individual patient data, generating a time-to-event for each patient based on the total number at risk at $t = 0$.

### 5.3.4 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)?

The following sections describe the parametric survival analysis of the PFS and OS data listed in Table 5.10 above.

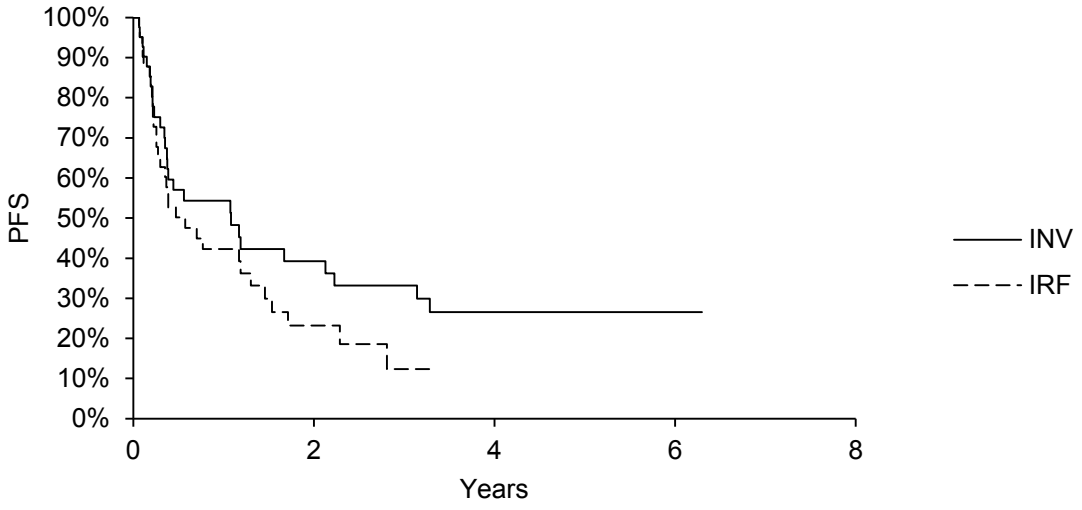
#### *5.3.4.1 Progression-free survival*

***Brentuximab vedotin (no SCT): PFS per INV***

Two assessments of disease progression were conducted in SG035-0004; per independent review facility (IRF) and per investigator (INV). The INV data were used in the base case as this provided longer follow-up (maximum follow-up per INV was 76 months vs. 40 months per IRF) (Figure 5.3) and was considered more reflective of the assessments used in the self-control data. However, the IRF data are included as a scenario analysis to reflect the assessment used for the primary endpoint in SG035-0004.

Pro et al.[6] report that a subset of patients in SG035-0004 may have been cured with single-agent brentuximab vedotin. This is observable in the Kaplan-Meier curve for PFS per INV for the subset of 41 patients who did not receive SCT which plateaus after approximately 3 years of follow-up, reflecting that the mortality rate is equal to the expected rate in the general population.[69] This trend was not observed for PFS per IRF however this is likely due to insufficient follow-up.

**Figure 5.3: Kaplan-Meier curves for brentuximab vedotin (no SCT) PFS**




As such, these data were modelled using a specific type of parametric survival model referred to as a 'cure model'. Lambert [69] describes a particular type of cure model that incorporates background mortality for each individual and thus is suited to endpoints such as PFS where some patients will die of other causes. Mixture cure models assume a proportion of patients are cured, and not at risk of the event, and the residual uncured proportion are at risk of the event and have a survival function which tends to zero. This assumption does not

invalidate use of this model since it may fit the data well and is a useful mathematical function with an asymptote at the cure fraction.[69]

These models were fitted in SAS using the PSPMCM macro described in Corbière 2007.[70] This mixture cure model can be described as follows:

$$S(t) = S^*(t)\left[\pi\left(S(t|u)\right) + 1 - \pi\right]$$

where $t$ is time, $S^*(t)$ is expected survival in the general population based on national mortality statistics, $S(t|u)$ is the survival function for uncured patients and $\pi$ is the probability of not being cured.

The process for selecting the most appropriate parametric model was based on an assessment of the within-trial and extrapolation predictions. It is essential to consider both of these criteria as any given which are clinically implausible. It is equally likely that a parametric model may provide accurate long -term estimates for an endpoint but poorly fit the within-trial data. In this case, the extrapolation prediction was assessed based on the plausibility of the cure fraction. The methods used for assessing each distribution are presented in Table 5.11 and reflect those detailed in the NICE DSU Technical Support Document 14.[71]

**Table 5.11: Methods for assessing the suitability of parametric survival models**

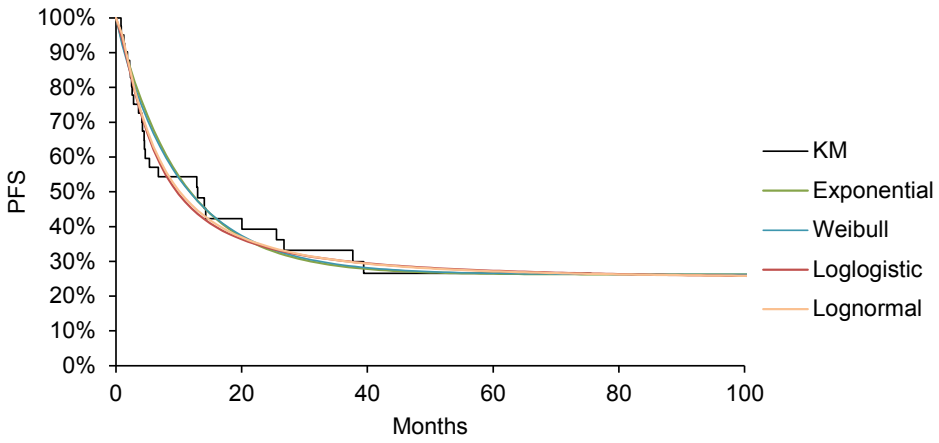
| Criteria | Method | Description |
|---|---|---|
| Within-trial period | AIC & BIC statistics | Assess the relative fit of parametric models whilst accounting for the number of parameters |
| | Cox-Snell residuals | Assess how closely a parametric function follows the Kaplan-Meier function |
| | Visual inspection | Assess how closely a parametric function follows the Kaplan-Meier function and the clinical plausibility of the prediction in relation to other endpoints |
| Extrapolation period | Visual inspection | Assess the clinical plausibility of the cure fraction or the point at which 99%/100% of patients have experienced the event |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | |

An overlay of the Kaplan-Meier curve for PFS per INV for the subset of 41 patients who did not receive SCT and the parametric curves demonstrating within-trial fit are presented in Figure 5.4. The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.12 and the Cox-Snell Residual plots in Appendix 15.

**Table 5.12: Cure, AIC and BIC statistics for brentuximab vedotin (no SCT) PFS per INV**

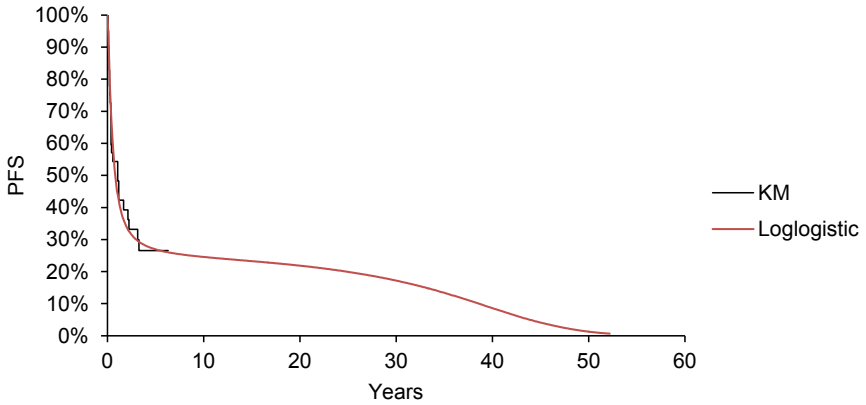
| | Exponential | Weibull | Lognormal | Log-logistic |
|---|---|---|---|---|
| Cure fraction | 26% | 26% | 25% | 24% |
| AIC | 228.1 | 230.0 | 225.9 | 137.9 |
| BIC | 235.0 | 238.6 | 234.5 | 146.5 |
| AIC rank | 3 | 4 | 2 | 1 |
| BIC rank | 3 | 4 | 2 | 1 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | | |

**Figure 5.4: Parametric models for brentuximab vedotin (no SCT) PFS per INV**




There was little difference between the candidate models in terms of within-trial fit and cure fractions. The log-logistic and lognormal models provided the best fit in terms of Cox-Snell residuals. The log-logistic model provided a significantly better fit compared to the other models based on AIC and BIC hence was selected for the base case analysis; the corresponding lifetime extrapolations are presented in Figure 5.5. The exponential model is used in the sensitivity analyses to explore an alternative estimate of the cure fraction.

**Figure 5.5: Lifetime extrapolation of brentuximab vedotin (no SCT) PFS per INV**



In addition, a standard parametric model was also used to explore the uncertainty in the long term extrapolation. The gamma distribution was selected as the best fitting distribution among the range of candidate models; these were fitted in SAS using the LIFEREG procedure. A comparison of the within-trial and long term extrapolations of this model vs. the log-logistic cure model is presented in Figure 5.6 and Figure 5.7, respectively. These demonstrate how the standard model does not capture the plateau in the KM curve as accurately as the cure model, hence why the latter model was used in the base.

**Figure 5.6: Within-trial comparison of cure (log-logistic) and standard (gamma) model for brentuximab vedotin (no SCT) PFS per INV**

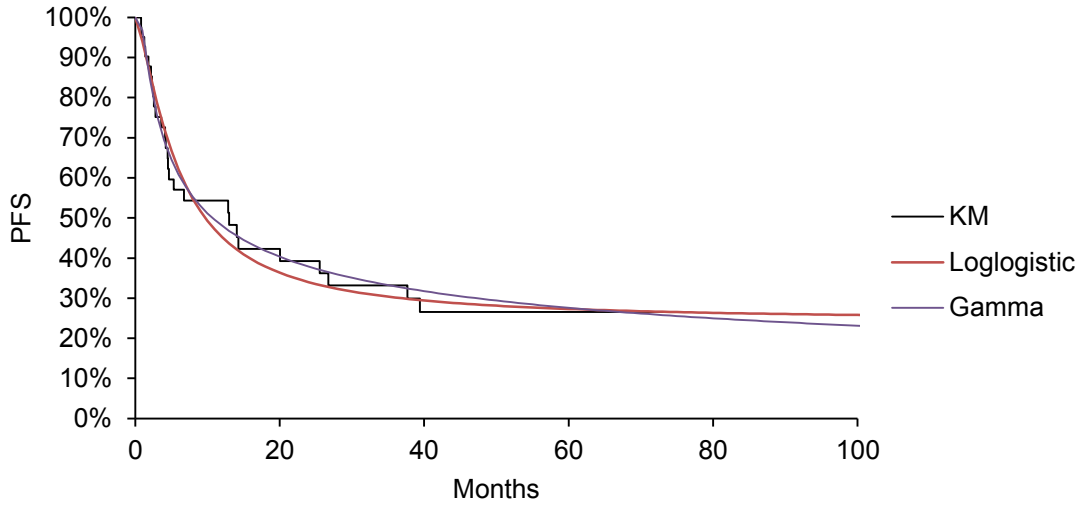
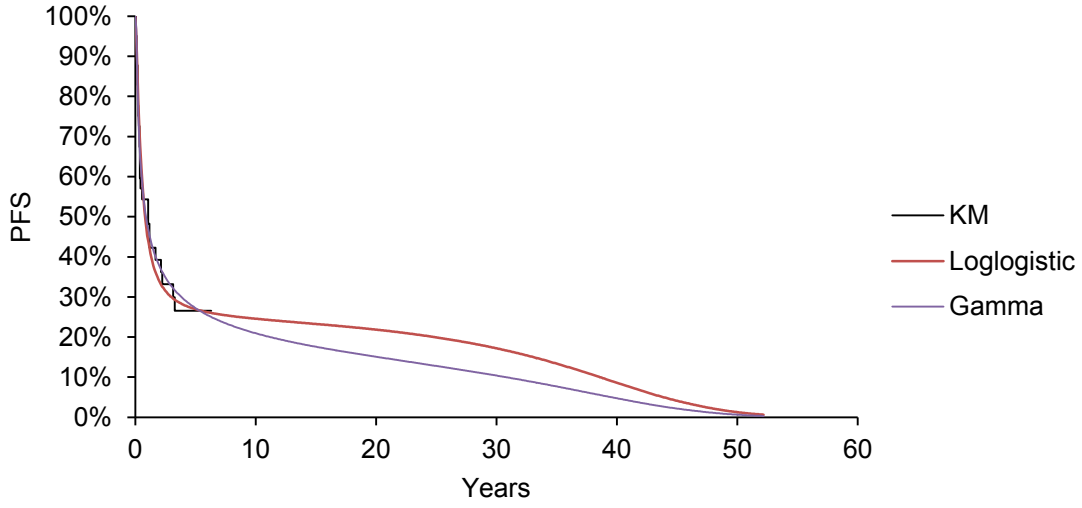



**Figure 5.7: Long term extrapolation comparison of cure (log-logistic) and standard (gamma) model for brentuximab vedotin (no SCT) PFS per INV**



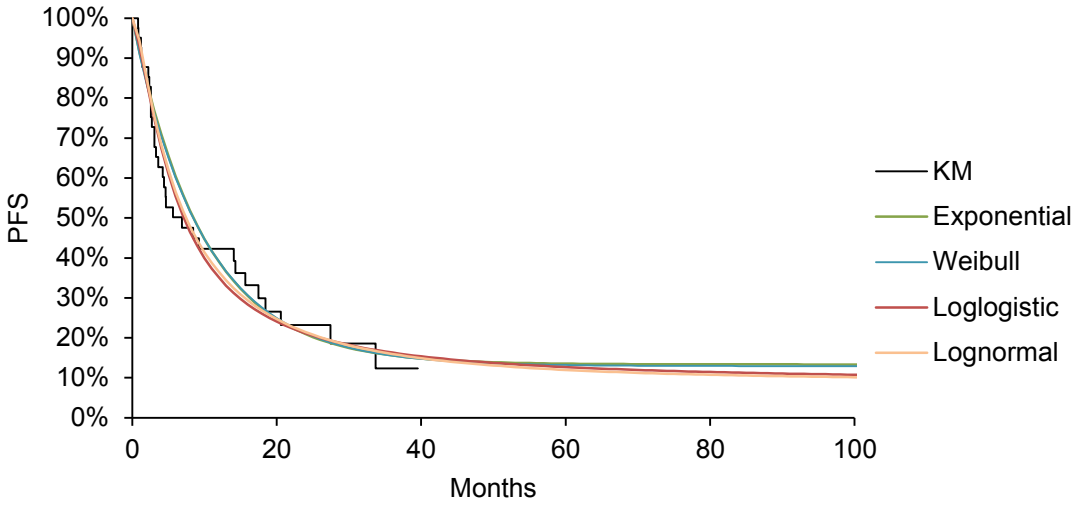
### *Brentuximab vedotin (no SCT): PFS per IRF*

The modelling approach and the process for selecting the most appropriate parametric model for this endpoint replicated that of PFS per INV. An overlay of the Kaplan-Meier curve for PFS per IRF for the subset of 41 patients who did not receive SCT and the parametric curves demonstrating within-trial fit are presented in Figure 5.8. The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.13 and the Cox-Snell Residual plots in Appendix 15.

**Table 5.13: Cure, AIC and BIC statistics for brentuximab vedotin (no SCT) PFS per IRF**

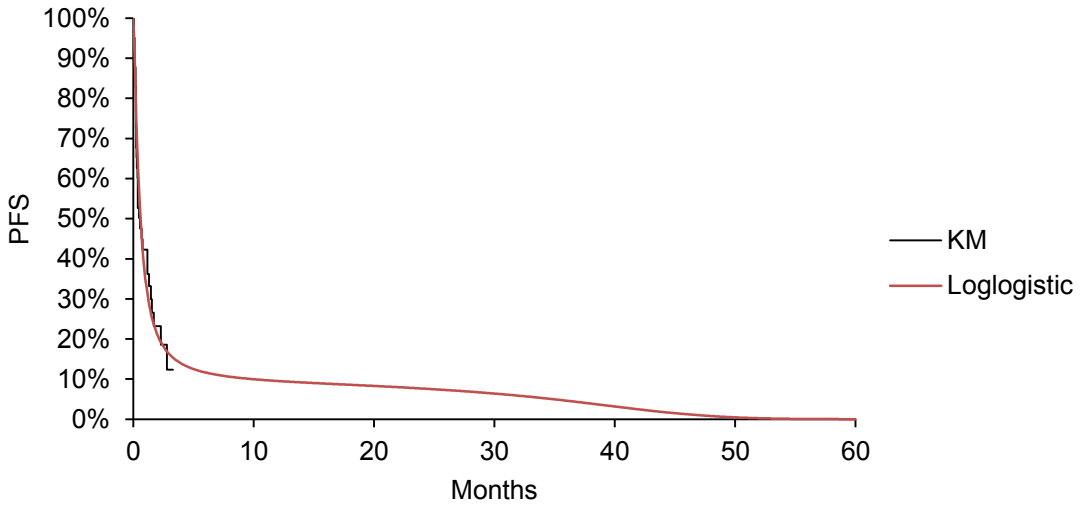
| | Exponential | Weibull | Lognormal | Log-logistic |
|---|---|---|---|---|
| Cure fraction | 13% | 13% | 9% | 9% |
| AIC | 233.4 | 235.4 | 230.3 | 135.6 |
| BIC | 240.2 | 243.9 | 238.8 | 144.2 |
| AIC rank | 3 | 4 | 2 | 1 |
| BIC rank | 3 | 4 | 2 | 1 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | | |

**Figure 5.8: Parametric models for brentuximab vedotin (no SCT) PFS per IRF**




As with PFS per INV, there was little difference between the candidate models in terms of within-trial fit, however the cure fraction was 4% lower for the lognormal and log-logistic models. The log-logistic model provided a significantly better fit compared to the other models based on AIC and BIC hence was selected for the base case analysis; the corresponding lifetime extrapolations are presented in Figure 5.9. The exponential model is used in the sensitivity analyses to explore an alternative estimate of the cure fraction.

**Figure 5.9: Lifetime extrapolation of brentuximab vedotin (no SCT) PFS per IRF**




***Chemotherapy (no SCT)***

This endpoint was modelled using PFS achieved on the most recent cancer-related systemic therapy (prior to brentuximab vedotin) for the subset of 39 patients in SG035-0004 who received this therapy in the R/R setting. These data are complete given it was necessary for patients to have failed this treatment in order for them to be recruited in SG035-0004, however they were still modelled parametrically to enable the uncertainty to be captured more accurately than when using the Kaplan-Meier data directly.

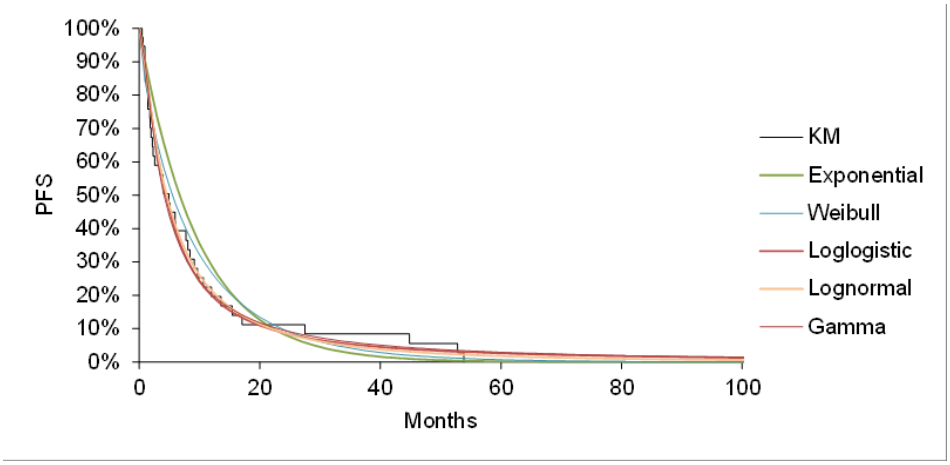
Standard parametric models, rather than cure models, were used for these data given conventional chemotherapy approaches are not curative.[46] Exponential, Weibull, lognormal, log-logistic and gamma models were fitted in SAS using the LIFEREG procedure. The process for selecting the most appropriate model replicated that for brentuximab vedotin, aside from long term extrapolations, which were assessed based on the clinical plausibility of the time at which 99% of patients had experienced the event rather than the cure fraction.

An overlay of the Kaplan-Meier and the parametric curves to demonstrate within-trial fit are presented in Figure 10. The corresponding AIC and BIC statistics and 1% PFS estimates are presented in Table 5.14 and the Cox-Snell Residual plots in Appendix 15.

**Table 5.14: AIC and BIC statistics & 99% PFS estimates for chemotherapy (no SCT) PFS**

| | Exponential | Weibull | Lognormal | Log-logistic | Gamma |
|---|---|---|---|---|---|
| 99% PFS (years) | 3.7 | 4.5 | 6.6 | 10.3 | 10.5 |
| AIC | 129.892 | 128.964 | 122.257 | 124.414 | 123.526 |
| BIC | 131.556 | 132.291 | 125.584 | 127.742 | 128.517 |
| AIC rank | 5 | 4 | 1 | 3 | 2 |
| BIC rank | 4 | 5 | 1 | 2 | 3 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | | | |

**Figure 5.10: Parametric models for chemotherapy (no SCT) PFS**




Source: Mak et al., (2013)[12]

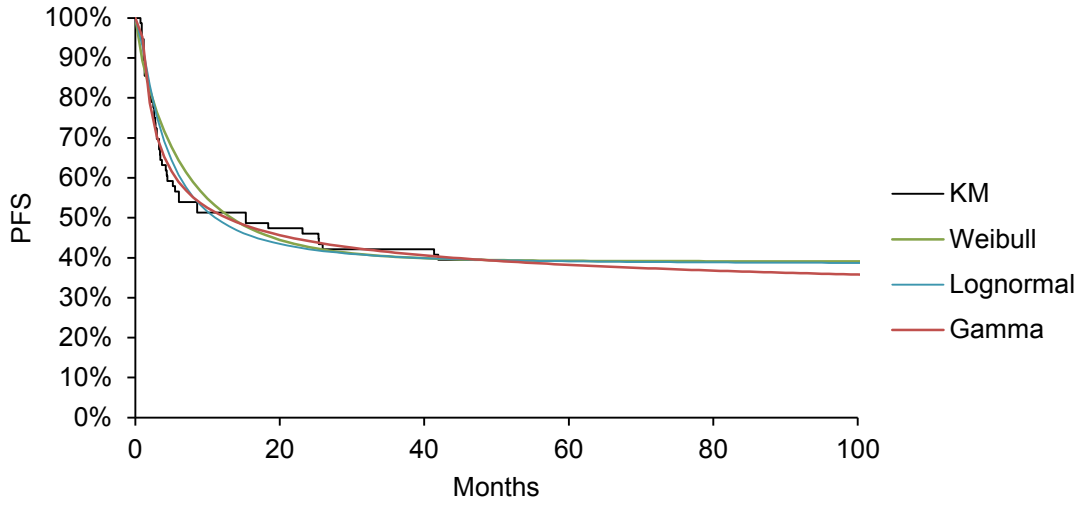
### *ASCT*

This endpoint was modelled using PFS for 115 patients who underwent ASCT reported by Smith et al.,[13] The modelling approach and the process for selecting the most appropriate parametric model replicated that of PFS for brentuximab vedotin (no SCT). An overlay of the Kaplan-Meier curve for PFS and the parametric cure models demonstrating within-trial fit are presented in Figure 5.11. The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.15. Cox-Snell residual plots could not be generated in Stata.

**Table 5.15: Cure, AIC and BIC statistics for PFS for ASCT**

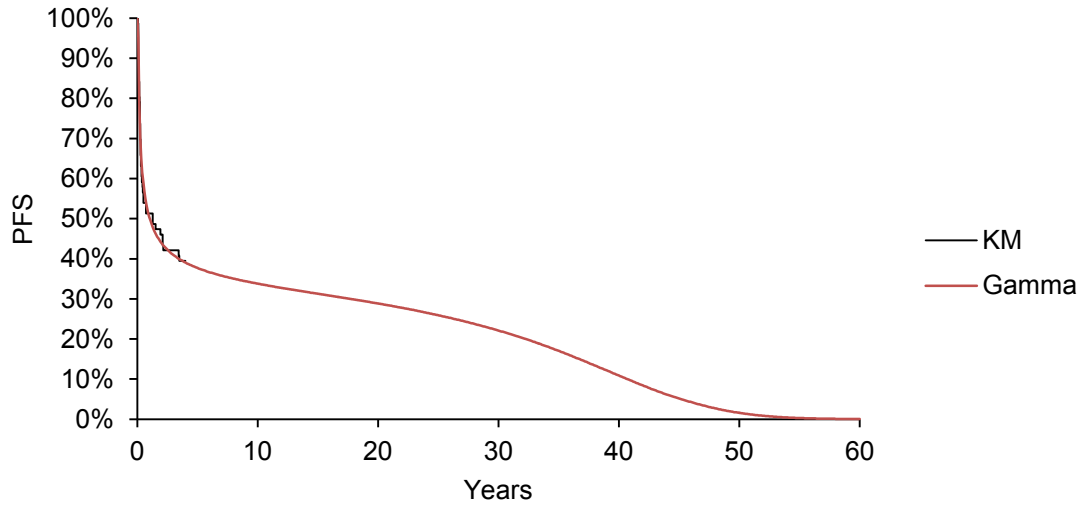
| | Weibull | Lognormal | Gamma |
|---|---|---|---|
| Cure fraction | 39% | 39% | 26% |
| AIC | 382.18 | 368.91 | 358.50 |
| BIC | 389.17 | 375.90 | 367.82 |
| AIC rank | 3 | 2 | 1 |
| BIC rank | 3 | 2 | 1 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | |

**Figure 5.11: Parametric models for ASCT PFS**




The lognormal and gamma models provided the best within-trial fit based on visual inspection; the gamma model was selected for the base case based on AIC and BIC. The corresponding lifetime extrapolation is presented in Figure 5.12. Notably the cure fraction for the Weibull and lognormal models were 13% higher than the gamma model; the lognormal model was therefore used in the sensitivity analyses to explore an alternative estimate of the cure fraction.

**Figure 5.12: Lifetime extrapolation of PFS for ASCT**




Given PFS was measured from the date of transplantation, a zero-risk period equal to the time from initiation of salvage therapy to ASCT was applied in the model. This was based on the 8 patients who received ASCT in SG035-0004 for whom the median time-to-transplant was 29.7 weeks.

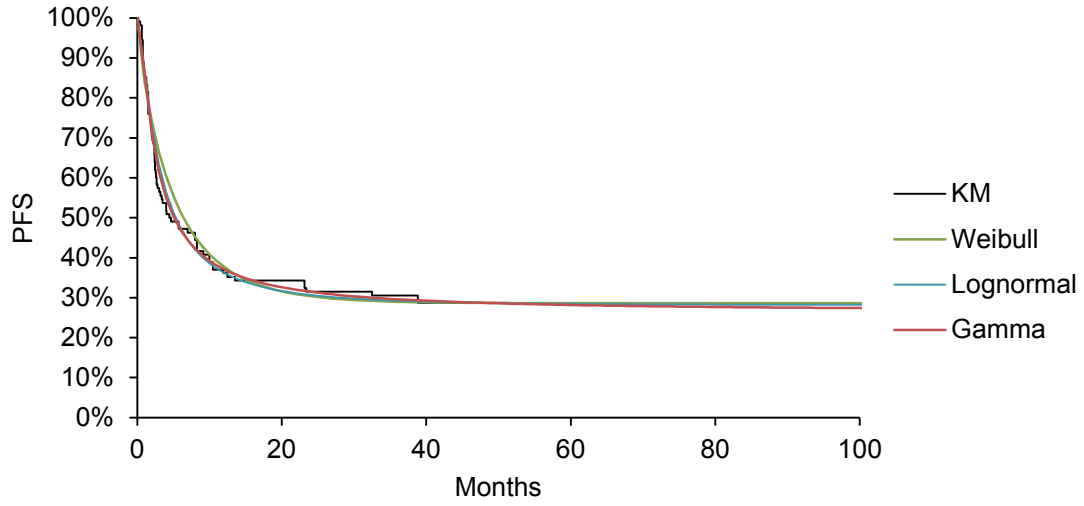
### *Allo-SCT*

This endpoint was modelled using PFS for the 126 patients who underwent allo-SCT reported by Smith et al.,[13] The modelling approach and the process for selecting the most appropriate parametric model replicated that of ASCT. An overlay of the Kaplan-Meier curve for PFS and the parametric cure models demonstrating within-trial fit are presented in Figure 5.13. The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.16. Cox-Snell residual plots could not be generated in Stata.

**Table 5.16: Cure, AIC and BIC statistics for PFS for allo-SCT**

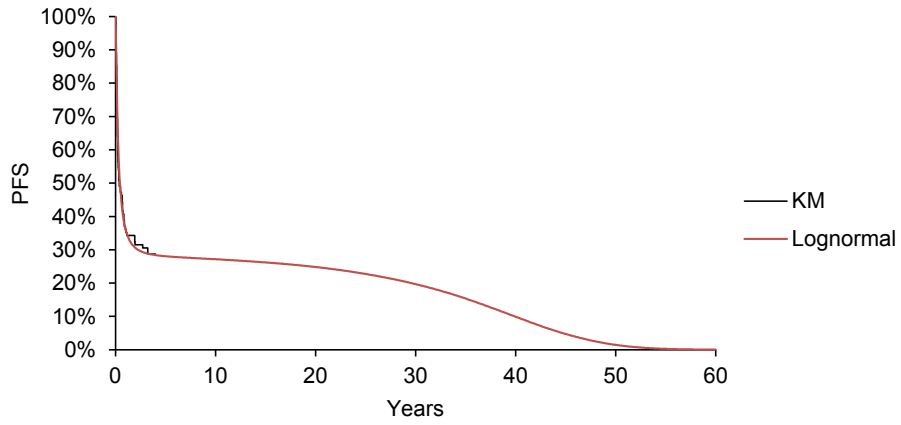
| | Weibull | Lognormal | Gamma |
|---|---|---|---|
| Cure fraction | 29% | 28% | 27% |
| AIC | 551.20 | 533.38 | 539.60 |
| BIC | 559.24 | 541.43 | 550.33 |
| AIC rank | 3 | 1 | 2 |
| BIC rank | 3 | 1 | 2 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | |

**Figure 5.13: Parametric models for PFS for allo-SCT**




There was little difference between the candidate models in terms of within-trial fit based on visual inspection or in terms of the cure fractions. The lognormal model provided the best fit based on AIC and BIC hence was selected for the base case analysis; the corresponding lifetime extrapolations are presented in Figure 5.14. Figure 5.14The gamma model is used as the second-best fitting model in the sensitivity analyses.

**Figure 5.14: Lifetime extrapolation of PFS for allo-SCT**



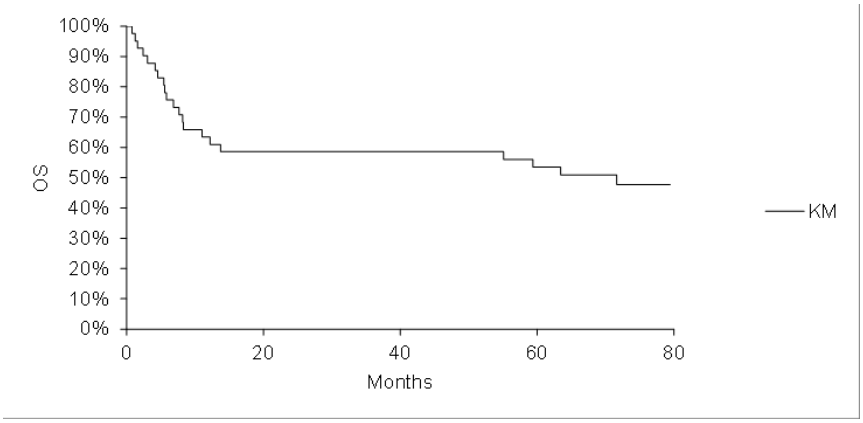

PFS for allo-SCT was also measured from the date of transplantation hence a zero-risk period equal to the time from initiation of salvage therapy to allo-SCT was applied in the model. This was based on the 9 patients who received allo-SCT in SG035-0004 whose median time-to-transplant was 47.9 weeks.

### *5.3.4.2 Overall survival*

#### *Brentuximab (no SCT)*

This was modelled using OS data from SG035-0004 for the subset of 41 patients who did not receive SCT. A plateau in the corresponding Kaplan-Meier curve is observed after approximately 1.3 years (Figure 5.15), reflecting that the mortality rate is equal to the expected mortality rate in the general population.[69] As such, cure models were used for modelling these data hence the modelling approach and the process for selecting the most appropriate parametric model for this endpoint replicated that of PFS for brentuximab.

**Figure 5.15: Kaplan-Meier curve for brentuximab vedotin (no SCT) OS**

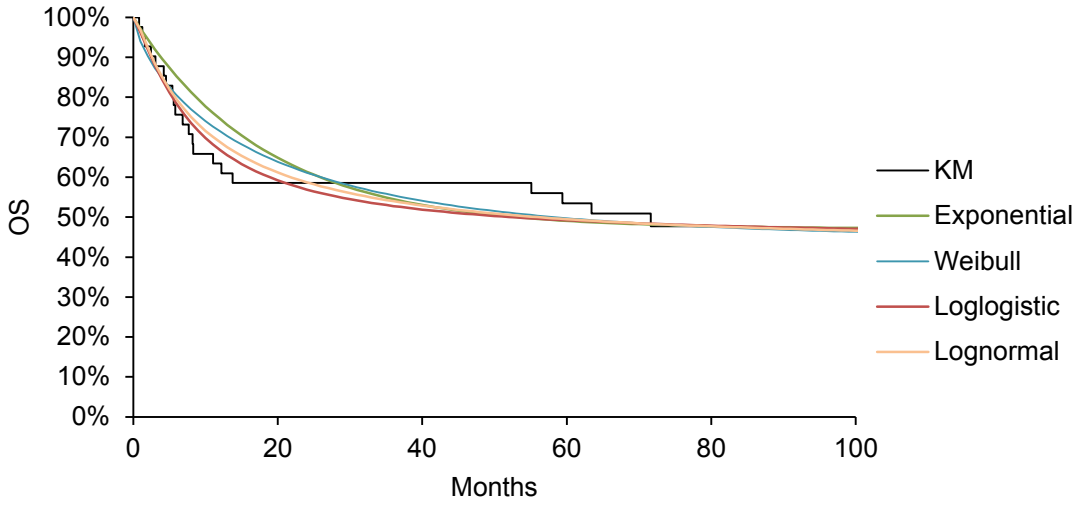



An overlay of the Kaplan-Meier curve for OS and the parametric cure models demonstrating within-trial fit are presented in Figure 5.17. The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.17 and Cox-Snell Residual plots in Appendix 15.

**Table 5.17: Cure, AIC and BIC statistics for brentuximab vedotin (no SCT) OS**

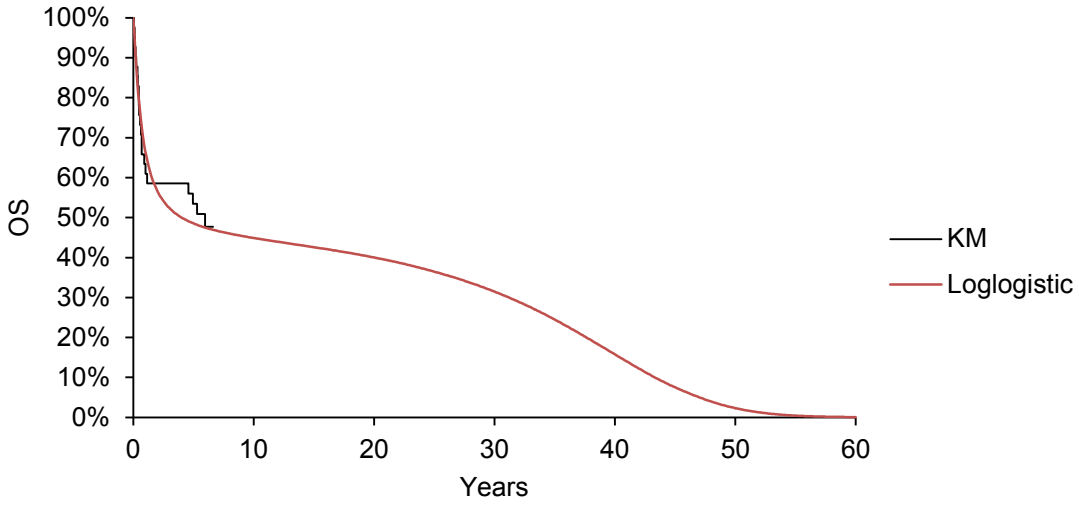
| | Exponential | Weibull | Lognormal | Log-logistic |
|---|---|---|---|---|
| Cure fraction | 47% | 45% | 44% | 44% |
| AIC | 223.9 | 222.9 | 218.4 | 133.4 |
| BIC | 230.8 | 231.5 | 226.9 | 142.0 |
| AIC rank | 4 | 3 | 2 | 1 |
| BIC rank | 3 | 4 | 2 | 1 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | | |

**Figure 5.16: Parametric models for brentuximab vedotin (no SCT) OS**




All of the candidate models appear to overestimate OS between approximately 10 and 30 months, and underestimate OS thereafter until approximately 80 months. However, the lognormal and log-logistic models provided the best within-trial fit among the candidate models based visual inspection and had the same cure fraction. The log-logistic model provided a significantly better fit based on AIC and BIC hence was selected for the base case analysis; the corresponding lifetime extrapolations are presented in Figure 5.18.

**Figure 5.17: Lifetime extrapolation of brentuximab vedotin (no SCT) OS**




To address the potential overestimation of OS between approximately 10 and 30 months and underestimation thereafter until approximately 80 months, the Kaplan-Meier data are

used directly in the sensitivity analyses. These are extrapolated using the same general population hazard used for the cure model.

To inform a scenario analysis in which both PFS and OS for brentuximab are modelled using standard rather than cure models, standard models were also fitted in SAS using the LIFEREG procedure. The gamma distribution was selected as the best fitting distribution among the range of candidate models. A comparison of the within-trial and long term extrapolations of this model vs. the log-logistic cure model is presented in Figure 5.19 and Figure 5.20 respectively. These demonstrate how the standard model does not capture the plateau in the KM curve as accurately as the cure model, hence why the latter model was used in the base case analysis.

**Figure 5.18: Within-trial comparison of cure (log-logistic) and standard (gamma) model for brentuximab vedotin (no SCT) OS**

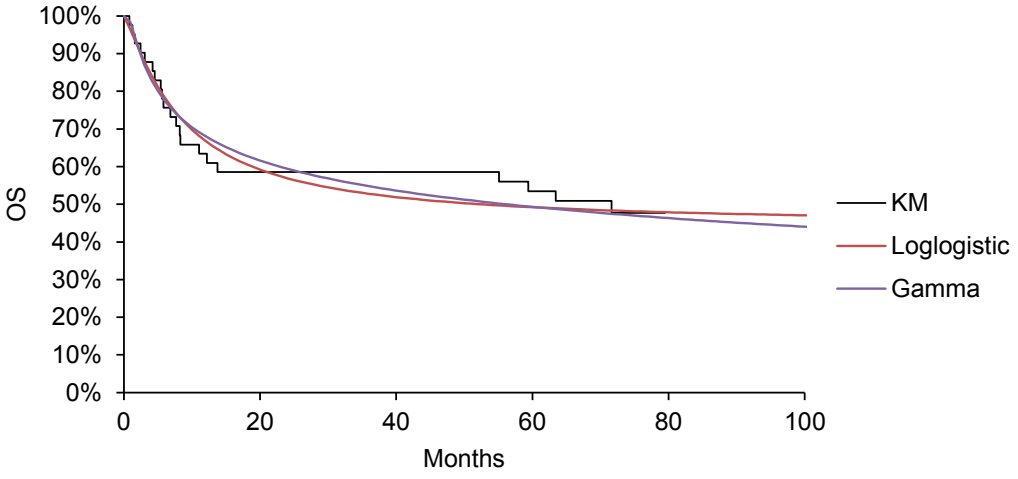
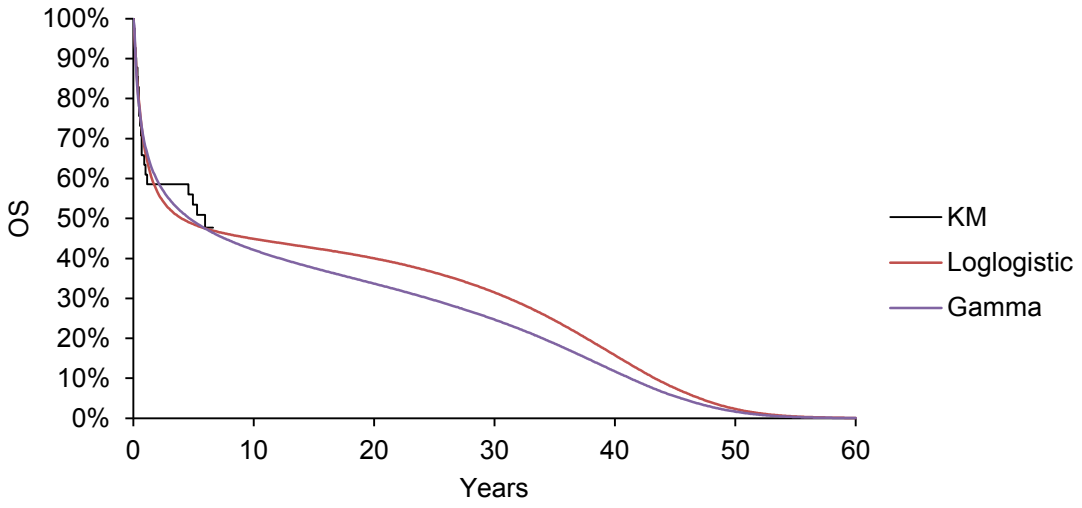


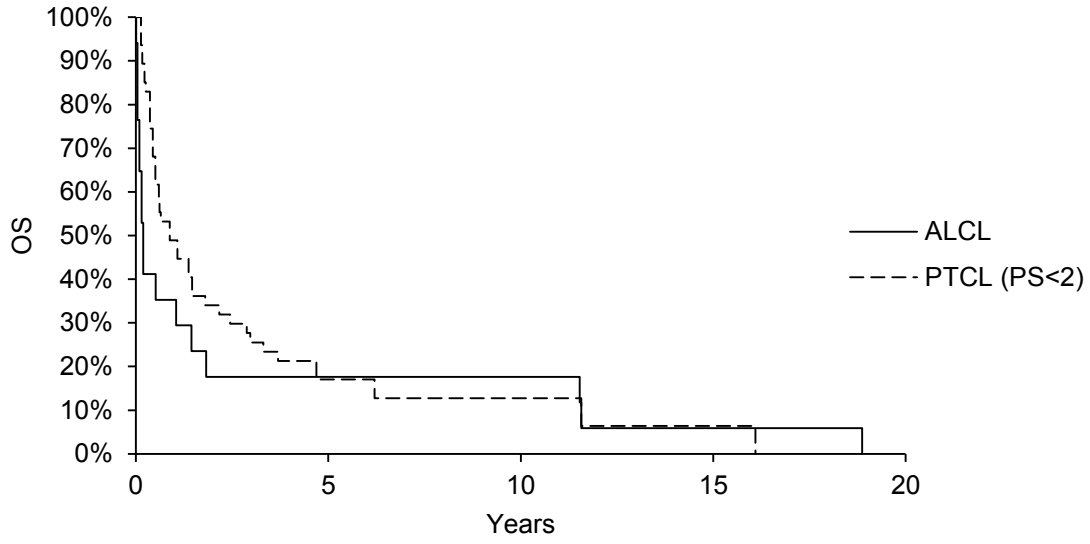
**Figure 5.19: Long term extrapolation comparison of cure (log logistic) and standard (Gamma) model for brentuximab vedotin (no SCT) OS**




## Chemotherapy (no SCT)

This was modelled using data from Mak et al. (2013).[12] As for PFS, Kaplan-Meier curves for OS were available for two subgroups of patients treated with chemotherapy; PTCL patients with performance status <2 (*n* = 47) and ALCL patients (*n* = 17) (Figure 5.22).

**Figure 5.20: Kaplan-Meier curves for chemotherapy OS from Mak et al., (2013)**




Source: Mak et al., (2013)[12]

Clinical expert opinion was that PTCL subtype was more prognostic of OS than performance status hence the ALCL data were preferred for the base case analysis. However, a comparison of these data with the base case PFS curve showed that PFS > OS until 5.5 months, which can occur when modelling PFS and OS using different data sources. This issue was not observed when using the PTCL data hence this was used in the base case analysis. The ALCL data were included to inform a scenario analysis in which both PFS and OS are modelled using the ALCL Kaplan-Meier data.

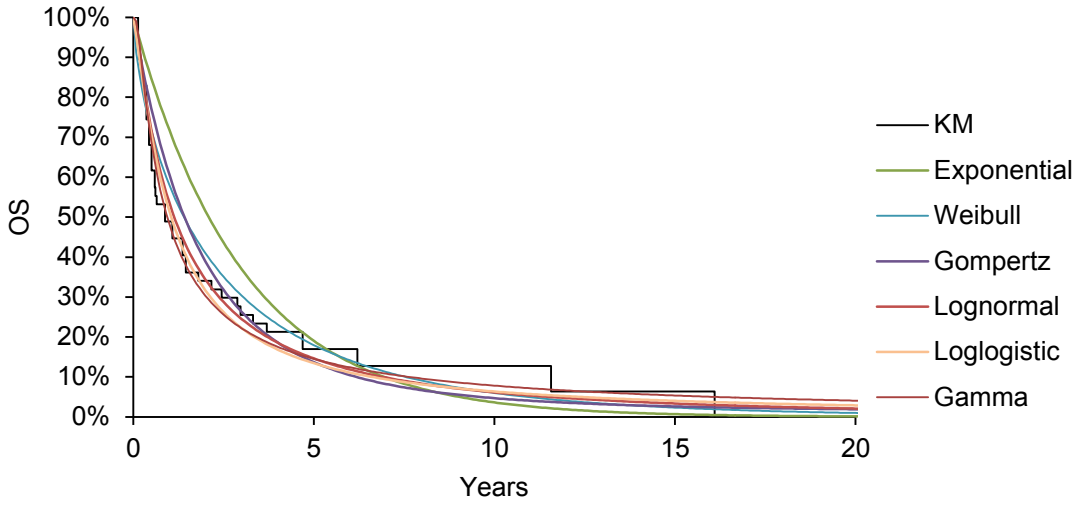
Standard parametric models, rather than cure models, were used for these data given conventional chemotherapy approaches are not curative.[46] These models were fitted in Stata using the streg [72]command. The modelling approach and process for selecting the most appropriate model was therefore equivalent to PFS for chemotherapy (no SCT).

An overlay of the Kaplan-Meier and the parametric curves to demonstrate within-trial fit are presented in **Error! Reference source not found.**. The corresponding AIC and BIC tatistics and 1% PFS estimates are presented in Table 5.17 and the Cox-Snell Residual plots in  Appendix 15.

**Table 5.18: AIC and BIC statistics & 99% PFS estimates for chemotherapy (no SCT) PFS**

| | Exponential | Weibull | Gompertz | Lognormal | Log-logistic | Gamma |
|---|---|---|---|---|---|---|
| 99% PFS (years) | 13.8 | 19.9 | NR | 30.1 | 49.3 | NR |
| AIC | 187.88 | 178.41 | 180.32 | 169.66 | 172.79 | 169.53 |
| BIC | 189.73 | 182.11 | 184.02 | 173.36 | 176.49 | 175.09 |
| AIC rank | 6 | 4 | 5 | 2 | 3 | 1 |
| BIC rank | 6 | 4 | 5 | 1 | 3 | 2 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reached at 60 years | | | | | | |

**Figure 5.21: Parametric models for chemotherapy (no SCT) OS**




The lognormal, log-logistic and gamma models provided the best fit based on visual inspection, Cox-Snell residual plots and AIC and BIC statistics; of which the lognormal model provided the best fit based on BIC. Although these outcomes would not be realised due to the competing risk of general population mortality, the gamma model had not reached 1% by 60 years hence were not considered. As such, the lognormal model was selected.

Notably, the lognormal model predicts all patients will have died by approximately 42.9 years whereas the corresponding Kaplan-Meier estimate was 16 years. This was not considered to invalidate use of the lognormal model given the uncertainty in the tail of Kaplan-Meier curve however a sensitivity analysis was conducted modelling the Kaplan-Meier data directly to explore the impact of the long tail of the parametric extrapolation.

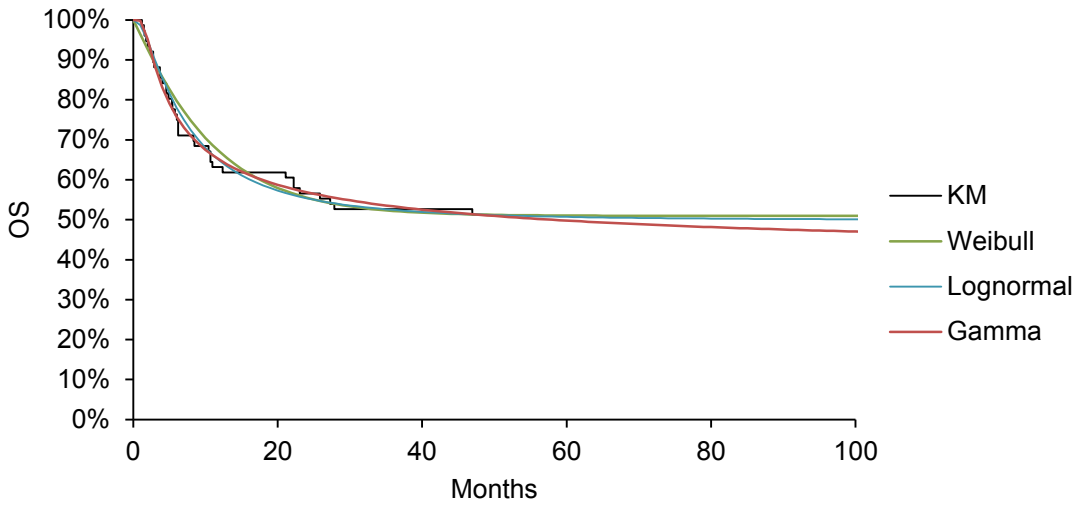
### ASCT

This endpoint was modelled using OS for the same 115 patients reported by Smith et al. which informed PFS for ASCT. An overlay of the Kaplan-Meier curve for OS and the parametric cure models demonstrating within-trial fit are presented in **Error! Reference ource not found.**. The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.18. Cox-Snell residual plots could not be generated in Stata.

**Table 5.19: Cure, AIC and BIC statistics for OS for ASCT**

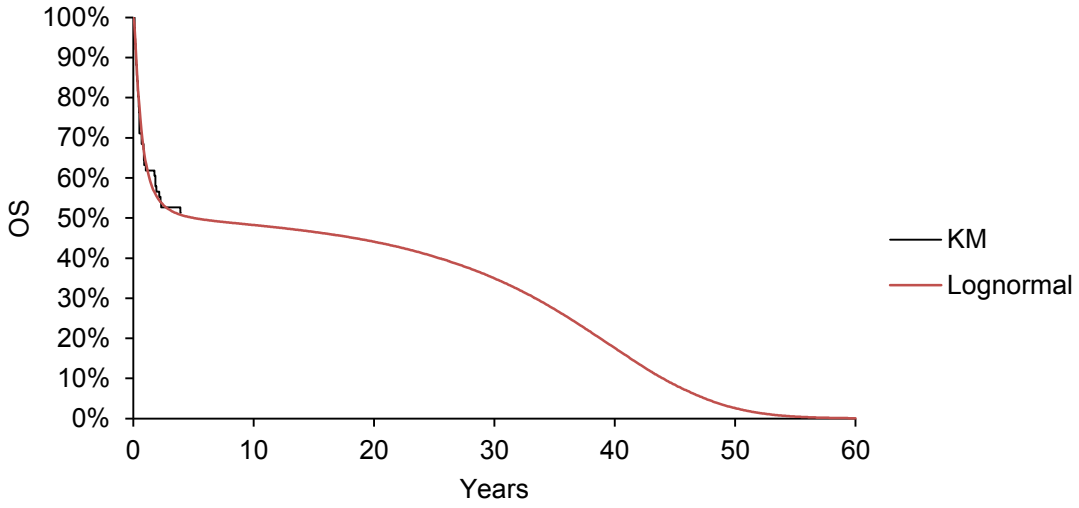
| | Weibull | Lognormal | Gamma |
|---|---|---|---|
| Cure fraction | 51% | 50% | 38% |
| AIC | 355.35 | 348.72 | 347.82 |
| BIC | 362.35 | 355.72 | 357.15 |
| AIC rank | 3 | 2 | 1 |
| BIC rank | 3 | 1 | 2 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | |

**Figure 5.22: Parametric models for ASCT OS**




There was little difference between the candidate models in terms of within-trial fit based on visual inspection. As such, the lognormal model was selected for the base case based on BIC. The corresponding lifetime extrapolations are presented in **Error! Reference source ot found.** Notably the cure fraction for the gamma model was 12% lower than the lognormal model hence this was used in the sensitivity analyses to explore an alternative estimate of this parameter.

**Figure 5.23: Lifetime extrapolation of OS for ASCT**




The same zero-risk period that was applied for PFS (29.7 weeks) was also applied for OS.

In an attempt to more accurately reflect outcomes for this decision problem, a sensitivity analysis was conducted in which the cure fractions for PFS and OS for ASCT were calibrated to the 3-year PFS and OS estimates (50% and 65% respectively) for the 39 ALCL patients beyond CR1 reported by Smith et al.[13] This imposes the assumption that the cure time point is 3 years post-ASCT rather than 5 years as is applied in the base case.

### Allo-SCT

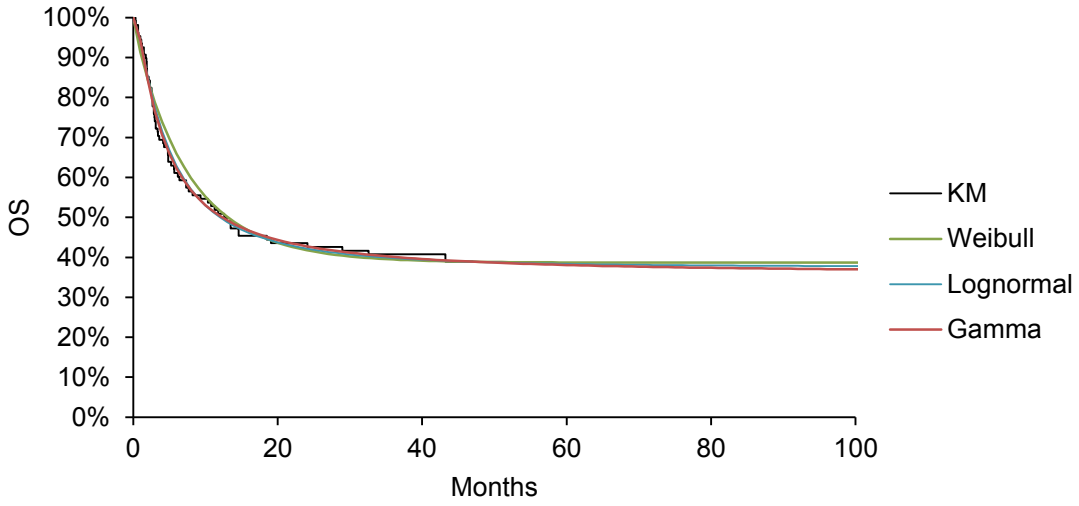
This endpoint was modelled using OS for the same 126 patients reported by Smith et al.,[13] which informed PFS for allo-SCT. An overlay of the Kaplan-Meier curve for OS and the parametric cure models demonstrating within-trial fit are presented in

Figure **5.24** The corresponding cure fractions and AIC and BIC statistics are presented in Table 5.20. Cox-Snell residual plots could not be generated in Stata.

**Table 5.20: Cure, AIC and BIC statistics for OS for ASCT**

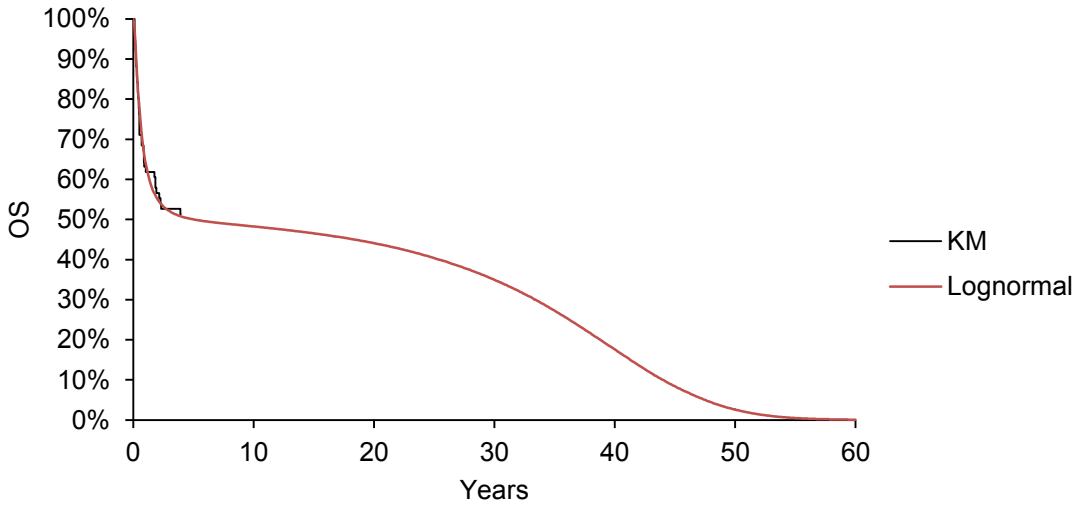
| | Weibull | Lognormal | Gamma |
|---|---|---|---|
| Cure fraction | 39% | 38% | 36% |
| AIC | 548.95 | 538.39 | 539.60 |
| BIC | 556.99 | 546.44 | 550.33 |
| AIC rank | 3 | 1 | 2 |
| BIC rank | 3 | 1 | 2 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion | | | |

**Figure 5.24: Parametric models for allo-SCT OS**




There was little difference between the candidate models in terms of the cure fractions or within-trial fit based on visual inspection. As such, the model was selected for the base case based on AIC and BIC. The corresponding lifetime extrapolations are presented in Figure 5.25 The gamma model was included in the sensitivity analysis as the second-best fitting model.

**Figure 5.25: Lifetime extrapolation of OS for allo-SCT**




The same zero-risk period that was applied for PFS (49.7 weeks) was also applied for OS in the analysis.

In an attempt to more accurately reflect outcomes for the decision problem for this appraisal, a sensitivity analysis was conducted in which the cure fractions for PFS and OS for allo-SCT

were calibrated to the 3-year PFS and OS estimates (35% and 41% respectively) for the subset of 51 ALCL patients reported by Smith et al.;[13] unlike ASCT, estimates for patients beyond CR1 were not reported. This imposes the assumption that the cure time point is 3 years post-ASCT rather than 5 years as is applied in the base case.

#### *5.3.4.3 General population*

The plateaus in the Kaplan-Meier curves which inform PFS and OS reflect the mortality rate equating to the expected rate in the general population,[69] which is indicative of long term survival or cure. Irrespective of which type of parametric survival model (cure or standard) was used to extrapolate these data, general population mortality was applied as a competing risk to ensure the long term extrapolations were clinically plausible. These data were taken from the UK National Life Tables (2013-15) [73]and are modelled directly rather than parametrically.

There is uncertainty relating to how the mortality rate for patients who are long term survivors after treatment for R/R sALCL compares to the general population. Clinical expert opinion was that long term survivors would still be at risk of secondary malignancies due to residuals effects of SCT or pre-SCT therapy and hence face an excess mortality risk compared to the general population; however the magnitude of this risk is uncertain.

The following issues were addressed as part of the survey of 4 UK clinical experts: i) the excess mortality risk for cured patients relative to the general population and ii) whether this excess hazard would differ across treatments. Three experts indicated that mortality risk is greatest for patients who receive SCT relative to no SCT; with mortality risk being higher in patients who receive allo-SCT. In addition, it was suggested by one clinical expert that the excess mortality risk associated with brentuximab relative to chemotherapy is uncertain, but highlighted that assuming the same risk as chemotherapy would be conservative. Excess mortality risks associated with each treatment were provided by one clinical expert (Table 5.21); these values were used in the base case analysis.

**Table 5.21: Excess mortality risks by treatment**

| Cohort | Excess mortality risk |
|---|---|
| Brentuximab (no SCT) | 5% |
| Brentuximab, SCT | 10% |
| Chemotherapy (no SCT) | 7% |
| Chemotherapy, SCT | 10% |

### 5.3.5 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)?

Given the absence of a study of sufficient sample size reporting PFS and OS for brentuximab vedotin + ASCT and brentuximab vedotin + allo-SCT, PFS and OS for these

cohorts were assumed equal to chemotherapy + ASCT and chemotherapy + allo-SCT. As such, differences in the proportion of patients who receive either ASCT or allo-SCT across treatment arms will yield differences in expected PFS and OS across treatment arms.

This assumption does not take into account any possible interaction effect, conditional on disease status at transplant, of brentuximab vedotin vs. chemotherapy on PFS and OS for ASCT and allo-SCT. Clinical expert opinion derived from the clinical expert survey (see section 5.3.8) was that the existence of this interaction effect is unknown.

It should be noted that if PFS and OS for these cohorts were forced to be equal by setting the transplant rates to be equal across treatment arms, the model would still predict a difference in expected PFS and OS due to the difference in these outcomes across treatment arms for the patients who do not receive ASCT or allo-SCT [i.e. brentuximab vedotin (no SCT) and chemotherapy (no SCT)].

### 5.3.6 Demonstrate how the transition probabilities were calculated from the clinical data

Given a partitioned survival (area under the curve) approach was used to estimate health state occupancy, it was not necessary to derive transition probabilities. Rather, the proportion of patients in the PFS state over time is estimated directly from the PFS curves, and the proportion of patients in the PPS state is estimated as the difference between the OS curve and the PFS curve.

### 5.3.7 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation

Data from the clinical trials used to populate the model indicate that the probability of progression and overall survival varies over time. Health state occupancy is estimated directly from the parametric survival models fitted to data from these studies and in the base case, all survival models across the model cohorts assume a baseline hazard that is a function of time.

### 5.3.8 If clinical experts assessed the applicability of values available or estimated any values.

A survey of clinical experts was obtained to support assumptions used within this submission and in the economic modelling. Four clinical experts in the field of relapsed and refractory sALCL completed a questionnaire designed to obtain a better understanding about the patient population, the use of brentuximab vedotin and other agents in UK clinical practice for R/R sALCL, and obtain opinion on a number of model parameter inputs. All four clinical experts specialised in haematology and were from hospitals located in England and Wales. The response rate to the questionnaire was 100%.

Topics in the questionnaire addressed:

- The use of brentuximab vedotin in current UK practice, in particular as a salvage therapy
- The definition of “cured” in a relapsed or refractory sALCL setting, the utility and the mortality associated with a “cured” patient
- The relative utility of patients in the first 6 months after an ASCT/ allo-SCT or after long-term remission without SCT and after 6 months compared with an age and gender matched population
- The generalisability of resource use in the SG035-0004 clinical trial with UK clinical practice. Where there were differences clinicians provided estimates of resource use associated with follow-up and monitoring.
- The use of radiotherapy in addition to chemotherapy in a relapsed or refractory sALCL setting

The Takeda field force further validated the responses from external UK clinicians as being consistent with the rest of the country. Table 5.22 provides the details of expert selection and data extraction. The questionnaire is included as Appendix 16.

**Table 5.22: Details of expert selection and data extraction**

| | **Details** |
|---|---|
| The criteria for selecting experts | Four experts considered key opinion leaders in the relapsed or refractory sALCL setting were approached for feedback. |
| The number of experts approached | Four |
| The number of experts who participated | Four |
| Declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought | One clinician had received honoraria from Takeda for a talk. No declarations of interest for the remaining three clinicians. |
| The method used to collect the opinions and questions asked | A questionnaire was devised addressing:<br>• The use of brentuximab vedotin in current UK practice, in particular as a salvage therapy<br>• The definition of “cured” in a relapsed or refractory sALCL setting, the utility and the mortality associated with a “cured” patient<br>• The relative utility of patients in the first 6 months after an ASCT/ allo-SCT or after long-term remission without SCT and after 6 months compared with an age and gender matched population<br>• The generalisability of resource use in the SG035-0004 clinical trial with UK clinical practice. Where there were differences clinicians provided estimates of resource use associated with follow-up and monitoring.<br>• The use of radiotherapy in addition to chemotherapy in a relapsed or refractory sALCL setting<br>The questionnaire was discussed either in person or over the telephone with each clinician. |
| Whether iteration was used in the collation of opinions and if so, how it was used | No iteration was used in the collation of opinions |
| **Key:** Allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; sALCL, systemic anaplastic large cell lymphoma | |

## 5.4 Measurement and valuation of health effects

### 5.4.1 Health-related quality-of-life data from clinical trials

No HRQoL data was collected in the brentuximab vedotin clinical trial for the relapsed or refractory sALCL indication; hence other sources of utility data were used.

### 5.4.2 Mapping

Mapping was not performed to derive utility estimates for the economic model.

### 5.4.3 Health-related quality-of-life studies

#### *5.4.3.1 Overview*

An extensive SLR to identify HRQL evidence was conducted during November 2016. The details of the search strategy and inclusion/exclusion criteria are provided in Appendix 11.

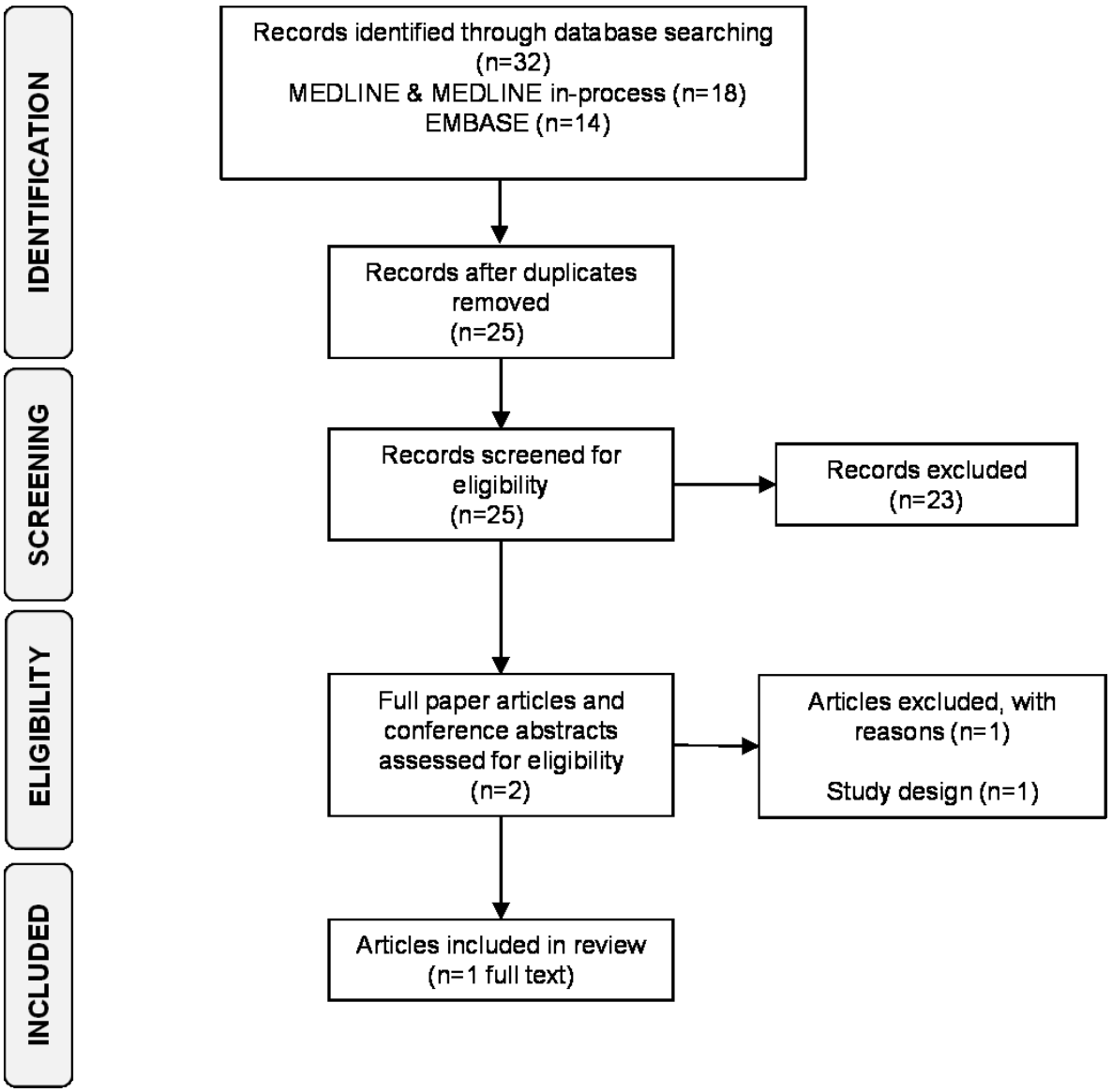
The SLR was performed to identify and summarise the relevant HRQL evidence for adult patients with R/R sALCL. Studies reporting utilities were included; all other studies reporting qualitative HRQL data or alternative outcomes were excluded. Due to the rarity of sALCL and the anticipated scarcity of evidence, no restrictions were imposed on interventions, publication design, location or date.

Primary screening of abstracts and secondary screening of full-texts were conducted by two independent reviewers. Data extraction from the included full-text of articles was also performed independently by two reviewers to ensure that everything was captured.

***Description of identified studies***

In total, 32 studies were identified from the electronic sources. Following removal of duplicates there were 25 papers eligible for screening. Primary screening of titles and abstracts against the pre-specified inclusion and exclusion criteria (as presented in Appendix 11) excluded 23 studies leaving 2 papers to be reviewed in full. One of these papers was excluded at the secondary screening stage based on an irrelevant study design. The other paper satisfied all inclusion and exclusion criteria, as such data were extracted from this source. The flow diagram of the economic SLR is presented in Figure 5.26.

**Figure 5.26: PRISMA diagram for HRQoL SLR**




Key: EED, Economic Evaluation Database; n, number; NHS, National Health Service; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

The one study included in the final review was Swinburn et al., (2015),[74] which is a vignette study which elicited time trade-off (TTO) valuations from members of the general public across seven countries, including: UK, Australia, Thailand, Taiwan, South Korea, Brazil and Mexico. Health state vignettes were developed to represent health states associated with RR sALCL and R/R HL patients. The study was initially intended to report utility scores separately for these populations; however, after observing minimal differences between the two patient populations results were pooled. The health states included: complete response, partial response, stable disease, stable disease plus presence of B-symptoms, complete response and acute graft-versus-host disease (aGvHD), complete response and chronic graft-versus-host disease (cGvHD), complete response and peripheral sensory neuropathy grade I/II, complete response and peripheral sensory neuropathy grade III. The paper

reported mean utility scores by country for each health state. Mean utility scores were also provided for the entire patient population. A summary of the results from Swinburn et al., (2015)[74] is presented in Table 5.23. The UK results were of most relevance for this submission.

**Table 5.23: Results associated with Swinburn et al., (2015)[74]**

| Study ID | Patient population | Method of valuation | Country | Sample size | Mean (SD) utility scores by health state | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CR | PR | SD | SD+B | CR + aGvHD | CR + cGvHD | CR+PSN I/II | CR+PSN III | PD |
| Swinburn 2015 [74] | R/R sALCL/ R/R HL | TTO | UK | 100 | 0.91 (0.08) | 0.79 (0.17) | 0.71 (0.20) | 0.59 (0.27) | 0.39 (0.28) | 0.52 (0.27) | 0.80 (0.17) | 0.56 (0.27) | 0.38 (0.28) |
| | | | Australia | 75 | 0.89 (0.16) | 0.77 (0.22) | 0.67 (0.26) | 0.56 (0.32) | 0.34 (0.31) | 0.51 (0.33) | 0.79 (0.24) | 0.51 (0.29) | 0.32 (0.31) |
| | | | Thailand | 75 | 0.73 (0.27) | 0.51 (0.30) | 0.30 (0.27) | 0.19 (0.25) | 0.12 (0.22) | 0.14 (0.22) | 0.42 (0.28) | 0.16 (0.22) | 0.07 (0.13) |
| | | | Taiwan | 75 | 0.60 (0.22) | 0.57 (0.22) | 0.49 (0.26) | 0.36 (0.31) | 0.20 (0.25) | 0.32 (0.27) | 0.45 (0.27) | 0.24 (0.26) | 0.23 (0.27) |
| | | | South Korea | 5 | 0.83 (0.16) | 0.73 (0.18) | 0.64 (0.22) | 0.60 (0.22) | 0.35 (0.27) | 0.41 (0.24) | 0.69 (0.19) | 0.41 (0.25) | 0.32 (0.26) |
| | | | Brazil | 101 | 0.76 (0.22) | 0.72 (0.23) | 0.64 (0.28) | 0.59 (0.31) | 0.45 (0.34) | 0.48 (0.32) | 0.66 (0.26) | 0.49 (0.33) | 0.34 (0.33) |
| | | | Mexico | 100 | 0.73 (0.27) | 0.63 (0.31) | 0.59 (0.31) | 0.59 (0.33) | 0.47 (0.35) | 0.49 (0.34) | 0.63 (0.30) | 0.49 (0.36) | 0.35 (0.39) |
| | | | Global | 601 | 0.78 (0.23) | 0.68 (0.26) | 0.59 (0.29) | 0.51 (0.32) | 0.34 (0.31) | 0.42 (0.31) | 0.64 (0.28) | 0.42 (0.32) | 0.30 (0.31) |

Key: aGvHD, acute graft-versus-host disease; B, presence of B-symptoms; cGvHD, chronic graft-versus-host disease; CR, complete response; PD, progressive disease; PR, partial response; PSN, peripheral sensory neuropathy grade; R/R, relapsed and/or refractory; sALCL, systemic anaplastic large cell lymphoma; SD, stable disease; TTO, time trade off; UK, United Kingdom

### 5.4.4 Adverse reactions

The expected QALY decrement associated with each AE was determined by the combination of the utility decrement for the event, the duration of the event and the proportion of patients experiencing the event.

Utility decrements were based on the Swinburn (2015)[74] study where available (i.e. only for Peripheral sensory neuropathy). No other studies were identified by the SLR of utilities in sALCL. Therefore, decrements for all other AEs were based on utility studies conducted in solid tumours and used in previous cancer STA's (Table 5.24).

**Table 5.24: Adverse event disutilities**

| Event grade | Event | Utility decrement | Source |
|---|---|---|---|
| 1-2 | Alopecia | 0.114 | Lloyd 2006 [75] |
| | Constipation | 0.103 | Assumed equivalent to Lloyd 2006 |
| | Diarrhoea | 0.103 | Lloyd 2006 [75] |
| | Fatigue | 0.115 | Lloyd 2006 [75] |
| | Myalgia | 0.069 | Doyle 2008 [76] |
| | Nausea | 0.103 | Lloyd 2006 [75] |
| | Neutropenia | 0.090 | Nafees 2008 [77] |
| | Peripheral sensory neuropathy | 0.1 | Swinburn 2015 [74] |
| | Pyrexia | 0.03 | Beusterein 2010 [78] |
| | Rash | 0.03 | Nafees 2008 |
| | Thrombocytopenia | 0.273 | ID414 MS [79] |
| | Upper respiratory tract infection | 0.20 | Beusterein 2010 [78] |
| | Vomiting | 0.103 | Assumed equivalent to nausea |
| | Anaemia | 0.09 | Beusterein 2010 [78] |
| | Petechiae | 0.00 | Assumed to have no utility impact |
| | Liver transferase elevation | 0.00 | Assumed to have no utility impact |
| | Leukocytopenia | 0.09 | Assumed equivalent to neutropenia |
| 3-4 | Diarrhoea | 0.103 | Lloyd 2006 [75] |
| | Neutropenia | 0.09 | Nafees 2008 [77] |
| | Peripheral sensory neuropathy | 0.331 | Swinburn 2015 [74] |
| | Thrombocytopenia | 0.273 | ID414 MS [79] |

| | | | |
|---|---|---|---|
| | Tumour lysis syndrome | 0.115 | Assumed equivalent to fatigue |
| | Nausea | 0.103 | Lloyd 2006 [75] |
| | Increased creatinine levels | 0.00 | Assumed to have no utility impact |
| | Respiratory failure | 0.090 | Assumed equivalent to neutropenia |
| | Sepsis | 0.20 | Assumed equivalent to pulmonary infection |
| | aGvHD | 0.51 | Oxford Outcomes 2011 |
| | Pulmonary infection | 0.20 | Beusterein 2010 [78] |
| | Anaemia | 0.09 | ID414 MS[79] |
| | Leukopenia | 0.09 | Assumed equivalent to neutropenia |

AE event durations (Table 5.25) were derived from an STA of pixantrone for the treatment of adults with R/R aggressive B-cell non-HL, in which the manufacturer's submission summarised HRQoL data from a number of solid tumour studies.[79]

**Table 5.25: Adverse event durations**

| Event grade | Event | Event duration | Source |
|---|---|---|---|
| 1-2 | Alopecia | 183 | Assumption from SG035-0003 |
| | Constipation | 6.0 | Assumed equivalent to vomiting |
| | Diarrhoea | 6.0 | Assumed equivalent to vomiting |
| | Fatigue | 31.5 | ID414 MS[79] |
| | Myalgia | 31.5 | Assumed equivalent to fatigue |
| | Nausea | 6.0 | ID414 MS[79] |
| | Neutropenia | 15.1 | ID414 MS[79] |
| | Peripheral sensory neuropathy | 3.0 | ID414 MS[79] – pain in extremity |
| | Pyrexia | 12.3 | ID414 MS[79] |
| | Rash | 6.0 | Assumed equivalent to vomiting |
| | Thrombocytopenia | 23.2 | ID414 MS[79] |
| | Upper respiratory tract infection | 15.1 | Assumed equivalent to neutropenia |
| | Vomiting | 6.0 | ID414 MS[79] |
| | Anaemia | 16.1 | ID414 MS[79] |
| | Petechiae | 0.0 | Assumed to have no utility impact |
| | Liver transferase elevation | 0.0 | Assumed to have no utility impact |
| | Leukocytopenia | 15.1 | Assumed equivalent to neutropenia |

| | | | |
|---|---|---|---|
| 3-4 | Diarrhoea | 6.0 | Assumed equivalent to vomiting |
| | Neutropenia | 15.1 | ID414 MS[79] |
| | Peripheral sensory neuropathy | 3.0 | ID414 MS[79] – pain in extremity |
| | Thrombocytopenia | 23.2 | ID414 MS[79] |
| | Tumour lysis syndrome | 31.5 | Assumed equivalent to fatigue |
| | Nausea | 6.0 | ID414 MS[79] |
| | Increased creatinine levels | 0.0 | Assumed to have no utility impact |
| | Respiratory failure | 15.1 | Assumed equivalent to neutropenia |
| | Sepsis | 23.2 | Assumed equivalent to thrombocytopenia |
| | aGVHD | 14.0 | Assumption |
| | Pulmonary infection | 15.1 | Assumed equivalent to neutropenia |
| | Anaemia | 16.1 | ID414 MS[79] |
| | Leukopenia | 15.1 | Assumed equivalent to neutropenia |

## 5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

### *5.4.5.1 Age adjusted utilities*

Given the mean age of the ITT population in SG035-0004 (47.7 years) and the overall survival data used in the model, it was necessary to incorporate the effect of aging on HRQoL. The impact of disease on patients' HRQoL was therefore modelled as a decrement from that of an equivalent member of the general population in terms of age.

During each cycle, the model generates an age-adjusted EQ-5D population norm based on reported UK values form Kind (1999).[80] The corresponding data used are presented in Table 5.26.

**Table 5.26: Population utility norms**

| Age (years) | | Utility | |
|---|---|---|---|
| **Min** | **Max** | **Mean** | **s.d.** |
| 25 | 34 | 0.93 | 0.15 |
| 35 | 44 | 0.91 | 0.16 |
| 45 | 54 | 0.85 | 0.25 |
| 55 | 64 | 0.80 | 0.26 |
| 65 | 74 | 0.78 | 0.26 |
| 75 | 100 | 0.73 | 0.27 |
| Source: Kind (1999)[80] | | | |

### *5.4.5.2 Impact of response on HRQoL*

In order to capture the impact of response on quality of life, the PFS health state utility for each cohort is weighted according to the proportion of patients in each response category (CR, PR, SD). Response rates were therefore re-scaled to exclude patients who experienced progressive disease.

If response is predictive of PFS, the distribution of patients in the PFS health state across the response categories will change over time. It should be noted that weighting the PFS utility based on a fixed set of response rates will not capture this effect. This was not explored in the model due to the absence of PFS data for the modelled cohorts stratified by response. Incorporation of this effect would favour treatments with superior response profiles hence omission of this effect will likely bias in favour of treatments which have poorer response profiles.

***No SCT cohorts***

Response rates for brentuximab (no SCT) were obtained from SG035-0004. Investigator-assessed rates are used in the base case to align with PFS data used in the base case; IRF-assessed rates are included as a sensitivity analysis.

Response rates for chemotherapy (no SCT) were taken from the self-control dataset of 39 patients in SG035-0004 whose most recent therapy was for R/R disease. Use of this dataset has the same benefits and potential biases as were described for PFS. Response rates for these cohorts are presented in Table 5.27.

**Table 5.27: Response rates used to weight utility in PFS health state for brentuximab (no SCT) and chemotherapy (no SCT)**

| Response | Brentuximab (no SCT) (Investigator) | Brentuximab (no SCT) (IRF) | Chemotherapy (no SCT) |
|---|---|---|---|
| CR | 59% | 53% | 57% |
| PR | 30% | 42% | 24% |
| SD | 11% | 6% | 19% |
| CR, complete response; PR, partial response; SD, stable disease | | | |

Utilities from Swinburn et al., (2015)[74] were used to model the impact of disease on quality of life. This study reports UK-specific health state utilities for R/R HL and sALCL patients receiving therapy, elicited using the time trade-off (TTO) method. The vignette study elicited time-trade off valuations of health states from 100 members of the general public in the UK. Disease states were developed based on a review of literature and clinician and patient interviews. Health states for which valuations were elicited were; CR, PR, SD, SD with B-symptoms, and PD. Utilities for these health states are presented in Table 5.28.

These values were converted to disutilities so they could be applied directly to the age-adjusted population norm. The CR utility estimate (0.91) is equal to the age-adjusted populating norm based on the mean age (38 years) of UK participants in Swinburn et al. (2015),[74] implying there is no utility decrement for patients with R/R sALCL who achieve CR. Clinical expert opinion was that patients achieving CR would experience a decrement of approximately 5% compared to the age-adjusted population norm; this was incorporated when calculating decrements for the model health states.

**Table 5.28: Health state utilities**

| Health state | Mean | s.d. | Decrement |
|---|---|---|---|
| Base | 0.95 | N/A | N/A |
| CR | 0.91 | 0.08 | -0.05 |
| PR | 0.79 | 0.17 | -0.16 |
| SD | 0.71 | 0.20 | -0.24 |
| PD | 0.38 | 0.28 | -0.57 |
| CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; s.d., standard deviation; N/A, not applicable | | | |

Given the potential for patients to achieve long term survival, it was necessary to estimate the impact of this outcome on utility. In the absence of data in the literature, clinical experts were also consulted to elicit how the utility of a 'cured' patient would compare to that of an age-equivalent member of the general population. Two experts indicated that such patients would have a utility 5% lower than the age-adjusted population norm and one indicated that

utility would be 2-5% lower. As such, the base case assumes a 5% decrement for long term survivors compared to the age-adjusted population norm.

Clinical experts were also asked at what time point following initiation of salvage therapy patients would be considered cured. Three experts stated 5 years and two stated two years. The long term survivor utility, which represents a percentage decrement of the age-adjusted population norm, was therefore applied to patients who are progression-free from 5 years; a sensitivity analysis was conducted applying this utility from 2 years.

Patients experiencing PD at any time were assumed to receive the decrement derived from Swinburn et al., (2015).[74]

***SCT cohorts***

Clinical expert opinion was that patients' quality of life varied considerably depending on which type of SCT a patient receives and the time post-SCT. Moreover, it was necessary to account for which salvage regimen (i.e. brentuximab or chemotherapy) was received prior to SCT. Therefore, the utilities for patients who receive ASCT or allo-SCT were stratified by the following intervals:

- Time from initiation of salvage therapy to SCT
- Time from SCT to progression or cure:
  - 0 to 6 months, post-SCT
  - 6 months to cure, post-SCT
- Time from cure to death

***Time from initiation of salvage therapy to SCT***

From initiation of salvage therapy to SCT, utility was modelled as per the approach described for the no SCT cohorts using the health state utilities reported by Swinburn et al.[74]

Response rates for brentuximab were based on the 8 and 9 patients who received ASCT and allo-SCT in SG035-0004, respectively (Table 5.27). Response rates for patients who received chemotherapy followed by SCT were not reported in the studies identified by the SLR. Moreover, the self-control dataset did not include patients who most recent therapy was SCT. Therefore, rates of disease status at transplant reported by Smith et al., (2013)[13] for patients receiving ASCT and allo-SCT were used as a proxy for response to chemotherapy followed by ASCT and allo-SCT respectively; the corresponding assumptions are presented in Table 5.29 and the rates in Table 5.30. These rates were thought to be reflective of salvage chemotherapy given all transplants in this study were conducted in the pre-brentuximab era (between 1996 and 2006).

**Table 5.29: Assumptions used to map disease status at transplant in Smith et al. (2013) to model response categories**

| Disease status | Definition reported in Smith et al., (2013)[13] | Model response category |
|---|---|---|
| CR2+ | Second complete remission | CR |
| Relapse sensitive | Relapsing from prior remission but with a partial remission to treatment for relapse | PR |
| Relapse other | Relapsing from prior remission with stable disease or progression thereafter | Equal distribution across SD and PD |

**Table 5.30: Response rates for salvage therapy, prior to SCT**

| Response | Brentuximab | | Chemotherapy | |
|---|---|---|---|---|
| | ASCT | Allo-SCT | ASCT | Allo-SCT |
| CR | 100% | 89% | 52% | 40% |
| PR | 0% | 11% | 37% | 42% |
| SD | 0% | 0% | 11% | 18% |
| CR, complete response; PR, partial response; SD, stable disease | | | | |

The time from initiation of salvage therapy to ASCT and allo-SCT was based on data from SG035-0004; the corresponding median times were 29.7 weeks and 49.7 weeks, respectively.

***Time from SCT to progression or cure***

Feedback obtained during the survey of UK clinical experts was that, due to the nature of each procedure, patients would experience a quality of life decrement following ASCT or allo-SCT over and above the impact of disease. The one study identified from the SLR of utility studies (Section 5.4.3) did not report utility estimates explicitly for patients who receive SCT. In the absence of data in the literature, clinical experts were asked to provide an estimate of these decrements. The associated data are presented in Table 5.31 and are stratified according to which type of SCT patients received and time post-SCT (0 to 6 months and 6 months to cure). The mean of the responses for each type of SCT and time interval was used in the base case analysis.

**Table 5.31: Utility decrements for patient in CR post-ASCT and post-allo-SCT**

| SCT | Time, post-SCT (months) | | Decrement for patient in CR vs. age-adjusted population norm | | | |
|---|---|---|---|---|---|---|
| | Start | End | Expert 1 | Expert 2 | Expert 3 | Mean used in model |
| ASCT | 0 | 6 | 40% | 35% | 20% | 32% |
| | 6 | 60 | 5% | 15% | 10% | 10% |
| Allo-SCT | 0 | 6 | 50% | 50% | 50% | 50% |
| | 6 | 60 | 30% | 35% | 20% | 28% |

These decrements were applied to the age-adjusted population norm utility to derive the CR utilities for ASCT and allo-SCT in each time interval. The utilities for PR and SD in each time interval were then derived by subtracting the difference between the respective utility and the CR utility reported by Swinburn et al.,[74]. This approach ensures the difference between the responder categories is retained.

The same approach yielded a utility of -0.05 for patients in PD for the first 6 months post-allo-SCT. Despite the nature of this procedure, this was considered implausible hence the PD utilities for ASCT and allo-SCT were calculated by multiplying the PD utility reported by Swinburn et al.,[74] (0.38) by the decrements provided by the clinical expert in each interval. Although inconsistent with the approach used for responders, this approach avoids the assumption that patients who experience PD in the first 6 months post-allo-SCT are in a state worse than death, and generates utilities which are lower than the SD utility for all intervals.

The corresponding utilities and associated decrements which were applied to the age-adjusted population norm in each cycle are presented in Table 5.32

**Table 5.32: Utility decrements for patients post-ASCT and post-allo-SCT**

| SCT | Health state | 0-6 months | | 6 months to cure | |
|---|---|---|---|---|---|
| | | Utility | Decrement | Utility | Decrement |
| ASCT | CR | 0.65 | -0.30 | 0.86 | -0.10 |
| | PR | 0.54 | -0.41 | 0.74 | -0.21 |
| | SD | 0.45 | -0.50 | 0.66 | -0.29 |
| | PD | 0.26 | -0.69 | 0.34 | -0.61 |
| Allo-SCT | CR | 0.48 | -0.48 | 0.68 | -0.27 |
| | PR | 0.36 | -0.59 | 0.57 | -0.38 |
| | SD | 0.28 | -0.67 | 0.49 | -0.47 |
| | PD | 0.19 | -0.76 | 0.27 | -0.68 |

In each interval, utilities were weighted based on response as per the approach described for the no SCT cohorts. Ideally, response rates for ASCT and allo-SCT would have been obtained from the same source as the PFS and OS data; however these were not reported by Smith et al.[13]

As such, response rates for ASCT were based on Nademanee et al., (2011),[65] a retrospective analysis of 67 patients with PTCL (30 ALCL patients) who underwent high-dose therapy and ASCT. This study was identified by the clinical SLR (Section 4.1), and reported that 27 patients were in CR at current follow-up [median 65.8 months (range: 24.5-216)] and 34 experienced relapse/progressive disease post-ASCT. The number of patients in PR and SD was therefore calculated as the residual (67-34-27 = 6); patients were assumed to be equally distributed across these categories (i.e. PR = 3; SD = 3). This approach assumes that rates of disease status after a median follow-up of 65.8 months are reflective of response to ASCT.

Response rates for allo-SCT were based on Le Gouill et al., (2008),[31] a retrospective analysis of 77 aggressive T-cell lymphoma (ATCL) patients (27 ALCL patients) who received allo-SCT, using data from the Société Française de Greffe de Moelle-Thérapie Cellulaire register. In this study, 19 out of 27 ALCL patients achieved a CR and 6 experienced disease progression/relapse post-SCT.

The response rates used for ASCT and allo-SCT are presented in Table 5.33.

**Table 5.33: Response rates used to weight utility in the PFS health state for SCT**

| Response | ASCT | Allo-SCT |
|---|---|---|
| CR | 82% | 100% |
| PR | 9% | 0% |
| SD | 9% | 0% |

This approach assumes that response to ASCT and allo-SCT is independent of whether patients receive brentuximab or chemotherapy as salvage therapy. This assumption will fail to capture any interaction effect, conditional on disease status at transplant, of brentuximab vs. chemotherapy on PFS and OS for ASCT and allo-SCT. Feedback obtained during the survey of UK clinical experts (Section 5.3.8) was that the existence of this interaction effect is unknown due to the absence of long term follow-up for patients receiving ASCT or allo-SCT following brentuximab.

***Time from cure to death***

As per the no SCT cohorts, the utility for patients residing in the PFS health state from the cure time point is assumed to revert to the age-adjusted population norm with a 5% decrement. For ASCT and allo-SCT, the cure time point was adjusted to incorporate the corresponding time from initiation of salvage therapy to SCT.

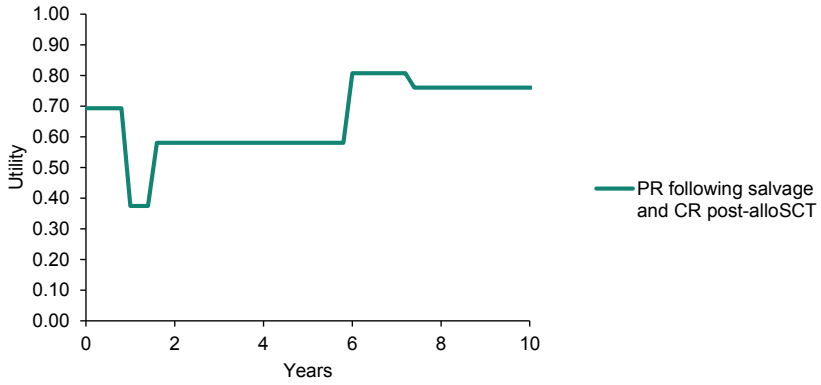
### *Summary of approach for modelling utility for SCT cohorts*

Figure 5.27 plots the utility over 10 years of a hypothetical patient who achieves a PR following salvage treatment and then undergoes allo-SCT and subsequently achieves a CR. A description of each interval and the corresponding utility is presented in Table 5.34

**Table 5.34: Utility profile of hypothetical patient**

| Interval (years) | Description of interval | Description of utility |
|---|---|---|
| 0.00-0.92 | Partial response to salvage therapy until allo-SCT | Age-adjusted population norm incorporating the decrement for PR |
| 0.92-1.42 | First 6 months post-allo-SCT | The decrease at the start of this interval reflects the impact of the patient undergoing allo-SCT |
| 1.42-5.92 | 6-60 months post-allo-SCT | The increase at the start of this interval reflects clinical expert opinion that the decrement associated with allo-SCT for a patient in CR compared to age-adjusted population norm will reduce from 50% to 28% |
| 5.92-death | Cure until death | The increase at the start of this interval reflects the patient being considered cured after remaining progression-free for 5 years post-allo-SCT. Utility will follow the trajectory of the population norm with a 5% decrement thereafter |

**Figure 5.27: Plot of utility for hypothetical patient**




The PD utility for SCT cohorts was obtained by applying the decrement associated with the time that had elapsed since and the type of SCT (Table 5.35). Beyond 60 months post-SCT, the PD utility was calculated as per the no SCT cohorts; by applying the decrement for PD calculated from the utilities reported by Swinburn et al.,[74] to the age-adjusted population norm.

## *5.4.5.3 Summary of the utility values used in the economic model*

**Table 5.35: Summary of utility values for cost-effectiveness analysis**

| State | Mean utility | se | Justification |
|---|---|---|---|
| CR | 0.91 | 0.01 | Utilities values published in |

| | | | |
|---|---|---|---|
| PR | 0.79 | 0.01 | Swinburn et al., 2015 [74] |
| SD | 0.71 | 0.02 | |
| PD | 0.38 | 0.02 | |
| Decrement 0-6 months post-ASCT for CR vs general population - clinical expert 1 | 40% | 20% | Decrements post-ASCT for CR vs general population |
| Decrement 0-6 months post-ASCT for CR vs general population - clinical expert 2 | 35% | 20% | |
| Decrement 0-6 months post-ASCT for CR vs general population - clinical expert 3 | 20% | 20% | |
| Decrement >6 months post-ASCT for CR vs general population - clinical expert 1 | 5% | 20% | |
| Decrement >6 months post-ASCT for CR vs general population - clinical expert 2 | 15% | 20% | |
| Decrement >6 months post-ASCT for CR vs general population - clinical expert 3 | 10% | 20% | |
| Decrement 0-6 months post-allo-SCT for CR vs general population - clinical expert 1 | 50% | 20% | Decrements post-allo-SCT for CR vs. general population |
| Decrement 0-6 months post-allo-SCT for CR vs general population - clinical expert 2 | 50% | 20% | |
| Decrement 0-6 months post-allo-SCT for CR vs general population - clinical expert 3 | 50% | 20% | |
| Decrement >6 months post-allo-SCT for CR vs general population - clinical expert 1 | 30% | 20% | |
| Decrement >6 months post-allo-SCT for CR vs general population - clinical expert 2 | 35% | 20% | |
| Decrement >6 months post-allo-SCT for CR vs general population - clinical expert 3 | 20% | 20% | |
| General population norm; 25-34 years | 0.93 | 0.01 | EQ-5D population norms from Kind et al., (1999)[80] |
| General population norm; 35-44 years | 0.91 | 0.01 | |
| General population norm; 45-54 years | 0.85 | 0.01 | |
| General population norm; 55-64 years | 0.80 | 0.01 | |
| General population norm; 65-74 years | 0.78 | 0.01 | |
| General population norm; 75-100 years | 0.73 | 0.02 | |
| Cured time point (years) | 5 | - | Cured time point |
| Cure decrement vs. general population | 5% | - | Cured utility decrement |
| Grade 1-2 Alopecia | -0.11 | 0.01 | Adverse event disutilities |
| Grade 1-2 Constipation | -0.10 | 0.01 | |
| Grade 1-2 Diarrhoea | -0.10 | 0.01 | |
| Grade 1-2 Fatigue | -0.12 | 0.01 | |
| Grade 1-2 Myalgia | -0.07 | 0.01 | |
| Grade 1-2 Nausea | -0.10 | 0.01 | |
| Grade 1-2 Neutropenia | -0.09 | 0.01 | |
| Grade 1-2 Peripheral sensory neuropathy | -0.10 | 0.01 | |
| Grade 1-2 Pyrexia | -0.03 | 0.00 | |
| Grade 1-2 Rash | -0.03 | 0.00 | |
| Grade 1-2 Thrombocytopenia | -0.27 | 0.03 | |
| Grade 1-2 Upper respiratory tract infection | -0.20 | 0.02 | |
| Grade 1-2 Vomiting | -0.10 | 0.01 | |

| | | | |
|---|---|---|---|
| Grade 1-2 Anaemia | -0.09 | 0.01 | |
| Grade 1-2 Petechiae | 0.00 | 0.00 | |
| Grade 1-2 Liver transferase elevation | 0.00 | 0.00 | |
| Grade 1-2 Leukocytopenia | -0.09 | 0.01 | |
| Grade 3-4 Diarrhoea | -0.10 | 0.01 | |
| Grade 3-4 Neutropenia | -0.09 | 0.01 | |
| Grade 3-4 Peripheral sensory neuropathy | -0.33 | 0.03 | |
| Grade 3-4 Thrombocytopenia | -0.27 | 0.03 | |
| Grade 3-4 Tumour lysis syndrome | -0.12 | 0.01 | |
| Grade 3-4 Nausea | -0.10 | 0.01 | |
| Grade 3-4 Increased creatinine levels | 0.00 | 0.00 | |
| Grade 3-4 Respiratory failure | -0.09 | 0.01 | |
| Grade 3-4 Sepsis | -0.20 | 0.02 | |
| Grade 3-4 aGVHD | -0.51 | 0.05 | |
| Grade 3-4 Pulmonary infection | -0.20 | 0.02 | |
| Grade 3-4 Anaemia | -0.09 | 0.01 | |
| Grade 3-4 Leukopenia | -0.09 | 0.01 | |

## 5.5 Cost and healthcare resource use identification, measurement and valuation

### 5.5.1 Resource identification, measurement and valuation studies

An extensive systematic literature review (SLR) to identify cost-effectiveness and cost and resource use evidence was conducted during November 2016. The details of the search strategy and inclusion/ exclusion criteria are provided in Appendix 11). No studies of relevance relating to resource use/costs were identified from the economic SLR (see section 5.1)

### 5.5.2 Intervention and comparators' costs and resource use

#### *5.5.2.1 Brentuximab vedotin*

Patients are modelled to receive brentuximab vedotin intravenously once every 3 weeks at a dose of 1.8mg/kg for a maximum of 16 cycles as per the SG035-0004 trial (Table 5.36).

Relative dose intensity (RDI) adjustment is included to reflect the ratio of actual to scheduled drug delivery. Specifically, the actual dose delivered may differ from the planned dose per treatment cycle due to missing or delayed doses and toxicity-related dose reductions.

Mean body weight (kg) for the ITT population (76.35 kg) is used to determine the number of vials required per patient given the per-kg dose and the RDI. The base case analysis assumes full wastage as patient numbers in each centre would likely be too low to allow for any vial sharing. Given all patients had discontinued treatment at the time of data cut-off for

the primary analysis the acquisition cost is calculated based on the mean number of cycles administered in SG035-0004. These are calculated separately for each SCT cohort (i.e. no SCT and SCT) to enable differences in time-on-treatment to be captured when modelling alternative proportions of patients receiving SCT to what was observed in SG035-0004.

**Table 5.36: Brentuximab vedotin exposure, by cohort**

| Cohort | RDI | | Number of cycles | | Source |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| SCT | 94.6% | 12.23% | 8.8 | 3.58 | SG035-0004; patients who did receive subsequent SCT (*n*=17) |
| No SCT | 94.5% | 11.18% | 8.0 | 5.26 | SG035-0004; patients who didn't receive subsequent SCT (*n*=41) |

The unit cost for brentuximab vedotin was sourced from the British National Formulary (BNF) 2016 [16](Table 5.37). An approved simple patient access scheme (PAS) which offers a confidential discount of [redacted]% on the NHS List Price was applied. The corresponding estimated net acquisition cost per cycle (with PAS) is [redacted] (average patient requires 3 vials per cycle) including full wastage for both the SCT and non-SCT cohorts. Combining this with the mean number of cycles corresponds to a total cost per patient of £[redacted].and £[redacted] for the SCT and non-SCT cohorts respectively.

Due to the difficulty in identifying a distribution capable of describing the distribution of number of cycles in SG035-004 the number of cycles in the no STC and SCT cohorts was randomly sampled from the individual patient data with replacement.

**Table 5.37: Brentuximab vedotin drug acquisition cost**

| Drug | Units (mg) | Vial size | Price | Source | Net Price with PAS |
|---|---|---|---|---|---|
| Brentuximab vedotin | 50 | 1 | £2,500 | BNF 2016 | £[redacted] |

Patients receiving brentuximab vedotin require a single infusion per cycle to administer the drug. This was assumed to occur in the outpatient setting as per SG035-0004. The relevant HRG code (SB12Z) was determined based on the infusion time reported in Pro et al., (2012)[2] (30 minutes) and the definitions provided in the Reference costs guidance (Table 5.38).

**Table 5.38: Reference costs guidance on chemotherapy delivery**

| HRG | Definition | Description |
|---|---|---|
| SB12Z | Deliver simple parenteral chemotherapy | 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 | 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 | 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 | Delivery of any pattern of outpatient chemotherapy regimen, |

| | | |
|---|---|---|
| | chemotherapy cycle | other than the first attendance, i.e. day 8 of a day 1 and 8 regimen or days 8 and 15 of a day 1, 8 and 15 regimen. |

The unit cost associated with HRG code SB12Z in the outpatient setting is £198.93 (£188.79 LQ; £219.26 UQ). This was sourced from the NHS reference costs 2015/2016.[81]

### *5.5.2.2 Chemotherapy*

To address uncertainty regarding which chemotherapy regimens are used in UK practice, clinical experts were asked which regimens were most relevant to UK practice and the corresponding proportions of patients receiving each of these regimens, as part of the clinical expert survey (Section 5.3.8 ). These data are presented in Table 5.39

**Table 5.39: Proportion of patients receiving each chemotherapy regimen**

| Chemotherapy regimen | Proportion of patients |
|---|---|
| ICE | 25% |
| ESHAP | 25% |
| DHAP | 25% |
| GDP | 12.5% |
| Gem-P | 12.5% |
| DHAP, dexamethasone, high-dose cytarabine and cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; GDP, gemcitabine, dexamethasone and cisplatin; ICE, ifosfamide, carboplatin and etoposide | |

To explore the impact of the chemotherapy regimen distribution, a sensitivity analysis is run assuming all patients are treated with the most and least expensive treatment choices.

Dosing and mean time-on-treatment for these regimens were sourced from the corresponding publications cited in the NCCN guidelines.[24] None of these publications reported data on RDI hence this was assumed to be 100% for all regimens. A sensitivity analysis is conducted assuming that RDI for the chemotherapy regimens is equivalent to brentuximab vedotin. Median cycles were used for regimens where the publication did not report mean cycles. In publications which reported the number of cycles received in terms of a range (e.g. 6-8 cycles), the midpoint of this range was used. The corresponding unit costs were sourced from the BNF 72 (2016).[16] These data are presented in Table 5.40

**Table 5.40: Chemotherapy regimens, time on treatment and unit costs**

| Regimen | Drug | Dose (mg) | Per unit* | Admin. / cycle | Cycle length (days) | Number of cycles¥ | Product size (mg) | Price | Dosing source |
|---|---|---|---|---|---|---|---|---|---|
| ICE | Etoposide | 100 | $m^2$ | 3 | 14 | 3 | 100 | £12.15 | Zelenetz (2003)[56] |
| | Carboplatin | 800 | N/A | 1 | 14 | | 150 | £50.00 | |
| | Ifosfamide | 5000 | $m^2$ | 1 | 14 | | 1000 | £66.08 | |
| ESHAP | Cisplatin | 25 | $m^2$ | 4 | 21 | 7 | 50 | £24.50 | Velasquez (1988)[57] |
| | Methylprednisolone | 500 | N/A | 5 | 21 | | 2000 | £48.32 | |
| | Etoposide | 40 | $m^2$ | 4 | 21 | | 100 | £12.15 | |
| | Cytarabine | 2000 | $m^2$ | 1 | 21 | | 2000 | £77.50 | |
| DHAP | Dexamethasone | 40 | N/A | 4 | 21 | 8 | 200 | £78.00 | Velasquez (1994)[58] |
| | Cisplatin | 100 | $m^2$ | 1 | 21 | | 50 | £24.50 | |
| | Cytarabine | 2000 | $m^2$ | 2 | 21 | | 2000 | £77.50 | |
| GDP | Gemcitabine | 1250 | $m^2$ | 2 | 21 | 6 | 200 | £29.80 | Dong (2013)[59] ɣ |
| | Dexamethasone | 40 | $m^2$ | 4 | 21 | | 200 | £78.00 | |
| | Cisplatin | 25 | $m^2$ | 3 | 21 | | 50 | £24.50 | |
| Gem-P | Gemcitabine | 1000 | $m^2$ | 2 | 28 | 6β | 200 | £29.80 | Arkenau (2007)[60] |
| | Cisplatin | 100 | $m^2$ | 3 | 28 | | 50 | £24.50 | |
| | Methylprednisolone | 1000 | N/A | 5 | 28 | | 2000 | £48.32 | |

*N/A indicates fixed dose; ¥standard error of 10% assumed where uncertainty estimates were not reported; ɣ Dong (2013) selected in preference to Crump (2004) based on date of publication; βmean cycles assumed equivalent to GDP

The relevant administration setting (e.g. outpatient or regular day/night admissions) was determined based on the publications used to inform dosing schedules. The relevant HRG codes were determined based on the infusion times reported in the same publications and the descriptions provided in the Reference costs guidance [81](Table 5.41). Unit costs were sourced from the NHS reference costs 2015/2016 (Table 5.41).[81]

**Table 5.41: Chemotherapy regimens administration HRG codes and unit costs**

| Regimen | Setting | Day of cycle | Drugs administered | HRG code | Unit cost | | |
|---|---|---|---|---|---|---|---|
| | | | | | Mean | Lower quartile | Upper quartile |
| ICE | Day case and regular day/night admission | 1 | Etoposide | SB14Z | £406.63 | £258.49 | £520.85 |
| | | 2 | Etoposide, carboplatin, ifosfamide | SB15Z | £361.03 | £206.37 | £426.59 |
| | | 3 | Etoposide | SB15Z | £361.03 | £206.37 | £426.59 |
| ESHAP | Day case and regular day/night admission | 1 | Cisplatin, methylprednisolone, etoposide | SB14Z | £406.63 | £258.49 | £520.85 |
| | | 2 | Cisplatin, methylprednisolone, etoposide | SB15Z | £361.03 | £206.37 | £426.59 |
| | | 3 | Cisplatin, methylprednisolone, etoposide | SB15Z | £361.03 | £206.37 | £426.59 |
| | | 4 | Cisplatin, methylprednisolone, etoposide | SB15Z | £361.03 | £206.37 | £426.59 |
| | | 5 | Cisplatin, methylprednisolone | SB15Z | £361.03 | £206.37 | £426.59 |
| DHAP | Day case and regular day/night admission | 1 | Cisplatin | SB14Z | £406.63 | £258.49 | £520.85 |
| | | 3 | Cytarabine | SB15Z | £361.03 | £206.37 | £426.59 |
| GDP | Outpatient | 1 | Gemcitabine, cisplatin | SB13Z | £265.01 | £205.82 | £368.50 |
| | | 8 | Gemcitabine | SB15Z | £211.99 | £164.62 | £246.09 |
| Gem-P | Outpatient* | 1 | Gemcitabine, methylprednisolone¥ | SB13Z | £265.01 | £205.82 | £368.50 |
| | | 8 | Gemcitabine | SB15Z | £211.99 | £164.62 | £246.09 |
| | | 15 | Gemcitabine, cisplatin | SB15Z | £211.99 | £164.62 | £246.09 |

*Assumed equivalent to GDP; ¥assumed to be oral treatment and pack administered on day 1 of cycle

### *5.5.2.3 Radiotherapy*

The NCCN guidelines [24] recommend palliative radiotherapy for patients who are not considered candidates for SCT. In the absence of data from the literature, five clinical experts were consulted to elicit the frequency of radiotherapy administration. Three experts reported that <5% receive radiotherapy, one reported 10% and another reported 40%. In the base case, it was assumed that 5% of patients would receive radiotherapy; 40% is assumed in a sensitivity analysis. This is allocated as a one off, outpatient cost upon initiation of chemotherapy (Table 5.42). Unit costs were based on the NHS reference costs 2015-2016.[81]

**Table 5.42: Radiotherapy use and unit costs**

| Resource | Attendances | Mean | Lower quartile | Upper quartile | HRG code |
|---|---|---|---|---|---|
| Preparation for simple radiotherapy with imaging and dosimetry | 1 | £338.57 | £233.51 | £386.72 | SC45Z |
| Deliver a fraction of treatment on a megavoltage machine | 15 | £104.77 | £71.35 | £135.09 | SC22Z |

### *5.5.2.4 Concomitant medications*

The NCCN [82] guidelines recommend antifungal, antiviral and antibacterial agents for the prevention and treatment of cancer-related infections. Clinical expert opinion was consulted to elicit which medications were relevant for patients with R/R sALCL. The following medications were cited as relevant for patients receiving GDP and Gem-P:

- Acyclovir
- Levofloxacin
- Growth colony stimulating factor (G-CSF)

Regimens for acyclovir and levofloxacin were based on the NCCN guidelines. The cost of filgrastim was assigned for G-CSF based on the NHS guideline for the use of G-CSF in adult patients. Pack prices were sourced from the BNF 72 (2016).[16] These data are presented in Table 5.43 and the corresponding cost by treatment is presented in Table 5.44.

**Table 5.43: Concomitant medications**

| Regimen | Dose | Admins per day | Days per cycle | Admins per cycle | Product size | Cost |
|---|---|---|---|---|---|---|
| Filgrastim | 300mg | 1 | 7 | 7 | 300mg | £52.70 |
| Levofloxacin | 500mg | 1 | 7 | 7 | 2500mg | £11.57 |
| Acyclovir | 400mg | 2 | 7 | 14 | 5000mg | £2.85 |

**Table 5.44: Concomitant medication costs by treatment**

| Regimen | Cost per cycle | Cost per week |
|---|---|---|
| GDP | £388.29 | £129.43 |
| Gem-P | £388.29 | £97.07 |

The NCCN guidelines also recommend anti-emesis for oncology patients.[83] Guidelines for anti-emesis recommend regimens based on anti-emesis risk. These regimens and associated unit costs are presented in Table 5.45.

**Table 5.45: Recommended anti-emesis regimens by risk group**

| Risk group | Treatment | Daily dose (mg) | Admins per cycle | Product size (mg) | Unit cost | Total cost per cycle |
|---|---|---|---|---|---|---|
| Low | Dexamethasone | 12mg | 1 | 200 | £78.00 | £4.68 |
| Moderate | Ondansetron | 24mg | 1 | 120 | £5.37 | £11.82 |
| | Dexamethasone | 12mg | 1 | 200 | £78.00 | |
| | Dexamethasone | 8mg | 2 | 200 | £78.00 | |
| High | Ondansetron | 24mg | 1 | 120 | £5.37 | £35.73 |
| | Dexamethasone | 12mg | 1 | 200 | £78.00 | |
| | Aprepitant | 125mg | 1 | 285 | £47.42 | |
| | Dexamethasone | 8mg | 3 | 200 | £78.00 | |
| | Aprepitant | 80mg | 2 | N/A* | N/A | |

*Cost captured by first administration - 3-day pack of one 125-mg capsule and two 80-mg capsules

The NCCN guidelines were reviewed to determine the risk group corresponding to each regimen. These data and the corresponding total cost per cycle are presented in Table 5.46.

**Table 5.46: Concomitant medication costs by treatment**

| Regimen | Drug | Risk group | Cost per cycle | |
|---|---|---|---|---|
| | | | By regimen | Total |
| Brentuximab | Brentuximab | Low | £4.68 | £4.68 |
| ICE | Etoposide | Low | £4.68 | £35.73 |
| | Carboplatin | Moderate | £11.82 | |
| | Ifosfamide | High | £35.73 | |
| ESHAP | Cisplatin | High | £35.73 | £35.73 |
| | Methylprednisolone | N/A | N/A | |
| | Etoposide | Low | £4.68 | |
| | Cytarabine | Moderate | £11.82 | |
| DHAP | Dexamethasone | N/A | N/A | £35.73 |
| | Cisplatin | High | £35.73 | |
| | Cytarabine | Moderate | £11.82 | |
| GDP | Gemcitabine | Low | £4.68 | £35.73 |
| | Dexamethasone | N/A | N/A | |
| | Cisplatin | High | £35.73 | |
| Gem-P | Gemcitabine | Low | £4.68 | £35.73 |
| | Cisplatin | High | £35.73 | |
| | Methylprednisolone | N/A | N/A | |

## 5.5.3 Health-state unit costs and resource use

### *5.5.3.1 Overview*

Relevant components of follow-up care were identified by a review the NCCN guidelines for PTCL:[24]

- CT scans
- PET scans
- Complete blood count
- Biochemistry
- Physical exam

### *5.5.3.2 Brentuximab, no SCT and chemotherapy, no SCT*

In the absence of recommendations in the NCCN regarding the frequency at which these are conducted, the corresponding frequencies from SG035-0004 were presented during the survey of UK clinical experts (Section 5.3.8) to determine whether they were reflective of clinical practice for patients who are on-treatment. The feedback from the clinical expert survey was that the frequency of CT and PET scans observed in SG035-0004 was too high relative to clinical practice and thus alternative frequencies were provided. Clinical expert

opinion was that the frequencies of follow-up care do not differ by salvage therapy. In light of this, on-treatment follow-up care for chemotherapy was assumed equivalent to brentuximab.

These data were converted into weekly frequencies based on the regimen cycle length and are presented in Table 5.47; for chemotherapy the weighted-average cycle length across the chemotherapy regimens was used.

**Table 5.47: Brentuximab and chemotherapy on-treatment resource use**

| Resource | Frequency | Frequency per week in model | |
|---|---|---|---|
| | | Brentuximab | Chemotherapy |
| CT scan | 3 scans whilst on treatment | 0.13 | 0.17 |
| PET scan | 2 scans whilst on treatment | 0.08 | 0.11 |
| Consultation | Once every treatment cycle | 0.33 | 0.33 |
| Blood count | Once every treatment cycle | 0.33 | 0.33 |
| Biochemistry | Once every treatment cycle | 0.33 | 0.33 |

In the absence of frequencies for the off-treatment period prior to progression, four clinical experts were consulted elicit frequencies. The two experts who responded provided the following schedules:

> **Clinical expert 1**: Patients are followed up every 3-4 months for three years and then discharged. A CT/PET scan would be conducted at the end of salvage treatment.
>
> **Clinical expert 2:** Patients are followed up every 3-4 months for 2 years and every 6 months for a further 3-4 years. A CT/PET scan would be conducted at the end of salvage treatment.

It was assumed that patients would receive the costs of blood count, biochemistry and consultation at follow-up visits. The costs of CT/PET scans were assigned on completion of salvage therapy. Blood count, biochemistry and consultation frequencies were converted into weekly frequencies and are presented in Table 5.48.

**Table 5.48: Follow-up care off-treatment**

| Clinical expert | Time, off-treatment (years) | | Frequency per week | | | | |
|---|---|---|---|---|---|---|---|
| | Start | End | CT scan | PET scan | Blood count | Biochemistry | Consultation |
| 1 | 0 | 3 | One post-treatment | One post-treatment | 0.07 | 0.07 | 0.07 |
| | 3 | 6.5 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 0 | 2 | One post-treatment | One post-treatment | 0.07 | 0.07 | 0.07 |
| | 2 | 5.5 | 0.00 | 0.00 | 0.04 | 0.04 | 0.04 |

Standard error of 20% assumed for frequencies

### *5.5.3.3 ASCT*

As per the non-SCT cohorts, four clinical experts were consulted to elicit resource use frequencies post-transplant, of which two provided the following schedules:

> **Clinical expert 1**: Patients are followed up every 3-4 months for five years and then discharged. A PET scan and two CT scans would be conducted post-ASCT.
>
> **Clinical expert 2:** Patients are followed up every 3-4 months for 2 years and every 6 months for a further 3-4 years. A PET scan would be conducted 6 weeks post-ASCT.

As per the non-SCT cohorts, patients incurred the costs of blood count, biochemistry and consultation at follow-up visits. The costs of CT/PET scans were assigned 6 weeks post-ASCT based on clinical expert opinion. These data were converted into weekly frequencies and are presented in Table 5.49.

**Table 5.49: Follow-up care ASCT**

| Clinical expert | Time, off-treatment (years) | | Frequency per week | | | | |
|---|---|---|---|---|---|---|---|
| | Start | End | CT scan | PET scan | Blood count | Biochemistry | Consultation |
| 1 | 0 | 5 | Two post-transplant | One post-transplant | 0.07 | 0.07 | 0.07 |
| | 5 | 8.5 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 0 | 2 | 0.00 | One post-treatment | 0.07 | 0.07 | 0.07 |
| | 2 | 5.5 | 0.00 | 0.00 | 0.04 | 0.04 | 0.04 |

Standard error of 20% assumed for frequencies

#### *5.5.3.4 Allo-SCT*

As per ASCT, four clinical experts were consulted to elicit resource use frequencies post-transplant, of which two provided the following schedules:

> **Clinical expert 1**: Patients are followed up every other week for three months, then every six weeks until six months, then every three months until four years post-transplant, then every 6-12 months for lifetime.
>
> **Clinical expert 2:** Patients are followed up every week for three months, then every month for a further six months, then every three months for a further five years post-transplant.

In addition, both clinical experts provided frequencies of resource use for each component stratified by time post-transplant (Table 5.50). Clinical opinion was that resource use for patients receiving allo-SCT is highest in the first three months of treatment. In light of this, follow-up care was stratified into the following time periods:

- 0-3 months post-allo-SCT
- 3-36 months post-allo-SCT
- 36-60 months post-allo-SCT
- >60 months post-allo-SCT

**Table 5.50: Follow-up care allo-SCT**

| Resource | Clinical expert 1 | | | Clinical expert 2 | | |
|---|---|---|---|---|---|---|
| | 0-24 months post-allo-SCT | 24-36 months post-allo-SCT | 36-60 months post-allo-SCT | 0-24 months post-allo-SCT | 24-36 months post-allo-SCT | 36-60 months post-allo-SCT |
| CT scan | 1 every 4 months | 1 per year | 0 | 0 | 0 | 0 |
| PET scan | 1 every 6 months | 1 per year | 0 | 1 | 0 | 0 |
| Consultation | 1 per month | 1 every 3 months | 1 every 4-6 months | 1 per week | 4 per year | Two per year |
| Blood count | 1 per month | 1 every 3 months | 1 every 4-6 months | With clinic | With clinic | With clinic |
| Biochemistry | 1 per month | 1 every 3 months | 1 every 4-6 months | With clinic | With clinic | With clinic |

As per the non-SCT cohorts, patients incurred the costs of blood count, biochemistry and consultation at follow-up visits. These data were converted into weekly frequencies and are presented in Table 5.51.

**Table 5.51: Follow-up care allo-SCT**

| Clinical expert | Time, off-treatment (years) | | Frequency per week | | | | |
|---|---|---|---|---|---|---|---|
| | Start | End | CT scan | PET scan | Blood count | Biochemistry | Consultation |
| 1 | 0 | 0.25 | One post-transplant | One post-transplant | 0.5 | 0.5 | 0.5 |
| | 0.25 | 2 | 0.06 | 0.04 | 0.23 | 0.23 | 0.23 |
| | 2 | 3 | 0.02 | 0.02 | 0.08 | 0.08 | 0.08 |
| | 3 | 60 | 0.00 | 0.00 | 0.04 | 0.04 | 0.04 |
| 2 | 0 | 0.25 | One post-transplant | One post-transplant | 1 | 1 | 1 |
| | 0.25 | 2 | 0.00 | 0.01 | 0.23 | 0.23 | 0.23 |
| | 2 | 3 | 0.00 | 0.00 | 0.08 | 0.08 | 0.08 |
| | 3 | 5 | 0.00 | 0.00 | 0.04 | 0.04 | 0.04 |

Standard error of 20% assumed for frequencies

Unit costs of follow-up care are sourced from the NHS reference costs (2015-2016)[81] (Table 5.52). The expected annual cost of each component is calculated by combining the unit cost with the frequency.

**Table 5.52: Follow-up care costs**

| Resource | Unit cost | | | HRG code |
|---|---|---|---|---|
| | Mean | LQ | UQ | |
| CT scan | £120.70 | £88.30 | £138.91 | RD26Z |
| PET scan | £436.08 | £353.93 | £453.71 | RN02A |
| Blood count | £3.10 | £2.17 | £3.65 | DAPS05, Haematology |
| Biochemistry | £1.18 | £0.78 | £1.39 | DAPS04, Clinical biochemistry |
| Consultation | £166.02 | £111.27 | £208.90 | WF01A, Clinical haematology |

In post-progression, the total discounted costs of follow-up care in pre-progression for brentuximab (no SCT) and chemotherapy (no SCT) were weighted according to the proportion of patients receiving each treatment in post-progression (Section 5.5.4) and assigned as a payoff to patients upon progressive disease. This approach therefore assumes resource use frequencies are independent of health state.

The proportion of patients experiencing disease progression in each cycle was based on the PFS curve and the proportion of PFS events in SG035-0004 which were progressive disease rather than death (Table 5.53). In addition, post-progression therapy costs were not assigned to patients leaving the PFS health state after the cure time point as these events were assumed to be deaths from general population mortality rather than disease progression.

**Table 5.53: PFS per INV events**

| Event | PFS per INV | Source |
|---|---|---|
| PD | 24 | SG035-004 CSR - Table 14.2.18 |
| Death | 4 | SG035-004 CSR - Table 14.2.3.11 |

### 5.5.4 Post-progression therapy

Patients are assumed to incur a one-off discounted cost of either brentuximab vedotin or chemotherapy treatment upon disease progression. Costs were calculated using the regimens and the chemotherapy distribution applied in the pre-progression health state and include; drug acquisition, drug administration, concomitant medications and adverse events.

The post-progression therapy distribution for the brentuximab vedotin cohorts was based on data from SG035-0004. For brentuximab vedotin (no SCT), 8 out of 24 (33%) patients who progressed following treatment without SCT in SG035-0004 were retreated with brentuximab vedotin.[52] For brentuximab vedotin + ASCT and brentuximab vedotin + allo-SCT; 2 out of 4 (50%) patients who progressed following treatment with brentuximab and SCT in SG035-0004 were retreated with brentuximab vedotin. In both cases, the residual were assumed to receive chemotherapy in post-progression.

Clinical expert opinion from the clinical expert survey (see section 5.3.8 was that 80% of patients who receive chemotherapy after first relapse would receive brentuximab after second relapse. This was applied to all chemotherapy cohorts. The residual were assumed to be retreated with chemotherapy in post-progression. Table 5.54 summarises the post-progression therapy distribution stratified by cohort.

**Table 5.54: Post-progression therapy distribution**

| Cohort | Post-progression therapy | |
|---|---|---|
| | Brentuximab | Chemotherapy |
| Brentuximab vedotin (no SCT) | 33% | 67% |
| Brentuximab vedotin + ASCT | 50% | 50% |
| Brentuximab vedotin + allo-SCT | 50% | 50% |
| Chemotherapy (no SCT) | 80% | 20% |
| Chemotherapy + ASCT | 80% | 20% |
| Chemotherapy + allo-SCT | 80% | 20% |

### 5.5.5 Adverse reaction unit costs and resource use

Adverse events (AEs) were included in the model if they satisfied the following criteria:

- Grade 1-2 events occurring in ≥10% of patients for either comparator
- Grade 3-4 events occurring in ≥5% of patients for either comparator

The rates of AEs for patients on brentuximab vedotin were based on the treatment-related adverse events (TRAEs) which occurred in the ITT population of the SG035-0004 trial. The ITT population was used in preference to the SCT and no-SCT subgroups separately to determine AE inclusion due to small patient numbers in each of the subgroups.

AE rates for chemotherapy were obtained from the studies used to inform dosing schedules (Table 5.3). Zelenetz et al., (2003)[56] which informed dosing for ICE did not report AE rates. A targeted search was thus conducted to identify an alternative study which reported AE rates for patients who receive ICE for R/R PTCL. This search identified Mikesch et al., (2013);[84] a retrospective analysis of 31 patients with R/R aggressive PTCL who underwent DexaBEAM or ICE as salvage therapy prior to HDT and ASCT. This study reported AE rates as a proportion of the total number of cycles received which was used as a proxy for the proportion of patients.

Ideally, AE rates for allo-SCT would have been obtained from the same source as PFS and OS; however these were not reported by Smith et al., (2013)[13] hence these were taken from Le Gouill (2008);[31] a retrospective analysis of 77 aggressive T-cell lymphoma (ATCL) patients (27 ALCL patients) identified by the SLR. This study is discussed in Section 5.4.5.2. AE rates are presented in Table 5.55.

Unit costs for grade 1-2 AEs were based on day-case costs in the NHS reference costs 2015-2016.[81] The costs of grade 3-4 neutropenia, peripheral sensory neuropathy, anaemia, thrombocytopenia and aGvHD were costed using a bottom-up approach. These data are presented in Table 5.56.

**Table 5.55: Adverse event rates**

| Event grade | Event | Brentuximab no, SCT (n=41) | Brentuximab, SCT (n=17) | ICE (n=16) | ESHAP (n=122) | DHAP (n=90) | GDP (n=20) | Gem-P (n=16) | Allo-SCT (n=27) |
|---|---|---|---|---|---|---|---|---|---|
| 1-2 | Alopecia | 10% | 12% | 0% | 0% | 0% | 45% | 0% | 0% |
| | Constipation | 12% | 12% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Diarrhoea | 12% | 29% | 11% | 0% | 0% | 0% | 0% | 0% |
| | Fatigue | 22% | 24% | 0% | 0% | 0% | 50% | 0% | 0% |
| | Myalgia | 12% | 24% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Nausea | 32% | 12% | 29% | 49% | 0% | 90% | 0% | 0% |
| | Neutropenia | 0% | 0% | 25% | 0% | 0% | 55% | 0% | 0% |
| | Peripheral sensory neuropathy | 32% | 59% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Pyrexia | 12% | 6% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Rash | 12% | 6% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Thrombocytopenia | 7% | 24% | 32% | 0% | 0% | 10% | 0% | 0% |
| | Upper respiratory tract infection | 15% | 12% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Vomiting | 15% | 12% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Anaemia | 0% | 0% | 64% | 0% | 0% | 50% | 0% | 0% |
| | Petechiae | 0% | 0% | 0% | 0% | 0% | 10% | 0% | 0% |
| | Liver transferase elevation | 0% | 0% | 0% | 0% | 0% | 15% | 0% | 0% |
| | Leukocytopenia | 0% | 0% | 14% | 0% | 0% | 0% | 0% | 0% |
| 3-4 | Diarrhoea | 0% | 0% | 0% | 0% | 20% | 0% | 0% | 0% |
| | Neutropenia | 15% | 24% | 0% | 30% | 53% | 35% | 63% | 0% |
| | Peripheral sensory neuropathy | 10% | 18% | 0% | 0% | 0% | 0% | 0% | 0% |

| Event grade | Event | Brentuximab no, SCT (n=41) | Brentuximab, SCT (n=17) | ICE (n=16) | ESHAP (n=122) | DHAP (n=90) | GDP (n=20) | Gem-P (n=16) | Allo-SCT (n=27) |
|---|---|---|---|---|---|---|---|---|---|
| | Thrombocytopenia | 7% | 24% | 54% | 0% | 39% | 15% | 0% | 0% |
| | Tumour lysis syndrome | 0% | 0% | 0% | 0% | 6% | 0% | 0% | 0% |
| | Nausea | 0% | 0% | 0% | 6% | 0% | 5% | 0% | 0% |
| | Increased creatinine levels | 0% | 0% | 0% | 22% | 20% | 0% | 0% | 0% |
| | Respiratory failure | 0% | 0% | 0% | 0% | 7% | 0% | 0% | 0% |
| | Sepsis | 0% | 0% | 0% | 0% | 31% | 0% | 0% | 0% |
| | aGVHD | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 19% |
| | Pulmonary infection | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 11% |
| | Anaemia | 0% | 0% | 21% | 0% | 0% | 0% | 13% | 0% |
| | Leukopenia | 0% | 0% | 75% | 0% | 0% | 0% | 63% | 0% |
| Source | | SG035-0004 | SG035-0004 | Mikesch (2013)[84] | Velasquez (1994)[58] | Velasquez (1988)[57] | Dong (2013)[59] | Arkenau (2007)[60] | Le Gouill (2008)[31] |

**Table 5.56: Adverse event costs**

| Event grade | Event | Cost | LQ | UQ | Source |
|---|---|---|---|---|---|
| 1-2 | Alopecia | £0 | £0 | £0 | Assumed no cost |
| | Constipation | £399.56 | £217.10 | £460.98 | NHS reference costs 2015-2016;[81] Daycase; FZ90B; Abdominal pain without interventions |
| | Diarrhoea | £399.56 | £217.10 | £460.98 | NHS reference costs 2015-2016;[81] Daycase; FZ90B; Abdominal pain without interventions |
| | Fatigue | £0 | £0 | £0 | Assumed no cost |
| | Myalgia | £0 | £0 | £0 | Assumed no cost |
| | Nausea | £0 | £0 | £0 | Assumed no cost |
| | Neutropenia | £287.36 | £151.11 | £308.02 | NHS reference costs 2015-2016;[81] Daycase; SA35E; Agranulocytosis with CC Score 0-1 |
| | Peripheral sensory neuropathy | £516.26 | £212.92 | £590.01 | NHS reference costs 2015-2016;[81] Daycase; AA26H; Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2 |
| | Pyrexia | £287.36 | £151.11 | £308.02 | Assumed equal to neutropenia |
| | Rash | £0.00 | £0.00 | £0.00 | Assumed no cost |
| | Thrombocytopenia | £324.52 | £176.43 | £425.03 | NHS reference costs 2015-2016;[81] Daycase; SA12K; Thrombocytopenia with CC Score 0-1 |
| | Upper respiratory tract infection | £348.16 | £194.99 | £363.50 | NHS reference costs 2015-2016;[81] Daycase; PD11C; Paediatric, Acute Upper Respiratory Tract Infection or Common Cold, with CC Score 0 |
| | Vomiting | £399.56 | £217.10 | £460.98 | NHS reference costs 2015-2016;[81] Daycase; FZ90B; Abdominal pain without interventions |
| | Anaemia | £351.18 | £187.18 | £425.03 | NHS reference costs 2015-2016;[81] Daycase; SA03H; Haemolytic Anaemia with CC Score 0-2 |
| | Petechiae | £0.00 | £0.00 | £0.00 | Assumed no cost |
| | Liver transferase elevation | £0.00 | £0.00 | £0.00 | Assumed no cost |
| | Leukocytopenia | £287.36 | £151.11 | £308.02 | Assumed equal to neutropenia |

| Event grade | Event | Cost | LQ | UQ | Source |
|---|---|---|---|---|---|
| 3-4 | Diarrhoea | £862.34 | £272.78 | £1,222.70 | NHS reference costs 2015-2016;[81] Daycase; FZ90A; Abdominal pain with interventions |
| | Neutropenia | £852.40 | N/A | N/A | See G3/4 Microcosting table below |
| | Peripheral sensory neuropathy | £733.33 | N/A | N/A | See G3/4 Microcosting table below |
| | Thrombocytopenia | £886.07 | N/A | N/A | See G3/4 Microcosting table below |
| | Tumour lysis syndrome | £600.07 | £161.35 | £1,221.59 | Assumed equal to sepsis |
| | Nausea | £862.34 | £272.78 | £1,222.70 | Assumed equal to diarrhoea |
| | Increased creatinine levels | £605.82 | £242.96 | £1,068.88 | NHS reference costs 2015-2016;[81] Daycase; LA07Z; Acute Kidney Injury without Interventions, with CC Score 4-7 |
| | Respiratory failure | £906.70 | £806.98 | £1,088.36 | NHS reference costs 2015-2016;[81] Daycase; DZ27R; Respiratory Failure with Single Intervention, with CC Score 0-5 |
| | Sepsis | £600.07 | £161.35 | £1,221.59 | NHS reference costs 2015-2016;[81] Daycase; WJ06F; Sepsis with Single Intervention, with CC Score 0-4 |
| | aGVHD | £31,479.60 | £7,869.90 | | Lee 2000 ($28,100 converted to GBP and inflated to 2016 prices) |
| | Pulmonary infection | £653.66 | £335.94 | £791.80 | NHS reference costs 2015-2016;[81] Daycase; DZ22L; Unspecified Acute Lower Respiratory Infection, with Interventions, with CC Score 0-8 |
| | Anaemia | £387.20 | N/A | N/A | See G3/4 Microcosting table below |
| | Leukopenia | £852.40 | N/A | N/A | Assumed equal to neutropenia |

**Table 5.57: Bottom-up costing for grade 3-4 adverse events**

| Event | Resource use and cost |
|---|---|
| G3-4 Anaemia | Blood transfusion<br>2 units of blood at £122/unit (NHS Blood and Transplant, Blood and Components, Price List 2015/2016)<br>1 transfusion at £143.50 (NICE Blood transfusion costing 2015, (NG24, Staff hours)) |
| G3-4 Neutropenia | G-CSF administration (100% patients):<br>Haematologist consultation £66; IQR: £111 to £208 (NHS reference costs 2015-16: Consultant led follow-up attendance, non-admitted face to face, Clinical Haematology 303)<br>Pegfilgrastim: 6mg syringe £686 (BNF 2016) |
| G3-4 Thrombocytopenia | As for neutropenia, with the following addition:<br>10% of patients receive 1 unit of platelets:<br>1 unit of platelets £193/unit (NHS Blood and Transplant, Blood and Components, Price List 2015/2016)<br>1 transfusion (cost as for anaemia) |
| G3-4 Peripheral sensory neuropathy | Two neurologist appointments, £216; IQR: £152 to £240 for first appointment (NHS Reference costs 2013-14: Consultant led first attendance non-admitted face to face, Neurology 400); £161; IQR: £122 to £179 for second appointment (NHS Reference costs 2015-16, Consultant led follow-up attendance).<br>Gabapentin, regimen: 3000mg/day for 42 days. 100 x 600mg capsules £16 (BNF 2016)<br>Ten sessions with a physiotherapist at a cost of £34 (band 5), PSSRU 2016 |
| Acute GvHD | $28,100 estimate from Lee 2000 inflated to current prices ($38,014) and converted to GBP = £31,480 |

## 5.5.6 Miscellaneous unit costs and resource use

### *5.5.6.1 ASCT*

The cost of ASCT is based on clinical expert opinion from the BMT Unit at the Beatson West of Scotland Cancer Centre (WoSCC), Glasgow (£53,790). This cost was validated by clinical experts and was ultimately preferred to the use of NHS reference costs for ASCT as this is believed to underestimate the total cost of ASCT in clinical practice.

However, as a sensitivity analysis, the total cost of ASCT was estimated based on a combination of the NHS reference costs 2015-2016,[81] PSSRU (2016)[85] and the BNF 2016.[16] This captures the cost the donation, conditioning and transplant (Table 5.58). This produced a total cost of £10,884, which is considered to be an underestimate of the actual cost of ASCT.

**Table 5.58: Cost of ASCT derived based on NHS reference costs, PSSRU and BNF sources**

| Resource | % pts. | Mean cost | LQ | UQ | Source |
|---|---|---|---|---|---|
| Specialist nurse for filgrastim admin (d1-5) | 50%# | £36 | £4 | N/A | PSSRU 2016 [85] |
| Specialist nurse for filgrastim admin (d5) | 50%# | £36 | £4 | N/A | PSSRU 2016 [85] |
| PBSC donation | 91%^ | £831 | £387 | £1,072 | NHS ref cost: SA34Z Peripheral blood stem cell harvest, Day case |
| Bone marrow donation | 9% | £3,120 | £2,135 | £4,029 | NHS ref cost: SA18Z Bone marrow harvest, Elective inpatient |
| Filgrastim | 100% | 1 million units/kg for 5 days at a cost of £52.70 per 30 million unit vial | | | BNF 72 (2016)[16] |

#Percentages based on expert opinion, for the purposes of the PSA this is assumed to be equivalent to a sample of 25 patients;
^ Sourced from Smith (2013)[13]

### *5.5.6.2 BEAM conditioning*

Patients in Smith et al., (2013)[13] received a range of conditioning regimens prior to ASCT (TBI-containing, BEAM, cyclophosphamide and busulfan combination regimens). Clinical expert opinion was that BEAM conditioning was most relevant to UK practice. In light of this, 100% of patients who received ASCT were assumed to incur the cost of BEAM. Regimens were based on the European Group for Blood/Marrow Transplantation (EBMT) (2008) Principles of conditioning guidance[86] and the corresponding drug costs were sourced from the BNF 72 (2016).[16]. Drug cost are presented in Table 5.59. Administration was assumed to occur in the inpatient setting. The relevant administration HRG code (SB05Z) was determined based on the NHS OPCS-4 chemotherapy regimen list (2013)[87] (mean cost: £869.60; LQ: £309.76; UQ: £1,040.52).

**Table 5.59: Beam conditioning costs**

| Treatment | Dose (mg/m2) | Days | Product size | Price | Source |
|---|---|---|---|---|---|
| Carmustine (lomustine price used) | 300 | 1 | 800 | £455.62 | BNF 2016 |
| Etoposide | 200 | 4 | 100 | £12.15 | BNF 2016 |
| Cytarabine | 400 | 4 | 2000 | £77.50 | BNF 2016 |
| Melphalan | 140 | 1 | 50 | £42.88 | BNF 2016 |

### *5.5.6.3 Transplant*

The cost of the autograft transplant was sourced from the NHS reference costs 2015-2016 (Table 5.60).

**Table 5.60: Transplant cost**

| Procedure | Mean cost | Lower quartile | Upper quartile | HRG Code |
|---|---|---|---|---|
| Autograft | £7,742 | £3,792 | £10,963 | NHS ref cost: SA19A; 19 years and over, mean stay = 17 days, elective inpatient |

### *5.5.6.4 Allo-SCT*

The base case cost of allo-SCT was based on a weighted average of sibling donor (£70,326) and volunteer unrelated donor (£126,915) costs provided to Takeda by the BMT Unit at the Beatson West of Scotland Cancer Centre (WoSCC), Glasgow. The proportion of patients receiving each type of transplant was also based on clinical expert opinion from this centre. These data are presented in Table 5.61.

**Table 5.61: Cost of allo-SCT based on Beatson WoSCC data**

| Transplant type | % pts. | Mean cost | Weighted average cost |
|---|---|---|---|
| Allo-SCT (sibling donor) | 33% | £70,326 | £108,052 |
| Allo-SCT (volunteer unrelated donor) | 67% | £126,915 | |

Source: Personal communication, BMT Programme Director, Beatson WoSCC.

As per the cost for ASCT, the cost estimate in Table 5.61 was preferred to the use of NHS reference costs for allo-SCT as the latter source is believed to provide an underestimate of the total cost of allo-SCT in clinical practice. This was confirmed with clinical experts in England.

However, as a sensitivity analysis, the total cost of allo-SCT was also based on estimating the separate cost of preparation excluding donation, stem cell donation, conditioning, and transplant using a combination of sources for unit costs. This produced a total cost of £57,550. The cost of each component is presented below.

### *Cost of preparation excluding donation*

Table 5.62 presents the costs used for allo-SCT preparation. Costs were sourced from NHSBT 2010, and exclude costs of donor harvest and follow-up. For related donors, costs were obtained from NHSBT 2010 and adapted assuming on average four relatives were consulted for HLA typing. All costs were inflated to current prices using the HCHS Pay and Prices Index. The proportion of unrelated donors was obtained from Smith et al., (2013)[13] (16%).

**Table 5.62: Cost of allo-SCT**

| Transplant type | Mean cost | Lower quartile | Upper quartile |
|---|---|---|---|
| Unrelated donor | £33,473 | £22,184 | £44,762 |
| Related donor | £9,947 | £6,592 | £13,302 |

### *Costs of stem cell donation*

Costs used for stem cell donation are presented in Table 5.63.

**Table 5.63: Stem cell donation costs**

| Resource | % pts. | Mean cost | SE/LQ | UQ | Source |
|---|---|---|---|---|---|
| Specialist nurse for filgrastim admin (d1-5) | 50%# | £36 | £4 | N/A | PSSRU 2016 [85] |
| Specialist nurse for filgrastim admin (d5) | 50%# | £36 | £4 | N/A | PSSRU 2016 [85] |
| PBSC donation | 71%^ | £831 | £387 | £1,072 | NHS ref cost: SA34Z Peripheral blood stem cell harvest, Day case |
| Bone marrow donation | 29% | £3,120 | £2,135 | £4,029 | NHS ref cost: SA18Z Bone marrow harvest, Elective inpatient |
| Filgrastim | 100% | 1 million units/kg for 5 days at a cost of £52.70 per 30 million unit vial | | N/A | BNF 2016 [16] |

#Percentages based on expert opinion, for the purposes of the PSA this is assumed to be equivalent to a sample of 25 patients;
^ Sourced from Smith et al., (2013)[13]

### *Conditioning*

Patients are assumed to receive either myeloablative or non-myeloablative/reduced intensity conditioning. The proportion of patients receiving myeloablative and non-myeloablative was 59% and 36% respectively based on Smith et al., (2013).[13] Regimens were based on the

EBMT (2008) Principles of conditioning guidance[86] and the corresponding drug costs were sourced from the BNF 2016.[16] Administration was assumed to occur in the inpatient setting. The relevant administration HRG codes were determined based on the NHS OPCS-4 chemotherapy regimen list (2013)[87] and costs were sourced from the NHS reference costs 2015-2016.[81] Table 5.64 presents conditioning costs used.

**Table 5.64: Conditioning costs**

| Treatment | Drug | Dose (mg/kg) | No. days | Product size | Cost | HRG | Mean | LQ | UQ |
|---|---|---|---|---|---|---|---|---|---|
| Myeloablative | Busulfan | 4 | 4 | 50 | £65.22 | SB03Z | £422.68 | £89.46 | £578.80 |
| | Cyclophosphamide | 60 | 2 | 5000 | £139.00 | | | | |
| Non-myeloablative/ RIC | Busulfan | 4 | 2 | 50 | £65.22 | SB05Z | £869.60 | £309.76 | £1,040.52 |
| | Fludarabine | 30* | 6 | 50 | £155.00 | | | | |

*per $m^2$

### *Transplant costs*

The proportion of patients who receive PBSC transplant was sourced from Smith et al., (2013)[13] (71%). The proportions of patients receiving each type of donor transplant were also based on Smith et al., (2013)[13] and re-scaled to form the residual 29%. Costs were sourced from the NHS reference costs 2015-2016.[81]

**Table 5.65: Transplant costs**

| Resource | % | Mean cost | Lower quartile/ SE | Upper quartile | HRG |
|---|---|---|---|---|---|
| PBSC allogeneic transplant | 71% | £40,168 | £31,287 | £52,257 | NHS ref costs: SA40Z; Allogeneic PBSCT, Allogeneic (Donor Type Not Specified), Elective inpatient mean stay = 29.32 days |
| Haploidentical sibling transplant | 17% | £41,520 | £25,409 | £55,154 | NHS ref costs: SA23A, Allogeneic Graft (Haplo-Identical), 19 years and over, mean stay = 33.3 days |
| Matched related | 7% | £32,595 | £17,680 | £35,255 | NHS ref costs: SA20A, Allogeneic BMT (Sibling) 19 years and over, mean stay = 22.59 days |
| Matched unrelated | 5% | £42,589 | £22,853 | £58,068 | NHS ref costs: SA21A, Allogeneic BMT (volunteer unrelated donor) 19 years and over, mean stay = 31.42 days |

#### *5.5.6.5 Allo-SCT: immunosuppressive treatments costs*

All patients who received allo-SCT are assumed to incur the cost of cyclosporine in combination with methotrexate or mycophenolate mofetil (MMF) as recommended by the EBMT – ELN working group guidelines.[88] The proportion of patients receiving cyclosporine in combination with methotrexate was based on Smith et al. (2013) (37%). The proportion of patients receiving cyclosporine in combination with MMF is assumed to be the residual. Regimens were based on those provided in the EBMT – ELN working group guidelines.[88] Unit costs were sourced from the BNF 2016. These data are presented in Table 5.66.

**Table 5.66: Immunosuppressive treatments costs**

| Treatment | Dose | Duration | Product size | Cost |
|---|---|---|---|---|
| Cyclosporine (IV) | 3mg/kg/day | 3 months | 250mg | £11.01 |
| Methotrexate | 10mg/m2 | 4 days | 20mg | £17.84 |
| Mycophenolate mofetil | 30mg/kg/day | 3 months | 25000mg | £9.31 |

Standard error assumed to be half of the mean

## 5.6 Summary of base-case de novo analysis inputs and assumptions

### 5.6.1 Summary of base-case de novo analysis inputs

**Table 5.67: Summary of variables applied in the economic model**

| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: UQ and LQ or s.e. (distribution) | Reference to section in submission |
|---|---|---|---|
| **Baseline Characteristics of the 0004 trial** | | | |
| Male | 57% | s.e: 7% (beta) | 5.3.1 |
| Age | 47.7 | s.e: 2.21 (normal) | |
| Weight | 76.35 kg | s.e. 2.68 (normal) | |
| BSA | 1.88 | s.e: 0.04 (normal) | |
| **Clinical Data- Brentuximab 0004 trial** | | | |
| Response rates ITT (investigator) | | | |
| Complete response (n) | 38 | Dirichlet | 5.2 |
| Partial response (n) | 12 | Dirichlet | |
| Stable disease (n) | 4 | Dirichlet | |
| Progressive disease (n) | 2 | Dirichlet | |
| Unknown/other (n) | 2 | Dirichlet | |
| Response rates no SCT (investigator) | | | |
| Complete response (n) | 22 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 11 | Dirichlet | |
| Stable disease (n) | 4 | Dirichlet | |
| Progressive disease (n) | 2 | Dirichlet | |
| Unknown/other (n) | 2 | Dirichlet | |
| Response rates ASCT (investigator) | | | |
| Complete response (n) | 8 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 0 | Dirichlet | |
| Stable disease (n) | 0 | Dirichlet | |
| Progressive disease (n) | 0 | Dirichlet | |
| Unknown/other (n) | 0 | Dirichlet | |
| Response rates Allo-SCT (investigator) | | | |

| | | | |
|---|---|---|---|
| Complete response (n) | 8 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 1 | Dirichlet | |
| Stable disease (n) | 0 | Dirichlet | |
| Progressive disease (n) | 0 | Dirichlet | |
| Unknown/other (n) | 0 | Dirichlet | |
| Response rates ITT (IRF) | | | |
| Complete response (n) | 34 | Dirichlet | 5.2 |
| Partial response (n) | 16 | Dirichlet | |
| Stable disease (n) | 2 | Dirichlet | |
| Progressive disease (n) | 3 | Dirichlet | |
| Unknown/other (n) | 3 | Dirichlet | |
| Response rates no SCT (IRF) | | | |
| Complete response (n) | 19 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 15 | Dirichlet | |
| Stable disease (n) | 2 | Dirichlet | |
| Progressive disease (n) | 3 | Dirichlet | |
| Unknown/other (n) | 2 | Dirichlet | |
| Response rates ASCT (IRF) | | | |
| Complete response (n) | 7 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 0 | Dirichlet | |
| Stable disease (n) | 0 | Dirichlet | |
| Progressive disease (n) | 0 | Dirichlet | |
| Unknown/other (n) | 1 | Dirichlet | |
| Response rates Allo-SCT (IRF) | | | |
| Complete response (n) | 8 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 1 | Dirichlet | |
| Stable disease (n) | 0 | Dirichlet | |
| Progressive disease (n) | 0 | Dirichlet | |
| Unknown/other (n) | 0 | Dirichlet | |
| **Clinical Data- chemotherapy** | | | |

| | | | |
|---|---|---|---|
| Response rates ITT (self-control) | | | |
| Complete response (n) | 12 | Dirichlet | 5.2 |
| Partial response (n) | 5 | Dirichlet | |
| Stable disease (n) | 4 | Dirichlet | |
| Progressive disease (n) | 14 | Dirichlet | |
| Unknown/other (n) | 4 | Dirichlet | |
| Response rates ITT (Dong 2013) | | | |
| Complete response (n) | 12 | Dirichlet | 5.2 |
| Partial response (n) | 11 | Dirichlet | |
| Stable disease (n) | 1 | Dirichlet | |
| Progressive disease (n) | 2 | Dirichlet | |
| Unknown/other (n) | 0 | Dirichlet | |
| Response rates ITT (Crump 2004) | | | |
| Complete response (n) | 8 | Dirichlet | 5.2 |
| Partial response (n) | 17 | Dirichlet | |
| Stable disease (n) | 9 | Dirichlet | |
| Progressive disease (n) | 9 | Dirichlet | |
| Unknown/other (n) | 9 | Dirichlet | |
| Response rates no SCT | | | |
| Complete response (n) | 12 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 5 | Dirichlet | |
| Stable disease (n) | 4 | Dirichlet | |
| Progressive disease (n) | 14 | Dirichlet | |
| Unknown/other (n) | 4 | Dirichlet | |
| Response rates ASCT | | | |
| Complete response (n) | 24 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 17 | Dirichlet | |
| Stable disease (n) | 5 | Dirichlet | |
| Progressive disease (n) | 5 | Dirichlet | |
| Unknown/other (n) | 2 | Dirichlet | |

| | | | |
|---|---|---|---|
| Response rates Allo-SCT | | | |
| Complete response (n) | 20 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 21 | Dirichlet | |
| Stable disease (n) | 9 | Dirichlet | |
| Progressive disease (n) | 9 | Dirichlet | |
| Unknown/other (n) | 3 | Dirichlet | |
| **Clinical Data- ASCT** | | | |
| Complete response (n) | 27 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 3 | Dirichlet | |
| Stable disease (n) | 3 | Dirichlet | |
| Progressive disease (n) | 34 | Dirichlet | |
| Time to transplant (weeks) | 29.7 | s.d: 10.4 | 5.3.2 and 5.4.5.2 |
| ALCL 3 year PFS estimate | 0.50 | - | 5.3.2 |
| ALCL 3 year OS estimate | 0.65 | - | |
| **Clinical Data- Allo-SCT** | | | |
| Complete response (n) | 19 | Dirichlet | 5.4.5.2 |
| Partial response (n) | 0 | Dirichlet | |
| Stable disease (n) | 0 | Dirichlet | |
| Progressive disease (n) | 6 | Dirichlet | |
| Time to transplant (weeks) | 47.9 | s.d: 40.1 | 5.3.2 and 5.4.5.2 |
| ALCL 3 year PFS estimate | 0.35 | - | 5.3.2 |
| ALCL 3 year OS estimate | 0.41 | - | |
| **Excess mortality vs general population** | | | |
| Brentuximab vedotin (no SCT) | 5% | - | 5.3.4.3 |
| Chemotherapy (no SCT) | 7% | - | |
| ASCT | 10% | - | |
| Allo-SCT | 10% | - | |
| **Utilities** | | | |
| CR | 0.91 | 0.01 (beta) | 5.4.5 |
| PR | 0.79 | 0.01 (beta) | |

| | | | |
|---|---|---|---|
| SD | 0.71 | 0.02 (beta) | |
| PD | 0.38 | 0.02 (beta) | |
| Decrement 0-6 months post-ASCT for CR vs general population - clinical expert 1 | 40% | 20% (beta) | |
| Decrement 0-6 months post-ASCT for CR vs general population - clinical expert 2 | 35% | 20% (beta) | |
| Decrement 0-6 months post-ASCT for CR vs general population - clinical expert 3 | 20% | 20% (beta) | |
| Decrement >6 months post-ASCT for CR vs general population - clinical expert 1 | 5% | 20% (beta) | |
| Decrement >6 months post-ASCT for CR vs general population - clinical expert 2 | 15% | 20% (beta) | |
| Decrement >6 months post-ASCT for CR vs general population - clinical expert 3 | 10% | 20% (beta) | |
| Decrement 0-6 months post-Allo-SCT for CR vs general population - clinical expert 1 | 50% | 20% (beta) | |
| Decrement 0-6 months post-Allo-SCT for CR vs general population - clinical expert 2 | 50% | 20% (beta) | |
| Decrement 0-6 months post-Allo-SCT for CR vs general population - clinical expert 3 | 50% | 20% (beta) | |
| Decrement >6 months post-Allo-SCT for CR vs general population - clinical expert 1 | 30% | 20% (beta) | |
| Decrement >6 months post-Allo-SCT for CR vs general population - clinical expert 2 | 35% | 20% (beta) | |
| Decrement >6 months post-Allo-SCT for CR vs general population - clinical expert 3 | 20% | 20% (beta) | |
| General population norm; 25-34 years | 0.93 | 0.01 (beta) | |
| General population norm; 35-44 years | 0.91 | 0.01 (beta) | |
| General population norm; 45-54 years | 0.85 | 0.01 (beta) | |
| General population norm; 55-64 years | 0.80 | 0.01 (beta) | |
| General population norm; 65-74 years | 0.78 | 0.01 (beta) | |
| General population norm; 75-100 years | 0.73 | 0.02 (beta) | |
| Cured time point (years) | 5 | - | |
| Cure decrement vs. general population | 5% | - | |

| | | | |
|---|---|---|---|
| Grade 1-2 Alopecia | -0.11 | 0.01 (gamma) | 5.4.4 |
| Grade 1-2 Constipation | -0.10 | 0.01 (gamma) | |
| Grade 1-2 Diarrhoea | -0.10 | 0.01 (gamma) | |
| Grade 1-2 Fatigue | -0.12 | 0.01 (gamma) | |
| Grade 1-2 Myalgia | -0.07 | 0.01 (gamma) | |
| Grade 1-2 Nausea | -0.10 | 0.01 (gamma) | |
| Grade 1-2 Neutropenia | -0.09 | 0.01 (gamma) | |
| Grade 1-2 Peripheral sensory neuropathy | -0.10 | 0.01 (gamma) | |
| Grade 1-2 Pyrexia | -0.03 | 0.00 (gamma) | |
| Grade 1-2 Rash | -0.03 | 0.00 (gamma) | |
| Grade 1-2 Thrombocytopenia | -0.27 | 0.03 (gamma) | |
| Grade 1-2 Upper respiratory tract infection | -0.20 | 0.02 (gamma) | |
| Grade 1-2 Vomiting | -0.10 | 0.01 (gamma) | |
| Grade 1-2 Anaemia | -0.09 | 0.01 (gamma) | |
| Grade 1-2 Petechiae | 0.00 | 0.00 (gamma) | |
| Grade 1-2 Liver transferase elevation | 0.00 | 0.00 (gamma) | |
| Grade 1-2 Leukocytopenia | -0.09 | 0.01 (gamma) | |
| Grade 3-4 Diarrhoea | -0.10 | 0.01 (gamma) | |
| Grade 3-4 Neutropenia | -0.09 | 0.01 (gamma) | |
| Grade 3-4 Peripheral sensory neuropathy | -0.33 | 0.03 (gamma) | |
| Grade 3-4 Thrombocytopenia | -0.27 | 0.03 (gamma) | |
| Grade 3-4 Tumour lysis syndrome | -0.12 | 0.01 (gamma) | |
| Grade 3-4 Nausea | -0.10 | 0.01 (gamma) | |
| Grade 3-4 Increased creatinine levels | 0.00 | 0.00 (gamma) | |
| Grade 3-4 Respiratory failure | -0.09 | 0.01 (gamma) | |
| Grade 3-4 Sepsis | -0.20 | 0.02 (gamma) | |
| Grade 3-4 aGVHD | -0.51 | 0.05 (gamma) | |
| Grade 3-4 Pulmonary infection | -0.20 | 0.02 (gamma) | |
| Grade 3-4 Anaemia | -0.09 | 0.01 (gamma) | |
| Grade 3-4 Leukopenia | -0.09 | 0.01 (gamma) | |

| | | | |
|---|---|---|---|
| **Adverse event rates** | | | |
| **Brentuximab (no SCT)** | | | |
| Grade 1-2 Alopecia | 4% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 9% | Beta | |
| Grade 1-2 Diarrhoea | 11% | Beta | |
| Grade 1-2 Fatigue | 29% | Beta | |
| Grade 1-2 Myalgia | 12% | Beta | |
| Grade 1-2 Nausea | 30% | Beta | |
| Grade 1-2 Neutropenia | 0% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 39% | Beta | |
| Grade 1-2 Pyrexia | 11% | Beta | |
| Grade 1-2 Rash | 8% | Beta | |
| Grade 1-2 Thrombocytopenia | 3% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 17% | Beta | |
| Grade 1-2 Vomiting | 8% | Beta | |
| Grade 1-2 Anaemia | 0% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 20% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 8% | Beta | |
| Grade 3-4 Thrombocytopenia | 10% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |
| Grade 3-4 Nausea | 0% | Beta | |
| Grade 3-4 Increased creatinine levels | 0% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |
| Grade 3-4 Sepsis | 0% | Beta | |
| Grade 3-4 aGVHD | 0% | Beta | |
| Grade 3-4 Pulmonary infection | 0% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Anaemia | 0% | Beta | |
| Grade 3-4 Leukopenia | 0% | Beta | |
| **Brentuximab, SCT** | | | |
| Grade 1-2 Alopecia | 7% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 14% | Beta | |
| Grade 1-2 Diarrhoea | 25% | Beta | |
| Grade 1-2 Fatigue | 39% | Beta | |
| Grade 1-2 Myalgia | 39% | Beta | |
| Grade 1-2 Nausea | 21% | Beta | |
| Grade 1-2 Neutropenia | 0% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 79% | Beta | |
| Grade 1-2 Pyrexia | 8% | Beta | |
| Grade 1-2 Rash | 15% | Beta | |
| Grade 1-2 Thrombocytopenia | 24% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 7% | Beta | |
| Grade 1-2 Vomiting | 8% | Beta | |
| Grade 1-2 Anaemia | 0% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 33% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 25% | Beta | |
| Grade 3-4 Thrombocytopenia | 22% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |
| Grade 3-4 Nausea | 0% | Beta | |
| Grade 3-4 Increased creatinine levels | 0% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |
| Grade 3-4 Sepsis | 0% | Beta | |
| Grade 3-4 aGVHD | 0% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Pulmonary infection | 0% | Beta | |
| Grade 3-4 Anaemia | 0% | Beta | |
| Grade 3-4 Leukopenia | 0% | Beta | |
| **ICE** | | | |
| Grade 1-2 Alopecia | 0% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 0% | Beta | |
| Grade 1-2 Diarrhoea | 19% | Beta | |
| Grade 1-2 Fatigue | 0% | Beta | |
| Grade 1-2 Myalgia | 0% | Beta | |
| Grade 1-2 Nausea | 26% | Beta | |
| Grade 1-2 Neutropenia | 17% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 1-2 Pyrexia | 0% | Beta | |
| Grade 1-2 Rash | 0% | Beta | |
| Grade 1-2 Thrombocytopenia | 24% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 0% | Beta | |
| Grade 1-2 Vomiting | 0% | Beta | |
| Grade 1-2 Anaemia | 61% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 19% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 0% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 3-4 Thrombocytopenia | 42% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |
| Grade 3-4 Nausea | 0% | Beta | |
| Grade 3-4 Increased creatinine levels | 0% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |
| Grade 3-4 Sepsis | 0% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 aGVHD | 0% | Beta | |
| Grade 3-4 Pulmonary infection | 0% | Beta | |
| Grade 3-4 Anaemia | 27% | Beta | |
| Grade 3-4 Leukopenia | 71% | Beta | |
| **ESHAP** | | | |
| Grade 1-2 Alopecia | 0% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 0% | Beta | |
| Grade 1-2 Diarrhoea | 0% | Beta | |
| Grade 1-2 Fatigue | 0% | Beta | |
| Grade 1-2 Myalgia | 0% | Beta | |
| Grade 1-2 Nausea | 45% | Beta | |
| Grade 1-2 Neutropenia | 0% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 1-2 Pyrexia | 0% | Beta | |
| Grade 1-2 Rash | 0% | Beta | |
| Grade 1-2 Thrombocytopenia | 0% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 0% | Beta | |
| Grade 1-2 Vomiting | 0% | Beta | |
| Grade 1-2 Anaemia | 0% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 33% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 3-4 Thrombocytopenia | 0% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |
| Grade 3-4 Nausea | 5% | Beta | |
| Grade 3-4 Increased creatinine levels | 23% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Sepsis | 0% | Beta | |
| Grade 3-4 aGVHD | 0% | Beta | |
| Grade 3-4 Pulmonary infection | 0% | Beta | |
| Grade 3-4 Anaemia | 0% | Beta | |
| Grade 3-4 Leukopenia | 0% | Beta | |
| **DHAP** | | | |
| Grade 1-2 Alopecia | 0% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 0% | Beta | |
| Grade 1-2 Diarrhoea | 0% | Beta | |
| Grade 1-2 Fatigue | 0% | Beta | |
| Grade 1-2 Myalgia | 0% | Beta | |
| Grade 1-2 Nausea | 0% | Beta | |
| Grade 1-2 Neutropenia | 0% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 1-2 Pyrexia | 0% | Beta | |
| Grade 1-2 Rash | 0% | Beta | |
| Grade 1-2 Thrombocytopenia | 0% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 0% | Beta | |
| Grade 1-2 Vomiting | 0% | Beta | |
| Grade 1-2 Anaemia | 0% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 23% | Beta | |
| Grade 3-4 Neutropenia | 49% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 3-4 Thrombocytopenia | 47% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 9% | Beta | |
| Grade 3-4 Nausea | 0% | Beta | |
| Grade 3-4 Increased creatinine levels | 13% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Respiratory failure | 3% | Beta | |
| Grade 3-4 Sepsis | 27% | Beta | |
| Grade 3-4 aGVHD | 0% | Beta | |
| Grade 3-4 Pulmonary infection | 0% | Beta | |
| Grade 3-4 Anaemia | 0% | Beta | |
| Grade 3-4 Leukopenia | 0% | Beta | |
| **GDP** | | | |
| Grade 1-2 Alopecia | 49% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 0% | Beta | |
| Grade 1-2 Diarrhoea | 0% | Beta | |
| Grade 1-2 Fatigue | 35% | Beta | |
| Grade 1-2 Myalgia | 0% | Beta | |
| Grade 1-2 Nausea | 89% | Beta | |
| Grade 1-2 Neutropenia | 66% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 1-2 Pyrexia | 0% | Beta | |
| Grade 1-2 Rash | 0% | Beta | |
| Grade 1-2 Thrombocytopenia | 5% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 0% | Beta | |
| Grade 1-2 Vomiting | 0% | Beta | |
| Grade 1-2 Anaemia | 52% | Beta | |
| Grade 1-2 Petechiae | 15% | Beta | |
| Grade 1-2 Liver transferase elevation | 11% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 31% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 3-4 Thrombocytopenia | 11% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |
| Grade 3-4 Nausea | 10% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Increased creatinine levels | 0% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |
| Grade 3-4 Sepsis | 0% | Beta | |
| Grade 3-4 aGVHD | 0% | Beta | |
| Grade 3-4 Pulmonary infection | 0% | Beta | |
| Grade 3-4 Anaemia | 0% | Beta | |
| Grade 3-4 Leukopenia | 0% | Beta | |
| **Gem-P** | | | |
| Grade 1-2 Alopecia | 0% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 0% | Beta | |
| Grade 1-2 Diarrhoea | 0% | Beta | |
| Grade 1-2 Fatigue | 0% | Beta | |
| Grade 1-2 Myalgia | 0% | Beta | |
| Grade 1-2 Nausea | 0% | Beta | |
| Grade 1-2 Neutropenia | 0% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 1-2 Pyrexia | 0% | Beta | |
| Grade 1-2 Rash | 0% | Beta | |
| Grade 1-2 Thrombocytopenia | 0% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 0% | Beta | |
| Grade 1-2 Vomiting | 0% | Beta | |
| Grade 1-2 Anaemia | 0% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 57% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 3-4 Thrombocytopenia | 0% | Beta | |
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Nausea | 0% | Beta | |
| Grade 3-4 Increased creatinine levels | 0% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |
| Grade 3-4 Sepsis | 0% | Beta | |
| Grade 3-4 aGVHD | 0% | Beta | |
| Grade 3-4 Pulmonary infection | 0% | Beta | |
| Grade 3-4 Anaemia | 8% | Beta | |
| Grade 3-4 Leukopenia | 58% | Beta | |
| **Allo-SCT** | | | |
| Grade 1-2 Alopecia | 0% | Beta | 5.5.5 |
| Grade 1-2 Constipation | 0% | Beta | |
| Grade 1-2 Diarrhoea | 0% | Beta | |
| Grade 1-2 Fatigue | 0% | Beta | |
| Grade 1-2 Myalgia | 0% | Beta | |
| Grade 1-2 Nausea | 0% | Beta | |
| Grade 1-2 Neutropenia | 0% | Beta | |
| Grade 1-2 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 1-2 Pyrexia | 0% | Beta | |
| Grade 1-2 Rash | 0% | Beta | |
| Grade 1-2 Thrombocytopenia | 0% | Beta | |
| Grade 1-2 Upper respiratory tract infection | 0% | Beta | |
| Grade 1-2 Vomiting | 0% | Beta | |
| Grade 1-2 Anaemia | 0% | Beta | |
| Grade 1-2 Petechiae | 0% | Beta | |
| Grade 1-2 Liver transferase elevation | 0% | Beta | |
| Grade 1-2 Leukocytopenia | 0% | Beta | |
| Grade 3-4 Diarrhoea | 0% | Beta | |
| Grade 3-4 Neutropenia | 0% | Beta | |
| Grade 3-4 Peripheral sensory neuropathy | 0% | Beta | |
| Grade 3-4 Thrombocytopenia | 0% | Beta | |

| | | | |
|---|---|---|---|
| Grade 3-4 Tumour lysis syndrome | 0% | Beta | |
| Grade 3-4 Nausea | 0% | Beta | |
| Grade 3-4 Increased creatinine levels | 0% | Beta | |
| Grade 3-4 Respiratory failure | 0% | Beta | |
| Grade 3-4 Sepsis | 0% | Beta | |
| Grade 3-4 aGVHD | 27% | Beta | |
| Grade 3-4 Pulmonary infection | 18% | Beta | |
| Grade 3-4 Anaemia | 0% | Beta | |
| Grade 3-4 Leukopenia | 0% | Beta | |
| **Adverse event durations** | | | |
| Grade 1-2 Alopecia | 183.00 | 91.50 (gamma) | 5.4.4 |
| Grade 1-2 Constipation | 6.00 | 0.60 (gamma) | |
| Grade 1-2 Diarrhoea | 6.00 | 0.60 (gamma) | |
| Grade 1-2 Fatigue | 31.50 | 3.15 (gamma) | |
| Grade 1-2 Myalgia | 31.50 | 3.15 (gamma) | |
| Grade 1-2 Nausea | 6.00 | 0.60 (gamma) | |
| Grade 1-2 Neutropenia | 15.10 | 1.51 (gamma) | |
| Grade 1-2 Peripheral sensory neuropathy | 3.00 | 0.30 (gamma) | |
| Grade 1-2 Pyrexia | 12.30 | 1.23 (gamma) | |
| Grade 1-2 Rash | 6.00 | 0.60 (gamma) | |
| Grade 1-2 Thrombocytopenia | 23.20 | 2.32 (gamma) | |
| Grade 1-2 Upper respiratory tract infection | 15.10 | 1.51 (gamma) | |
| Grade 1-2 Vomiting | 6.00 | 0.60 (gamma) | |
| Grade 1-2 Anaemia | 16.10 | 1.61 (gamma) | |
| Grade 1-2 Petechiae | 0.00 | 0.00 (gamma) | |
| Grade 1-2 Liver transferase elevation | 0.00 | 0.00 (gamma) | |
| Grade 1-2 Leukocytopenia | 15.10 | 1.51 (gamma) | |
| Grade 3-4 Diarrhoea | 6.00 | 0.60 (gamma) | |
| Grade 3-4 Neutropenia | 15.10 | 1.51 (gamma) | |
| Grade 3-4 Peripheral sensory neuropathy | 3.00 | 0.30 (gamma) | |

| | | | |
|---|---|---|---|
| Grade 3-4 Thrombocytopenia | 23.20 | 2.32 (gamma) | |
| Grade 3-4 Tumour lysis syndrome | 31.50 | 3.15 (gamma) | |
| Grade 3-4 Nausea | 6.00 | 0.60 (gamma) | |
| Grade 3-4 Increased creatinine levels | 0.00 | 0.00 (gamma) | |
| Grade 3-4 Respiratory failure | 15.10 | 1.51 (gamma) | |
| Grade 3-4 Sepsis | 23.20 | 2.32 (gamma) | |
| Grade 3-4 aGVHD | 14.00 | 1.40 (gamma) | |
| Grade 3-4 Pulmonary infection | 15.10 | 1.51 (gamma) | |
| Grade 3-4 Anaemia | 16.10 | 1.61 (gamma) | |
| Grade 3-4 Leukopenia | 15.10 | 1.51 (gamma) | |
| **Proportions of patients receiving each chemotherapy regimen** | | | |
| ICE | 25% | 5% (beta) | 5.5.2.2 |
| ESHAP | 25% | 5% (beta) | |
| DHAP | 25% | 5% (beta) | |
| GDP | 13% | 3% (beta) | |
| Gem-P | 13% | 3% (beta) | |
| **Regimens** | | | |
| Brentuximab (mg/kg) | 1.8 | - | 5.5.2.1 and 5.5.2.2 |
| Brentuximab admins per cycle and cycle length | 1; 21 | - | |
| Brentuximab RDI (no SCT) | 94.5% | 2% (beta) | |
| Brentuximab RDI (SCT) | 94.6% | 3% (beta) | |
| ICE | | | |
| Etoposide (mg/m2) | 100 | - | |
| Etoposide admins per cycle and cycle length | 3; 14 | - | |
| Etoposide RDI | 100% | 1% (beta) | |
| Carboplatin (mg) | 800 | - | |
| Carboplatin admins per cycle and cycle length | 1; 21 | - | |
| Carboplatin RDI | 100% | 1% (beta) | |
| Ifosfamide (mg/m2) | 5000 | - | |
| Ifosfamide admins per cycle and cycle length | 1; 14 | - | |

| | | | |
|---|---|---|---|
| Ifosfamide RDI | 100% | 1% (beta) | |
| ESHAP | | | |
| Cisplatin (mg/m2) | 25 | - | |
| Cisplatin admins per cycle and cycle length | 4; 21 | - | |
| Cisplatin RDI | 100% | 1% (beta) | |
| Methylprednisolone (mg) | 500 | - | |
| Methylprednisolone admins per cycle and cycle length | 5; 21 | - | |
| Methylprednisolone RDI | 100% | 1% (beta) | |
| Etoposide (mg/m2) | 40 | - | |
| Etoposide admins per cycle and cycle length | 4; 21 | - | |
| Etoposide RDI | 100% | 1% (beta) | |
| Cytarabine (mg/m2) | 2000 | - | |
| Cytarabine admins per cycle and cycle length | 1; 21 | - | |
| Cytarabine RDI | 100% | 1% (beta) | |
| DHAP | | | |
| Dexamethasone (mg) | 40 | - | |
| Dexamethasone admins per cycle and cycle length | 4; 21 | - | |
| Dexamethasone RDI | 100% | 1% (beta) | |
| Cisplatin (mg/m2) | 100 | - | |
| Cisplatin admins per cycle and cycle length | 1;21 | - | |
| Cisplatin RDI | 100% | 1% (beta) | |
| Cytarabine (mg/m2) | 2000 | - | |
| Cytarabine admins per cycle and cycle length | 2; 21 | - | |
| Cytarabine RDI | 100% | 1% (beta) | |
| GDP | | | |
| Gemcitabine (mg/m2) | 1250 | - | |
| Gemcitabine admins per cycle and cycle length | 2; 21 | - | |
| Gemcitabine RDI | 100% | 1% (beta) | |
| Dexamethasone (mg/m2) | 40 | - | |
| Dexamethasone admins per cycle and cycle length | 4; 21 | - | |

| | | | |
|---|---|---|---|
| Dexamethasone RDI | 100% | 1% (beta) | |
| Cisplatin (mg/m2) | 25 | - | |
| Cisplatin admins per cycle and cycle length | 3; 21 | - | |
| Cisplatin RDI | 100% | 1% (beta) | |
| Gem-P | | | |
| Gemcitabine (mg/m2) | 1250 | - | |
| Gemcitabine admins per cycle and cycle length | 2; 28 | - | |
| Gemcitabine RDI | 100% | 1% (beta) | |
| Cisplatin (mg/m2) | 25 | - | |
| Cisplatin admins per cycle and cycle length | 3; 28 | - | |
| Cisplatin RDI | 100% | 1% (beta) | |
| Methylprednisolone (mg/m2) | 1000 | - | |
| Methylprednisolone admins per cycle and cycle length | 5; 28 | - | |
| Methylprednisolone RDI | 100% | 1% (beta) | |
| **Time on treatment** | | | |
| Brentuximab cycles (no SCT) | 8 | N/A | 5.5.2.1 and 5.5.2.2 |
| Brentuximab cycles (SCT) | 8.8 | N/A | |
| ICE cycles | 3 | 0.30 | |
| ESHAP cycles | 7 | 0.70 | |
| DHAP cycles | 8 | 0.80 | |
| GDP cycles | 6 | 0.60 | |
| Gem-P cycles | 6 | 0.60 | |
| **Prophylactic treatment** | | | |
| Filgrastim (mg) | 300 | - | 5.5.2.4 |
| Filgrastim admins per day and days per cycle | 1; 7 | - | |
| Levofloxacin (mg) | 500 | - | |
| Levofloxacin admins per day and days per cycle | 1; 7 | - | |
| Acyclovir (mg) | 400 | - | |
| Acyclovir admins per day and days per cycle | 2; 7 | - | |
| **Antiemetics** | | | |

| | | | |
|---|---|---|---|
| Low risk: dexamethasone (mg) | 12 | - | 5.5.2.4 |
| Low risk: dexamethasone admins per cycle | 1 | - | |
| Moderate risk: dexamethasone (mg) | 12 | - | |
| Moderate risk: dexamethasone admins per cycle | 1 | - | |
| Moderate risk: ondansetron (mg) | 20 | - | |
| Moderate risk: ondansetron admins per cycle | 1 | - | |
| Moderate risk: dexamethasone (mg) | 8 | - | |
| Moderate risk: dexamethasone admins per cycle | 2 | - | |
| High risk: dexamethasone (mg) | 12 | - | |
| High risk: dexamethasone admins per cycle | 1 | - | |
| High risk: ondansetron (mg) | 20 | - | |
| High risk: ondansetron admins per cycle | 1 | - | |
| High risk: aprepitant (mg) | 125 | - | |
| High risk: aprepitant admins per cycle | 1 | - | |
| High risk: dexamethasone (mg) | 8 | - | |
| High risk: dexamethasone admins per cycle | 3 | - | |
| High risk: aprepitant (mg) | 80 | - | |
| High risk: aprepitant admins per cycle | 2 | - | |
| **Radiotherapy** | | | |
| Proportion of patients receiving radiotherapy | 15% | 1% (beta) | 5.5.2.3 |
| Number of attendances for delivering a fraction of treatment on a megavoltage machine | 15 | 1.5 (gamma) | |
| **Follow-up care** | | | |
| CT scan frequency per week (on treatment with brentuximab) | 0.13 | 0.03 (gamma) | 5.5.3 |
| PET scan frequency per week (on treatment with brentuximab) | 0.08 | 0.02 (gamma) | |
| Blood count frequency per week (on treatment with brentuximab) | 0.33 | 0.07 (gamma) | |
| Biochemistry frequency per week (on treatment with brentuximab) | 0.33 | 0.07 (gamma) | |
| Consultation frequency per week (on treatment with | 0.33 | 0.07 (gamma) | |

| | | | |
|---|---|---|---|
| brentuximab) | | | |
| CT scan frequency per week (on treatment with chemotherapy) | 0.17 | 0.03 (gamma) | |
| PET scan frequency per week (on treatment with chemotherapy) | 0.11 | 0.02 (gamma) | |
| Blood count frequency per week (on treatment with chemotherapy) | 0.33 | 0.07 (gamma) | |
| Biochemistry frequency per week (on treatment with chemotherapy) | 0.33 | 0.07 (gamma) | |
| Consultation frequency per week (on treatment with chemotherapy) | 0.33 | 0.07 (gamma) | |
| CT scan frequency per week (off treatment) to 3 years – clinical expert 1 | Once | - | |
| PET scan frequency per week (off treatment) to 3 years – clinical expert 1 | Once | - | |
| Blood count frequency per week (off treatment) to 3 years – clinical expert 1 | 0.07 | 0.01 (gamma) | |
| Biochemistry frequency per week (off treatment) to 3 years – clinical expert 1 | 0.07 | 0.01 (gamma) | |
| Consultation frequency per week (off treatment) to 3 years – clinical expert 1) | 0.07 | 0.01 (gamma) | |
| CT scan frequency per week (off treatment) 3 years - lifetime – clinical expert 1 | 0.00 | 0.00 | |
| PET scan frequency per week (off treatment) 3 years - lifetime – clinical expert 1 | 0.00 | 0.00 | |
| Blood count frequency per week (off treatment) 3 years - lifetime – clinical expert 1 | 0.00 | 0.00 | |
| Biochemistry frequency per week (off treatment) 3 years - lifetime – clinical expert 1 | 0.00 | 0.00 | |
| Consultation frequency per week (off treatment) 3 years - lifetime – clinical expert 1 | 0.00 | 0.00 | |
| CT scan frequency per week (off treatment) to 2 years – clinical expert 2 | Once | - | |
| PET scan frequency per week (off treatment) to 2 years – clinical expert 2 | Once | - | |
| Blood count frequency per week (off treatment) to 2 years – clinical expert 2 | 0.07 | 0.01 (gamma) | |

| | | | |
|---|---|---|---|
| Biochemistry frequency per week (off treatment) to 2 years – clinical expert 2 | 0.07 | 0.01 (gamma) | |
| Consultation frequency per week (off treatment) to 2 years – clinical expert 2 | 0.07 | 0.01 (gamma) | |
| CT scan frequency per week (off treatment) 2 years – 4.5 – clinical expert 2 | 0.00 | 0.00 (gamma) | |
| PET scan frequency per week (off treatment) 2 years – 4.5 – clinical expert 1 | 0.00 | 0.00 (gamma) | |
| Blood count frequency per week (off treatment) 2 years – 4.5 – clinical expert 2 | 0.04 | 0.01 (gamma) | |
| Biochemistry frequency per week (off treatment) 2 years – 4.5 – clinical expert 2 | 0.04 | 0.01 (gamma) | |
| Consultation frequency per week (off treatment) 2 years – 4.5 – clinical expert 2 | 0.04 | 0.01 (gamma) | |
| ASCT CT scan frequency per week 0-5 years - clinical expert 1 | 2.00 | - | |
| ASCT PET scan frequency per week 0-5 years - clinical expert 1 | 1.00 | - | |
| ASCT Blood count frequency per week 0-5 years - clinical expert 1 | 0.07 | 0.01 (gamma) | |
| ASCT Biochemistry frequency per week 0-5 years - clinical expert 1 | 0.07 | 0.01 (gamma) | |
| ASCT Consultation frequency per week 0-5 years - clinical expert 1 | 0.07 | 0.01 (gamma) | |
| ASCT CT scan frequency per week 5+ years - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| ASCT PET scan frequency per week 5+ years - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| ASCT Blood count frequency per week 5+ years - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| ASCT Biochemistry frequency per week 5+ years - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| ASCT Consultation frequency per week 5+ years - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| ASCT CT scan frequency per week 0-2 years - clinical expert 2 | 0.00 | - | |
| ASCT PET scan frequency per week 0-2 years - clinical | 1.00 | - | |

| | | | |
|---|---|---|---|
| expert 2 | | | |
| ASCT Blood count frequency per week 0-2 years - clinical expert 2 | 0.07 | 0.01 (gamma) | |
| ASCT Biochemistry frequency per week 0-2 years - clinical expert 2 | 0.07 | 0.01 (gamma) | |
| ASCT Consultation frequency per week 0-2 years - clinical expert 2 | 0.07 | 0.01 (gamma) | |
| ASCT CT scan frequency per week 2+ years - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| ASCT PET scan frequency per week 2+ years - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| ASCT Blood count frequency per week 2+ years - clinical expert 2 | 0.04 | 0.01 (gamma) | |
| ASCT Biochemistry frequency per week 2+ years - clinical expert 2 | 0.04 | 0.01 (gamma) | |
| ASCT Consultation frequency per week 2+ years - clinical expert 2 | 0.04 | 0.01 (gamma) | |
| Allo-SCT CT scan frequency per week 0-3 months - clinical expert 1 | 1 | - | |
| Allo-SCT PET scan frequency per 0-3 months - clinical expert 1 | 1 | - | |
| Allo-SCT Blood count frequency per week 0-3 months - clinical expert 1 | 0.50 | 0.10 (gamma) | |
| Allo-SCT Biochemistry frequency per week 0-3 months - clinical expert 1 | 0.50 | 0.10 (gamma) | |
| Allo-SCT Consultation frequency per week 0-3 months - clinical expert 1 | 0.50 | 0.10 (gamma) | |
| Allo-SCT CT scan frequency per week 3-24 months - clinical expert 1 | 0.06 | 0.01 (gamma) | |
| Allo-SCT PET scan frequency per 3-24 months - clinical expert 1 | 0.04 | 0.01 (gamma) | |
| Allo-SCT Blood count frequency per week 3-24 months - clinical expert 1 | 0.23 | 0.05 (gamma) | |
| Allo-SCT Biochemistry frequency per week 3-24 months - clinical expert 1 | 0.23 | 0.05 (gamma) | |
| Allo-SCT Consultation frequency per week 3-24 months - clinical expert 1 | 0.23 | 0.05 (gamma) | |

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|---|---|---|---|
| Allo-SCT CT scan frequency per week 24-36 months - clinical expert 1 | 0.02 | 0.00 (gamma) | |
| Allo-SCT PET scan frequency per 24-36 months - clinical expert 1 | 0.02 | 0.00 (gamma) | |
| Allo-SCT Blood count frequency per week 24-36 months - clinical expert 1 | 0.08 | 0.02 (gamma) | |
| Allo-SCT Biochemistry frequency per week 24-36 months - clinical expert 1 | 0.08 | 0.02 (gamma) | |
| Allo-SCT Consultation frequency per week 24-36 months - clinical expert 1 | 0.08 | 0.02 (gamma) | |
| Allo-SCT CT scan frequency per week 36 months-lifetime - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| Allo-SCT PET scan frequency per 24-36 months - clinical expert 1 | 0.00 | 0.00 (gamma) | |
| Allo-SCT Blood count frequency per week 36 months-lifetime - clinical expert 1 | 0.04 | 0.01 (gamma) | |
| Allo-SCT Biochemistry frequency per week 36 months-lifetime - clinical expert 1 | 0.04 | 0.01 (gamma) | |
| Allo-SCT Consultation frequency per week 36 months-lifetime - clinical expert 1 | 0.04 | 0.01 (gamma) | |
| Allo-SCT CT scan frequency per week 0-3 months - clinical expert 2 | 1 | - | |
| Allo-SCT PET scan frequency per 0-3 months - clinical expert 2 | 1 | - | |
| Allo-SCT Blood count frequency per week 0-3 months - clinical expert 2 | 1.00 | 0.20 (gamma) | |
| Allo-SCT Biochemistry frequency per week 0-3 months - clinical expert 2 | 1.00 | 0.20 (gamma) | |
| Allo-SCT Consultation frequency per week 0-3 months - clinical expert 2 | 1.00 | 0.20 (gamma) | |
| Allo-SCT CT scan frequency per week 3-24 months - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| Allo-SCT PET scan frequency per 3-24 months - clinical expert 2 | 0.01 | 0.00 (gamma) | |
| Allo-SCT Blood count frequency per week 3-24 months - clinical expert 2 | 0.23 | 0.05 (gamma) | |
| Allo-SCT Biochemistry frequency per week 3-24 months - | 0.23 | 0.05 (gamma) | |

| | | | |
|---|---|---|---|
| clinical expert 2 | | | |
| Allo-SCT Consultation frequency per week 3-24 months - clinical expert 2 | 0.23 | 0.05 (gamma) | |
| Allo-SCT CT scan frequency per week 24-36 months - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| Allo-SCT PET scan frequency per 24-36 months - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| Allo-SCT Blood count frequency per week 24-36 months - clinical expert 2 | 0.08 | 0.02 (gamma) | |
| Allo-SCT Biochemistry frequency per week 24-36 months - clinical expert 2 | 0.08 | 0.02 (gamma) | |
| Allo-SCT Consultation frequency per week 24-36 months - clinical expert 2 | 0.08 | 0.02 (gamma) | |
| Allo-SCT CT scan frequency per week 36 -60 months - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| Allo-SCT PET scan frequency per 36 -60 months - clinical expert 2 | 0.00 | 0.00 (gamma) | |
| Allo-SCT Blood count frequency per week 36 -60 months - clinical expert 2 | 0.04 | 0.01 (gamma) | |
| Allo-SCT Biochemistry frequency per week 36 -60 months - clinical expert 2 | 0.04 | 0.01 (gamma) | |
| Allo-SCT Consultation frequency per week 36 -60 months - clinical expert 2 | 0.04 | 0.01 (gamma) | |
| **Post-progression therapy** | | | |
| Proportion on brentuximab (no SCT) who receive brentuximab | 33% | Beta | 5.5.4 |
| Proportion on brentuximab (no SCT) who receive chemotherapy | 67% | - | |
| Proportion on brentuximab + ASCT who receive brentuximab | 50% | Beta | |
| Proportion on brentuximab + ASCT who receive chemotherapy | 50% | - | |
| Proportion on brentuximab + Allo-SCT who receive brentuximab | 50% | Beta | |
| Proportion on brentuximab + Allo-SCT who receive chemotherapy | 50% | - | |
| Proportion on chemotherapy (no SCT) who receive | 80% | Beta | |

| | | | |
|---|---|---|---|
| brentuximab | | | |
| Proportion on chemotherapy (no SCT) who receive chemotherapy | 20% | - | |
| Proportion on chemotherapy + ASCT who receive brentuximab | 80% | Beta | |
| Proportion on chemotherapy + ASCT who receive chemotherapy | 20% | - | |
| Proportion on chemotherapy + Allo-SCT who receive brentuximab | 80% | Beta | |
| Proportion on chemotherapy + Allo-SCT who receive chemotherapy | 20% | - | |
| **Acquisition costs** | | | |
| Brentuximab | £2,500 | - | 5.5.2. |
| ICE | | | |
| Etoposide (100mg) | £12.15 | - | |
| Carboplatin (150mg) | £50.00 | - | |
| Ifosfamide (1000mg) | £66.08 | - | |
| ESHAP | | | |
| Cisplatin (50mg) | £24.50 | - | |
| Methylprednisolone (2000mg) | £48.32 | - | |
| Etoposide (100mg) | £12.15 | - | |
| Cytarabine (2000mg) | £77.50 | - | |
| DHAP | | | |
| Dexamethasone (200mg) | £78.00 | - | |
| Cisplatin (50mg) | £24.50 | - | |
| Cytarabine (2000mg) | £77.50 | - | |
| GDP | | | |
| Gemcitabine (200mg) | £29.80 | - | |
| Dexamethasone (200mg) | £78.00 | - | |
| Cisplatin (50mg) | £24.50 | - | |
| Gem-P | | | |
| Gemcitabine (200mg) | £29.80 | - | |

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|---|---|---|---|
| Cisplatin (50mg) | £24.50 | - | |
| Methylprednisolone (2000mg) | £48.32 | - | |
| **Administration costs** | | | |
| Outpatient: SB12Z | £198.93 | LQ: £188.89; UQ: £219.26 | 5.5.2 |
| Outpatient: SB13Z | £265.01 | LQ: £205.82; UQ: £368.50 | |
| Outpatient: SB15Z | £211.99 | LQ: £164.62; UQ: £246.09 | |
| Day case/regular day/night admission: SB14Z | £406.63 | LQ: £258.49; UQ: £520.85 | |
| Day case/regular day/night admission: SB15Z | £361.03 | LQ: £206.37; UQ: £426.59 | |
| **Prophylactic treatment costs** | | | |
| Filgrastim (300mg) | £52.70 | - | 5.5.2 |
| Levofloxacin (2500mg) | £11.57 | - | |
| Acyclovir (5000mg) | £2.85 | - | |
| **Antiemetics** | | | |
| Dexamethasone (200mg) | £78 | - | 5.5.2 |
| Ondansetron (120mg) | £5.37 | - | |
| Aprepitant (285mg) | £47.42 | - | |
| **Adverse events** | | | |
| Grade 1-2 Alopecia | £0.00 | LQ: £0; UQ: £0 | 5.5.5 |
| Grade 1-2 Constipation | £399.56 | LQ: £217.1; UQ: 460.98 | |
| Grade 1-2 Diarrhoea | £399.56 | LQ: £217.1; UQ: 460.98 | |
| Grade 1-2 Fatigue | £0.00 | LQ: £0; UQ: £0 | |
| Grade 1-2 Myalgia | £0.00 | LQ: £0; UQ: £0 | |
| Grade 1-2 Nausea | £0.00 | LQ: £0; UQ: £0 | |
| Grade 1-2 Neutropenia | £287.36 | LQ: £151.11; UQ: 308.02 | |
| Grade 1-2 Peripheral sensory neuropathy | £516.26 | LQ: £212.92; UQ: £590.01 | |
| Grade 1-2 Pyrexia | £287.36 | LQ: £151.11; UQ: £308.02 | |
| Grade 1-2 Rash | £0.00 | LQ: £0; UQ: £0 | |
| Grade 1-2 Thrombocytopenia | £324.52 | LQ: £176.43; UQ: £425.03 | |
| Grade 1-2 Upper respiratory tract infection | £348.16 | LQ: £194.99; UQ: £363.495 | |
| Grade 1-2 Vomiting | £399.56 | LQ: £217.1; £UQ: £460.9825 | |

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|---|---|---|---|
| Grade 1-2 Anaemia | £351.18 | LQ: £187.18; UQ: £425.03 | |
| Grade 1-2 Petechiae | £0.00 | LQ: £0; UQ: £0 | |
| Grade 1-2 Liver transferase elevation | £0.00 | LQ: £0; UQ: £0 | |
| Grade 1-2 Leukocytopenia | £287.36 | LQ: £151.11; UQ: £308.02 | |
| Grade 3-4 Diarrhoea | £862.34 | LQ: £272.78; UQ: £1222.70 | |
| Grade 3-4 Neutropenia: pegfilgrastim | £686.38 | - | |
| Grade 3-4 Neutropenia: administration | £166.02 | LQ: £111.27; UQ: £208.90 | |
| Grade 3-4 Peripheral sensory neuropathy: Neurologist appointment 1 | £216.58 | LQ: £152.16; UQ: £240.28 | |
| Grade 3-4 Peripheral sensory neuropathy: Neurologist appointment 2 | £160.76 | LQ: £121.89; UQ: £179.13 | |
| Grade 3-4 Peripheral sensory neuropathy: Physiotherapist | £34.00 | s.e: £3.40 | |
| Grade 3-4 Peripheral sensory neuropathy: Gabapentin | £16.00 | - | |
| Grade 3-4 thrombocytopenia: pegfilgrastim | £686.38 | - | |
| Grade 3-4 thrombocytopenia: administration | £166.02 | LQ: £111.27; UQ: £208.90 | |
| Grade 3-4 thrombocytopenia: platelets | £193.15 | - | |
| Grade 3-4 thrombocytopenia: transfusion | £143.50 | s.e: £14.35 | |
| Grade 3-4 Tumour lysis syndrome | £600.07 | LQ: £161.345; £UQ: 1221.59 | |
| Grade 3-4 Nausea | £862.34 | LQ: £272.78; UQ: £1222.7 | |
| Grade 3-4 Increased creatinine levels | £605.82 | LQ: £242.96; UQ: £1068.88 | |
| Grade 3-4 Respiratory failure | £906.70 | LQ: £806.98; UQ: £1088.36 | |
| Grade 3-4 Sepsis | £600.07 | LQ: £161.345; UQ: £1221.59 | |
| Grade 3-4 aGVHD | £31,479.60 | s.e: £7869.90 | |
| Grade 3-4 Pulmonary infection | £653.66 | LQ: £335.94; £UQ: 791.795 | |
| Grade 3-4 Anaemia: Red blood cells | £121.85 | - | |
| Grade 3-4 Anaemia: Transfusion | £143.50 | £14.35 | |

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|---|---|---|---|
| Grade 3-4 Leukopenia | £852.40 | - | |
| **Follow-up care costs** | | | |
| CT scan | £120.70 | LQ: £88.3; UQ: £138.91 | 5.5.3 |
| PET scan | £436.08 | LQ: £353.93; UQ: £453.71 | |
| Blood count | £3.10 | LQ: £2.17; UQ: £3.65 | |
| Biochemistry | £1.18 | LQ: £0.78; UQ: £1.39 | |
| Consultation | £166.02 | LQ: £111.27; UQ: £208.9 | |
| **Radiotherapy costs** | | | |
| Preparation for simple radiotherapy with imaging and dosimetry | £338.57 | LQ: £233.51; UQ: £386.72 | 5.5.2.3 |
| Deliver a fraction of treatment on a megavoltage machine | £104.77 | LQ: £71.35; UQ: £135.09 | |
| **SCT treatment pathway** | | | |
| Proportion intended for transplant (Mak 2013) | 29% | Beta | 5.2.3.4 |
| Proportion intended who transplant (Mak 2013) | 69% | Beta | |
| Proportion of CRs intended for transplant – clinical expert opinion | 100% | - | |
| Proportion of PRs intended for transplant - clinical expert opinion | 50% | - | |
| **ASCT NHS reference costs** | | | |
| PSBC donation (%) | 71% | Beta | 5.5.6.4 |
| Bone marrow donation (%) | 29% | Beta | |
| Specialist nurse for filgrastim admin (d1-5) | £58 | £6 (gamma) | |
| Specialist nurse for filgrastim admin (d5) | £58 | N/A | |
| PBSC donation | £831 | LQ: £387; UQ: £1072 (gamma) | |
| Bone marrow donation | £3,120 | LQ: £2135; UQ: £4029 (gamma) | |
| Filgrastim (1 million units for 5 days) (300mg) | £52.70 | - | |
| Carmustine dose (mg) and number of days | 300mg; 1 day | - | |
| Etoposide dose (mg) and number of days | 200mg; 4 days | - | |
| Cytarabine dose (mg) and number of days | 400mg; 4 days | - | |
| Melphalan dose (mg) and number of days | 140mg; 1 day | - | |
| Lomustine (800mg) | £455.62 | - | |

| | | | |
|---|---|---|---|
| Etoposide (100mg) | £12.15 | - | |
| Cytarabine (2000mg) | £77.50 | - | |
| Melphalan (50mg) | £42.88 | - | |
| Autograft | £7,742 | LQ: £3,792; UQ; £10,963 (gamma) | |
| **Clinical opinion cost** | £53,790 | - | |
| **Allo-SCT NHS reference costs** | | | |
| Cost of preparation excluding donation – unrelated donor | £33,473 | LQ: £22,182; UQ: £44,762 | 5.5.6.4 |
| Cost of preparation excluding donation – related donor | £9,947 | LQ: £6,592; UQ: £13,302 | |
| Specialist nurse for filgrastim admin (d1-5) | £58 | £6 (gamma) | |
| Specialist nurse for filgrastim admin (d5) | £58 | N/A | |
| PBSC donation | £831 | LQ: £387; UQ: £1072 (gamma) | |
| Bone marrow donation | £3,120 | LQ: £2135; UQ: £4029 (gamma) | |
| Filgrastim (1 million units for 5 days) (300mg) | £52.70 | - | |
| % receiving myeloablative regimens | 59% | Beta | |
| % receiving non-myeloablative/RIC regimens | 36% | Beta | |
| Myeloablative – Busulfan (mg/kg) and duration of treatment | 4mg; 4 days | - | |
| Myeloablative – Cyclophosphamide (mg/kg) and duration of treatment | 60mg; 2 days | - | |
| Non-myeloablative – Busulfan (mg/kg) and duration of treatment | 4mg; 2 days | - | |
| Non-myeloablative – Fludarabine (mg/m2) and duration of treatment | 30; 6 days | - | |
| Busulfan (50mg) | £65.22 | - | |
| Cyclophosphamide (5000mg) | £139.00 | - | |
| Busulfan (50mg) | £65.22 | - | |
| Fludarabine (50mg) | £155.00 | - | |
| Administration for myeloablative – SB03Z | £423 | LQ: £89; UQ: £579 (gamma) | |
| Administration for non-myeloablative – SB05Z | £870 | LQ: £310; UQ: £1,041 (gamma) | |
| PBSC allogeneic transplant % | 71% | Beta | |
| Haploidentical sibling transplant % | 60% | Beta | |
| Matched related % | 24% | Beta | |

| | | | |
|---|---|---|---|
| Matched unrelated % | 16% | Beta | |
| PBSC allogeneic transplant | £40,168 | LQ: £31,287; UQ: £52,257 (gamma) | |
| Haploidentical sibling transplant | £41,520 | LQ: £25,409; UQ: £55,154 (gamma) | |
| Matched related | £32,595 | LQ: £17,680; UQ: £35,255 (gamma) | |
| Matched unrelated | £42,589 | LQ: £22,853; UQ: £58,068 (gamma) | |
| **Clinical opinion** | | | |
| Sibling donor % | 33% | Beta | |
| Volunteer unrelated donor % | 67% | Beta | |
| Sibling donor | £70,326 | - | |
| Volunteer unrelated donor | £126,915 | - | |
| **Immunosuppressive treatment** | | | |
| Cyclosporin % | 100% | Beta | 5.5.6.5 |
| Methotrexate % | 37% | Beta | |
| Mycophenolate mofetil % | 63% | Beta | |
| Cyclosporin dose and duration of treatment | 3mg/kg; 91 days | - | |
| Methotrexate dose and duration of treatment | 10mg/m2; 4 days | - | |
| Mycophenolate mofetil dose and duration of treatment | 30mg/kg; 91 days | - | |
| Cyclosporin | £11.01 | - | |
| Methotrexate | £17.84 | - | |
| Mycophenolate mofetil | £9.31 | - | |

### 5.6.2 Summary of key model assumptions

A summary of key model assumptions is presented in Table 5.68

**Table 5.68: Summary of key model assumptions and justification**

| Assumption | Justification | Reference in submission |
|---|---|---|
| Proportion of patients receiving chemotherapy regimens | Clinical expert opinion | 5.2 |
| 100% of CRs and 50% of PRs were assumed to proceed to SCT in a scenario | Clinical expert opinion | 5.2 |
| Ratio of ASCT vs. allo-SCT observed in SG035-0004 is reflective of clinical practice | Best available evidence | 5.2 |
| PFS and OS for PTCL patients who received ASCT and allo-SCT are representative of R/R sALCL | | 5.3 |
| PFS and OS for ASCT and allo-SCT are independent of salvage treatment | No evidence is available for brentuximab + ASCT/allo-SCT. Clinical expert opinion was that the existence of an interaction effect, conditional on disease status at transplant, of brentuximab vs. chemotherapy on PFS and OS for SCT is unknown. | 5.3 and 5.4 |
| Excess mortality risk for cured patients who received brentuximab (vs. general population) is lower than for chemotherapy | Clinical expert opinion | 5.3 |
| Excess mortality risk for patients who received SCT (vs. general population) is higher than for the brentuximab and chemotherapy (no SCT) cohorts | Clinical expert opinion | 5.3 |
| Cured patients experience a 5% utility decrement vs the general population | Clinical expert opinion | 5.4 |
| Patients who are disease-free at 5 years received the utility decrement (vs. age-adjusted population norm) associated with cure | Clinical expert opinion | 5.4 |
| Rates of disease status at current follow-up [median 65.8 months (range: 24.5-216)] in Nademanee et al., (2011)[65] are reflective of response to ASCT | Best available evidence from SLR of clinical effectiveness. | 5.4 |
| Full wastage for drug acquisition costs | Patient numbers in each centre would likely be too low to allow for any vial sharing | 5.5 |
| Chemotherapy regimen RDI assumed to be 100% | RDI was not reported in any study which informed chemotherapy regimen doses. A scenario analysis is explored which assumes that RDI for chemotherapy regimens is equal to brentuximab. | 5.5 |
| On-treatment follow-up care for chemotherapy is equivalent to brentuximab | Clinical expert opinion | 5.5 |
| Proportion of patients receiving radiotherapy = 5% | Clinical expert opinion | 5.5 |

## 5.7 Base-case results (with PAS)

### 5.7.1 Base-case incremental cost effectiveness analysis results

The base case cost-effectiveness results are presented in Table 5.69; brentuximab vedotin is easily cost-effective compared to chemotherapy at NICE's standard decision thresholds of £20,000 and £30,000 per QALY, with a base case ICER of £8,829 per QALY gained. This is based on an incremental cost of £[redacted] incremental life years of 6.18 and incremental QALYs of [redacted] over a lifetime horizon.

**Table 5.69: Base-case results (with PAS)**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £[redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | £[redacted] | 9.53 | [redacted] | £[redacted] | 6.18 | [redacted] | £8,829 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

### 5.7.2 Clinical outcomes from the model

Clinical outcomes, in terms of mean time-in-state, predicted by the model are presented for each model cohort in Table 5.70 and for brentuximab vedotin vs chemotherapy in Table 5.71.The corresponding trials results are not presented given mean statistics are not reported for these outcomes in the corresponding clinical trial publications. The corresponding PFS and OS curves predicted by the model are presented in Figure 5.28 and Figure 5.28 respectively for each model cohort and Figure 5.30 and Figure 5.31 for brentuximab vedotin vs chemotherapy.

Patients receiving ASCT experience the longest mean PFS and OS reflecting the ability of this procedure to induce long-term disease control[65] and its lower mortality risk compared to allo-SCT. Patients receiving allo-SCT experience the second longest mean PFS, again reflecting the potentially curative nature of this procedure.[31]

Patients who receive brentuximab vedotin (no SCT) experience the second longest mean OS and an additional 8.5 years mean PFS compared to chemotherapy (no SCT). This reflects the lower mortality risk associated with brentuximab vedotin alone compared to allo-SCT and the subset of patients in SG035-0004 who are estimated to have long term survival with single-agent brentuximab vedotin.[6]

**Table 5.70: Clinical outcomes, by cohort**

| Cohort | Mean years | |
|---|---|---|
| | PFS | OS |
| Brentuximab vedotin (no SCT) | 9.29 | 16.43 |
| Brentuximab vedotin + ASCT | 12.52 | 18.06 |
| Brentuximab vedotin + allo-SCT | 10.84 | 14.18 |
| Chemotherapy (no SCT) | 0.80 | 2.79 |
| Chemotherapy + ASCT | 12.52 | 18.06 |
| Chemotherapy + allo-SCT | 10.84 | 14.18 |

**Figure 5.28: PFS, by cohort**

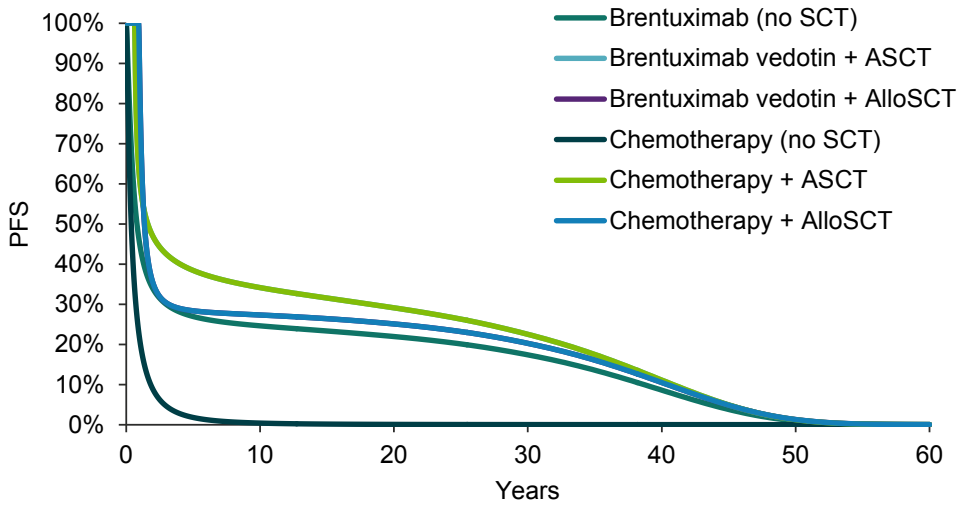
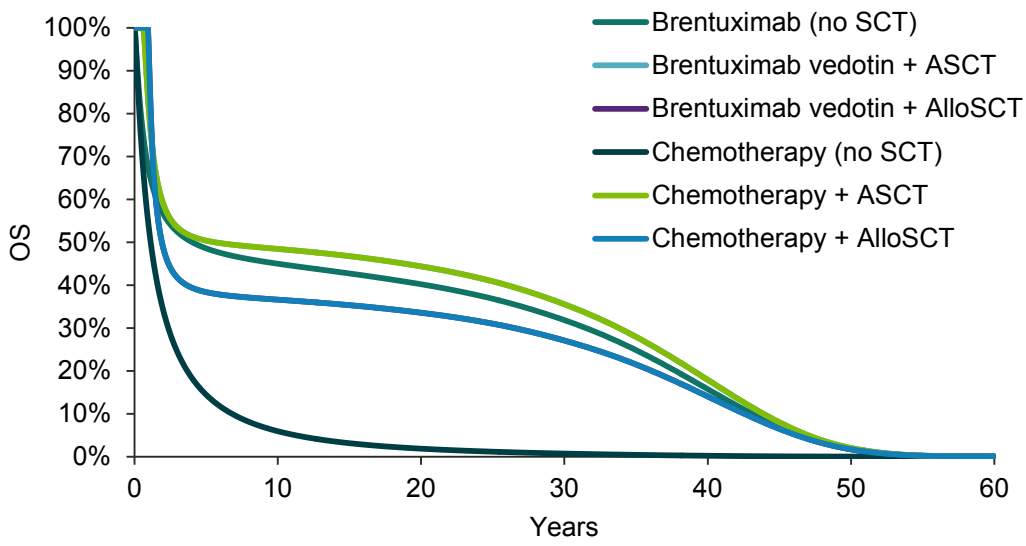


**Figure 5.29: OS, by cohort**




When weighting the clinical outcomes for each cohort to reflect the proportion of patients who proceed to ASCT and allo-SCT in each treatment arm, brentuximab vedotin is associated with the longest mean time-in-state for PFS and OS. This is primarily driven by the greater mean PFS and OS for brentuximab vedotin (no SCT) compared to chemotherapy (no SCT).

**Table 5.71: Clinical outcomes for brentuximab vedotin vs chemotherapy**

| Intervention and Comparator | Mean years | |
|---|---|---|
| | PFS | OS |
| Brentuximab vedotin | 9.97 | 16.31 |
| Chemotherapy | 2.31 | 4.64 |

**Figure 5.30: PFS for brentuximab vedotin vs chemotherapy**

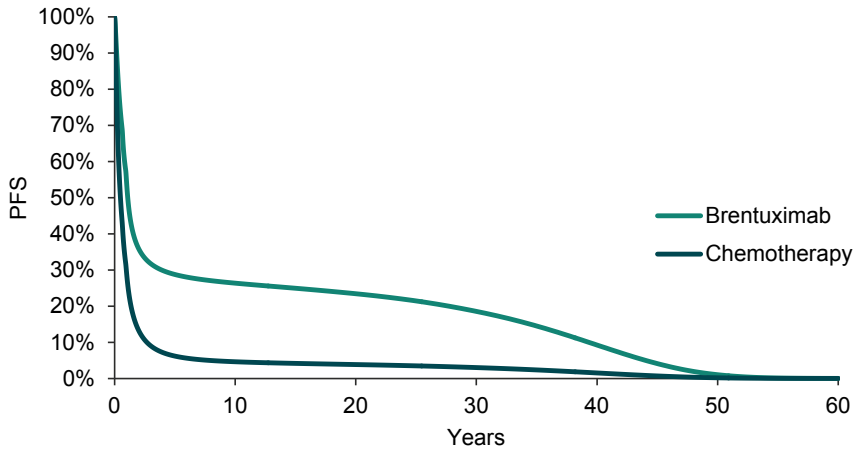
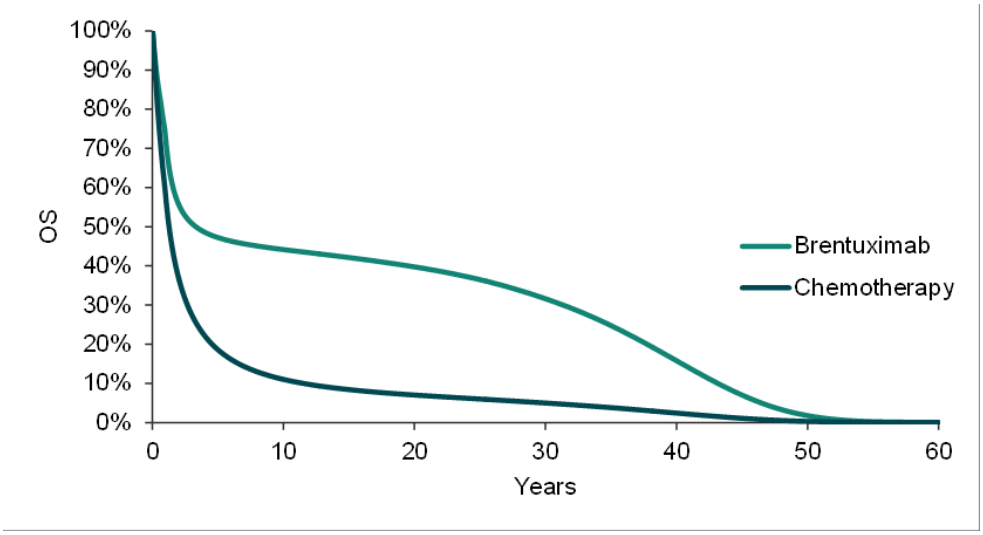


**Figure 5.31: OS for brentuximab vedotin vs chemotherapy**




## 5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregated QALYs are presented for each cohort in Table 5.72 and each comparator in Table 5.73.

In line with the clinical outcomes presented in Table 5.70, ASCT is associated with the greatest QALYs. Patients who receive brentuximab vedotin rather than chemotherapy prior to ASCT or Allo-SCT experience slightly greater QALYs due to the superior response profile of brentuximab vedotin compared to chemotherapy for these patients.

Patients who receive brentuximab vedotin (no SCT) experience greater total QALYs than patients who receive allo-SCT after brentuximab vedotin or chemotherapy due to gains in the PPS health state.

**Table 5.72: Summary of QALY gain by health state, by cohort**

| Health state | Intervention | | | Comparator | | |
|---|---|---|---|---|---|---|
| | Brentuximab (no SCT) | Brentuximab + ASCT | Brentuximab + allo-SCT | Chemo (no SCT) | Chemo + ASCT | Chemo + allo-SCT |
| PFS | 4.16 | 5.56 | 4.55 | 0.57 | 5.53 | 4.49 |
| PPS | 0.94 | 0.31 | 0.09 | 0.43 | 0.31 | 0.09 |
| AEs | 0.01 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 |
| Total | 5.12 | 5.89 | 4.67 | 1.01 | 5.85 | 4.60 |
| QALY, quality-adjusted life year; PFS, progression-free survival; PPS, post-progression survival; AE, adverse event | | | | | | |

After weighting the QALYs for each cohort to reflect the proportion of patients who proceed to ASCT and allo-SCT in each treatment arm, brentuximab vedotin yields incremental QALYs of 3.56; this is driven by QALYs accrued in the PFS health state which result from

the greater mean PFS for brentuximab vedotin (no SCT) compared to chemotherapy (no SCT). Brentuximab vedotin is associated with a marginally greater QALY loss for adverse events which is driven by the greater proportion of patients who receive allo-SCT and hence who are subject to the risk of aGvHD.

**Table 5.73: Summary of QALY gain by health state for brentuximab vedotin vs chemotherapy**

| Health state | Brentuximab vedotin | Chemotherapy | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| PFS | 4.41 | 1.18 | 3.23 | 3.23 | 91% |
| PPS | 0.72 | 0.39 | 0.33 | 0.33 | 9% |
| AEs | 0.02 | 0.02 | 0.00 | 0.00 | 0% |
| Total | 5.15 | 1.59 | 3.56 | 3.56 | 100% |

QALY, quality-adjusted life year; PFS, progression-free survival; PPS, post-progression survival; AE, adverse event; Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Disaggregated costs by resource category are presented for each cohort in Table 5.74 and for brentuximab vedotin vs chemotherapy in Table 5.75.

Both allo-SCT cohorts have the highest total costs followed by the ASCT cohorts, both of which are driven by the cost of SCT.

After weighting the costs of each cohort to reflect the proportion of patients who proceed to ASCT and allo-SCT in each treatment arm, brentuximab vedotin yields an incremental cost of £[redacted] compared to chemotherapy. This is driven by the cost of drug acquisition and SCT, given a greater proportion of patients proceed to SCT following brentuximab vedotin compared to chemotherapy. These costs are, to an extent, offset by savings in drug administration and post-progression therapy costs; the latter is driven by the greater proportion of chemotherapy patients who receive brentuximab vedotin in post-progression.

Disaggregated costs by health state are presented for each cohort in Table 5.76 and for brentuximab vedotin vs chemotherapy in Table 5.77.

**Table 5.74: Summary of costs by resource category, by cohort**

| Item | Intervention | | | Comparator | | |
|---|---|---|---|---|---|---|
| | Brentuximab vedotin (no SCT) | Brentuximab vedotin + ASCT | Brentuximab vedotin + allo-SCT | Chemotherapy (no SCT) | Chemotherapy + ASCT | Chemotherapy + allo-SCT |
| Acquisition | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Admin | £1,578 | £1,735 | £1,735 | £6,451 | £6,451 | £6,451 |
| Concomitant meds | £37 | £41 | £41 | £791 | £791 | £791 |
| AEs | £690 | £1,187 | £6,905 | £1,118 | £1,118 | £6,836 |
| SCT | £0 | £52,737 | £105,833 | £0 | £52,737 | £105,833 |
| Follow-up care (pre-progression) | £4,515 | £5,101 | £10,405 | £4,250 | £5,611 | £11,215 |
| Follow-up care (post-progression) | £2,659 | £2,240 | £2,576 | £3,510 | £2,172 | £2,499 |
| Post-progression therapies | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Total | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |

AE, adverse event; SCT, stem cell transplant

**Table 5.75: Summary of predicted costs by resource category for brentuximab vedotin vs chemotherapy**

| Item | Brentuximab vedotin | Chemotherapy | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Acquisition | £[redacted] | £[redacted] | £[redacted] | £[redacted] | [redacted] |
| Admin | £1,624 | £6,451 | -£4,827 | £4,827 | 15% |
| Concomitant meds | £38 | £791 | -£753 | £753 | 2% |
| AEs | £1,723 | £1,543 | £180 | £180 | 1% |
| SCT | £23,696 | £11,338 | £12,359 | £12,359 | 39% |
| Follow-up care (pre-progression) | £5,510 | £4,857 | £653 | £653 | 2% |
| Follow-up care (post-progression) | £2,588 | £3,347 | -£758 | £758 | 2% |
| Post-progression therapies | £[redacted] | £[redacted] | £[redacted] | £[redacted] | [redacted] |
| Total | £[redacted] | £[redacted] | £[redacted] | £[redacted] | [redacted] |

AE, adverse event; SCT, stem cell transplant

**Table 5.76: Summary of costs by health state, by cohort**

| Health state | Intervention | | | Comparator | | |
|---|---|---|---|---|---|---|
| | Brentuximab vedotin (no SCT) | Brentuximab vedotin + ASCT | Brentuximab vedotin + allo-SCT | Chemo (no SCT) | Chemo + ASCT | Chemo + allo-SCT |
| PFS | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| PPS | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| AEs | £690 | £1,187 | £6,905 | £1,118 | £1,118 | £6,836 |
| Total | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| PFS, progression-free survival; PPS, post-progression survival; AE, adverse event | | | | | | |

**Table 5.77: Summary of costs by health state for brentuximab vedotin vs chemotherapy**

| Health state | Brentuximab vedotin | Chemotherapy | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| PFS | £[redacted] | £28,693 | £[redacted] | £[redacted] | [redacted] |
| PPS | £[redacted] | £35,059 | £[redacted] | £[redacted] | [redacted] |
| AEs | £1,723 | £1,543 | £180 | £180 | 1% |
| Total | £[redacted] | £65,296 | £[redacted] | £[redacted] | [redacted] |
| PFS, progression-free survival; PPS, post-progression survival; AE, adverse event | | | | | |

## 5.8 Sensitivity analyses

### 5.8.1 Probabilistic sensitivity analysis

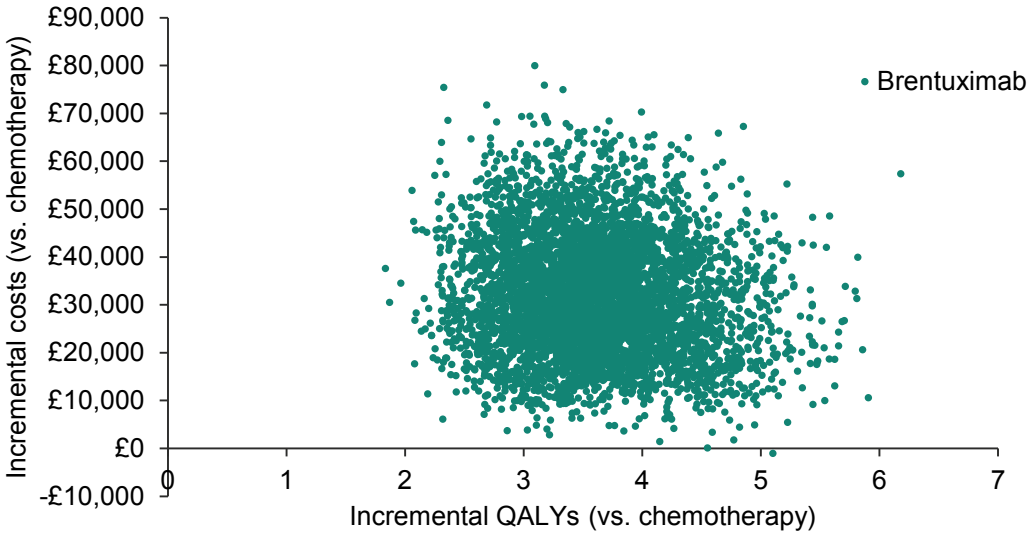
A PSA was conducted to address the uncertainty in the parameters used within the model by assigning distributions to input parameters and randomly sampling 5,000 Monte Carlo simulations. The distributions assigned to each type of parameter are presented in Table 5.78

**Table 5.78: Probabilistic sensitivity analysis distributions**

| Parameter | Distribution | Rationale |
|---|---|---|
| Discount rates | N/A | Not subject to sampling uncertainty |
| Response probabilities | Dirichlet | Constrained on an interval of 0 to 1 and reflect multinomial nature of response categories |
| Regression parameters | Multivariate normal | To capture correlation between normally distributed regression parameters |
| Kaplan-Meier | Beta | Constrained on an interval of 0 to 1 |
| Starting age | Normal | Assumption |
| Drug costs | N/A | Not subject to sampling uncertainty |
| Other unit costs | Gamma | Constrained on an interval of 0 to positive infinity |
| Brentuximab time on treatment | N/A | Sampling with replacement used to more accurately reflect the shape of the distribution |
| Chemotherapy time on treatment | Normal | Assumed to be normal in absence of data |
| Resource use rates | Gamma | Constrained on an interval of 0 to positive infinity |
| Resource use probabilities | Beta | Constrained on an interval of 0 to 1 |
| Health state utilities | Beta | Constrained on an interval of 0 to 1 |
| Adverse event disutilities | Gamma | Constrained on an interval of 0 to positive infinity |
| Adverse event durations | Gamma | Constrained on an interval of 0 to positive infinity |
| Adverse event probabilities | Beta | Constrained on an interval of 0 to 1 |
| N/A, not applicable as parameter was excluded from the probabilistic sensitivity analysis | | |

The joint distribution of incremental costs and QALYs for brentuximab vedotin compared to chemotherapy is presented in Figure 5.32. Uncertainty in the incremental cost-effectiveness of brentuximab vedotin is driven by uncertainty in incremental costs and QALYs.

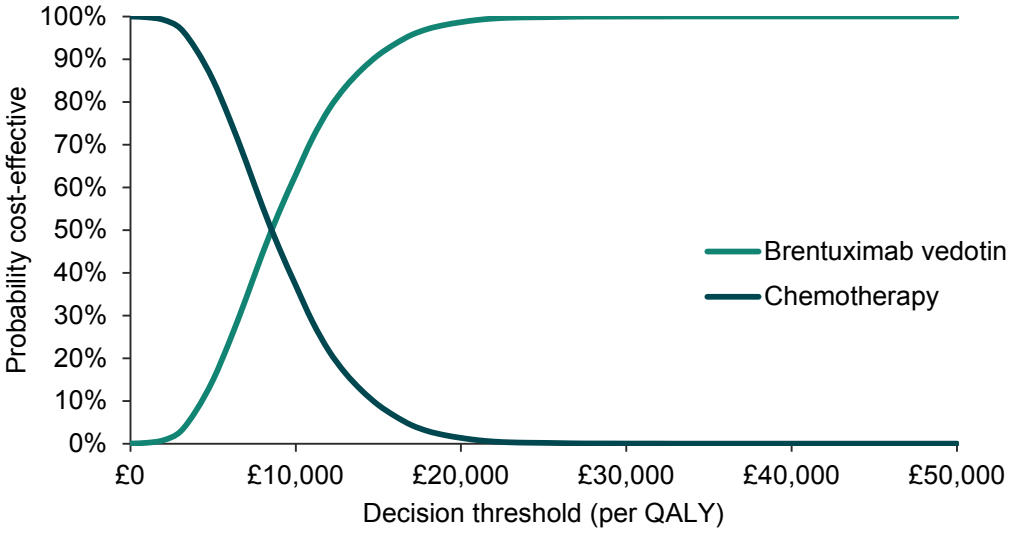
**Figure 5.32: Probabilistic simulations on a cost-effectiveness plane**




The cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) are presented in Figure 5.33 and Figure 5.34, respectively. The corresponding probabilities for decision thresholds of £20,000, £30,000 and £50,000 per QALY are presented in Table 5.79.

Brentuximab vedotin has a 99% probability of being cost-effective at a threshold of £20,000 per QALY. At £30,000 per QALY, brentuximab vedotin is cost-effective with 100% certainty.

**Figure 5.33: Cost-effectiveness acceptability curve**




The cost-effectiveness acceptability frontier is presented in Figure 5.34.

**Figure 5.34: Cost-effectiveness acceptability frontier**

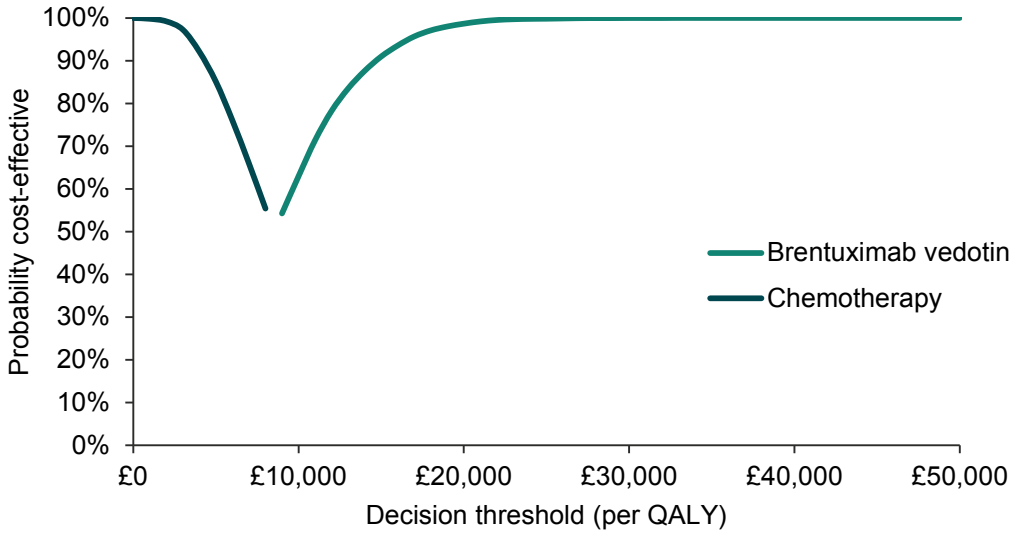



**Table 5.79: Probabilities of cost-effectiveness**

| Decision threshold (per QALY) | Brentuximab | Chemotherapy |
|---|---|---|
| £20,000 | 99% | 1% |
| £30,000 | 100% | 0% |
| £50,000 | 100% | 0% |

## 5.8.2 Deterministic sensitivity analysis

### *5.8.2.1 Scenario analysis*

The base case analysis involved a series of modelling assumptions including a number of parameters which were informed by the feedback obtained from the survey of UK clinical experts (Section 5.3.8). The impact of these assumptions on the cost-effectiveness estimates was explored through scenario analyses.

Table 5.80 presents the analyses that were conducted, the base case and analysis values, and the justification for including these analyses.

**Table 5.80: Description and justification for scenario analyses**

| Deterministic sensitivity analysis | Base case value | Analysis value | Justification for analysis |
|---|---|---|---|
| Discount rate (costs, benefits) | 3.50% (costs and benefits) | 1.50% (costs and benefits) | Specified in NICE methods guidance |
| Assessment type | Investigator assessed | Independent review facility | Align method of assessment for progression with primary endpoint in SG035-0004 |
| Source of response data for brentuximab patients receiving SCT | SG035-0004 | Equivalent to chemotherapy | Align with assumption that PFS and OS for ASCT and allo-SCT are independent of salvage treatment |
| Brentuximab (no SCT) PFS per INV distribution | Log-logistic | Exponential | Alternative modelling approach for PFS per INV |
| Brentuximab (no SCT) PFS per IRF distribution | Log-logistic | Exponential | Alternative modelling approach for PFS when adopting IRF assessment |
| Brentuximab (no SCT) OS distribution | Log-logistic | Kaplan-Meier | Address poor within-trial fit with parametric model |
| Brentuximab (no SCT) PFS and OS distribution | Log-logistic cure model | Gamma standard model | Explore the impact of using cure models rather than standard parametric models |
| Source of chemotherapy (no SCT) PFS data | Self-control | Mak (2013)[12] ALCL (n=17) | Explore the impact of patients achieving long term remission potentially not being captured in the self-control dataset |
| Source of chemotherapy (no SCT) PFS data | Self-control | Mak (2013)[12] PTCL PS<2 (n=47) | Explore the impact of patients achieving long term remission potentially not being captured in the self-control dataset and restrict to patients with PS<2 to align with the SG035-0004 eligibility criteria |
| Chemotherapy (no SCT) PFS distribution | Lognormal | Log-logistic | Alternative modelling approach for chemotherapy, no SCT PFS |
| Chemotherapy (no SCT) PFS hazard | Original data | Increased 25% | Explore impact of potential bias associated with self-control comparison of PFS for brentuximab (no SCT) vs. chemotherapy (no SCT) |
| Chemotherapy (no SCT) PFS hazard | Original data | Decreased 25% | Explore impact of potential bias associated with self-control comparison of PFS for brentuximab (no SCT) vs. chemotherapy (no SCT) |
| Source of chemotherapy (no SCT) OS data | Mak (2013)[12] PS<2 (n=47) | Mak (2013)[12] ALCL (n=17) | Address potential bias result from use of data for PTCL rather than ALCL patients, which clinical experts recognised was prognostic of OS |
| Source of chemotherapy (no SCT) PFS and OS data | PFS: Self-control and OS: Mak (2013)[12] PS<2 (n=47) | Mak (2013)[12] ALCL (n=17) | Explore implications of using different sets of patients to inform PFS and OS for chemotherapy (no SCT) and align histology with the decision problem |
| Chemotherapy (no SCT) OS distribution | Lognormal | Kaplan-Meier | Explore potential overestimation of maximum OS when using a parametric model |
| Chemotherapy (no SCT) OS hazard | Original data | Increased 25% | Explore impact of potential bias associated with unanchored indirect comparison of OS for brentuximab (no SCT) vs. chemotherapy (no |

| Deterministic sensitivity analysis | Base case value | Analysis value | Justification for analysis |
|---|---|---|---|
| | | | SCT) |
| Chemotherapy (no SCT) OS hazard | Original data | Decreased 25% | Explore impact of potential bias associated with unanchored indirect comparison of OS for brentuximab (no SCT) vs. chemotherapy (no SCT) |
| Chemotherapy (no SCT) PFS and OS hazards | Original data | Decreased 25% | Explore impact of potential bias associated with comparisons of PFS and OS for brentuximab (no SCT) vs. chemotherapy (no SCT) |
| ASCT PFS distribution | Gamma | Lognormal | Explore alternative estimate of the cure fraction for ASCT PFS |
| ASCT OS distribution | Lognormal | Gamma | Explore alternative estimate of the cure fraction for ASCT OS |
| ALCL calibration for ASCT | Exclude | Include | Explore differences in long-term outcomes associated with ASCT for R/R ALCL (as per the decision problem) vs. PTCL patients |
| Allo-SCT PFS distribution | Lognormal | Gamma | Alternative modelling approach for allo-SCT PFS |
| Allo-SCT OS distribution | Lognormal | Gamma | Alternative modelling approach for allo-SCT OS |
| ALCL calibration for Allo-SCT | Exclude | Include | Explore differences in long-term outcomes associated with ASCT for ALCL (as per the decision problem) vs. PTCL patients |
| ALCL calibration for ASCT and allo-SCT | Exclude | Include | Explore differences in long-term outcomes associated with SCT for ALCL (ASCT is R/R) vs. PTCL patients |
| Rate of stem cell transplant | Response-based (SG035-0004) | Response-based (clinical opinion) | Reflect clinical opinion that CRs and 'good PRs' proceed to SCT, and explore a greater proportion of patients proceeding to SCT in both arms |
| Rate of stem cell transplant | Response-based (SG035-0004) | Equal in both arms (Mak et al.,)[12] | Explore conservative assumption where SCT rates are equal between treatment arms |
| Proportion receiving ASCT vs. allo-SCT | Allo-SCT = 53% (SG035-0004) | Allo-SCT = 75% | Explore clinical expert opinion that more patients in the R/R setting receive allo-SCT than ASCT |
| 'Cured' time-point (years) | 5 years | 2 years | Explore uncertainty in time point at which cured patients are considered cured |
| Relative dose intensity | On | Off | Assume all patients receive the full dose of brentuximab |
| Chemotherapy relative dose intensity | 100% | Assumed equivalent to brentuximab | Explore uncertainty in RDI for chemotherapies by setting equal to brentuximab |
| Drug wastage | Full wastage | No wastage | Estimate cost-effectiveness with vial sharing |
| Cost of ASCT | Clinical expert opinion | NHS reference costs 2015-2016 | Utilise a bottom-up costing approach from a recommended source for costing UK NHS resources |
| Cost of allo-SCT | Clinical expert opinion | NHS reference costs 2015-2016 | Utilise a bottom-up costing approach from a recommended source for costing UK NHS resources |

| Deterministic sensitivity analysis | Base case value | Analysis value | Justification for analysis |
|---|---|---|---|
| Adverse event disutilities | Include | Exclude | Explore the impact of assumptions made to parameterise adverse event disutilities |
| Chemotherapy costs; all patients receive cheapest | Mix | ESHAP | Explore uncertainty in the salvage chemotherapy distribution |
| Chemotherapy costs; all patients receive most expensive | Mix | Gem-P | Explore uncertainty in the salvage chemotherapy distribution |
| Radiotherapy | 5% | 40% | Explore alternative clinical expert opinion regarding the proportion of patients who receive radiotherapy |

The results of the scenario analyses are presented in Table 5.81.

None of the analyses generated ICERs for brentuximab vedotin which exceeded £20,000 per QALY. The following scenarios generated ICERs +/-25% relative to the base case ICER:

- Discount rates of 1.5%

- Use of the IRF assessed data for brentuximab vedotin – the cure fraction for the IRF assessed data is lower than the INV assessed data which reduced PFS QALYs for brentuximab vedotin (no SCT). However, the IRF data suffers from lack of follow-up relative to the INV data (maximum follow-up; 40 months per IRF vs. 76 months per INV) and the IRF assessment is less reflective of the assessment of PFS with the last therapy received prior to SG035-0004 entry which informed PFS for chemotherapy (no SCT) in the base case.

- Use of an exponential distribution to estimate PFS for brentuximab vedotin (no SCT) per IRF – in comparison to the log-logistic model, the exponential model has a higher cure fraction (13% vs. 9%) hence reduces the ICER by approximately £1,000 relative to scenario described above. The result of this scenario is therefore driven primarily by the IRF assessment rather than the choice of distribution.

- Rate of SCT based on clinical expert opinion – this increases the proportion of CRs proceeding to SCT from 42% to 69% and the proportion of PRs proceeding to SCT from 8% to 35% (assuming 50% of PRs to salvage would be deemed 'good PRs'). This increases incremental costs (as more patients in the brentuximab vedotin arm receive SCT due to its superior response profile and hence accrue the high costs of the procedures) and decreases incremental QALYs (as fewer chemotherapy patients now experience the poor outcomes associated with chemotherapy (no SCT)).

**Table 5.81: Scenario analyses results**

| Deterministic sensitivity analysis | Base case value | DSA value | ICER for brentuximab vedotin (per QALY) | % change relative to the base case* |
|---|---|---|---|---|
| Base case | - | - | £8,829 | |
| Discount rate (costs, benefits) | 3.50% (costs and benefits) | 1.50% (costs and benefits) | £6,524 | -26% |
| Assessment type | Investigator assessed | Independent review facility | £12,415 | 41% |
| Source of response data for brentuximab patients receiving SCT | SG035-0004 | Equivalent to chemotherapy | £8,864 | 0% |
| Brentuximab (no SCT) PFS per INV distribution | Log-logistic | Exponential | £8,719 | -1% |
| Brentuximab (no SCT) PFS per IRF distribution | Log-logistic | Exponential | £11,401 | 29% |
| Brentuximab (no SCT) OS distribution | Log-logistic | Kaplan-Meier | £8,604 | -3% |
| Brentuximab (no SCT) PFS and OS distribution | Log-logistic cure model | Gamma standard model | £9,943 | 13% |
| Source of chemotherapy (no SCT) PFS data | Self-control | Mak (2013) ALCL (n=17) | £10,601 | 20% |
| Source of chemotherapy (no SCT) PFS data | Self-control | Mak (2013) PS<2 (n=47) | £10,503 | 19% |
| Chemotherapy (no SCT) PFS distribution | Lognormal | Log-logistic | £8,937 | 1% |
| Chemotherapy (no SCT) PFS hazard | Original data | Increased 25% | £8,475 | -4% |
| Chemotherapy (no SCT) PFS hazard | Original data | Decreased 25% | £9,647 | 9% |
| Source of chemotherapy (no SCT) OS data | Mak (2013) PS<2 (n=47) | Mak (2013) ALCL (n=17) | £8,016 | -9% |
| Source of chemotherapy (no SCT) PFS and OS data | PFS: Self-control and OS: Mak (2013) PS<2 (n=47) | Mak (2013) ALCL (n=17) | £9,656 | 9% |
| Chemotherapy (no SCT) OS distribution | Lognormal | Kaplan-Meier | £8,946 | 1% |
| Chemotherapy (no SCT) OS hazard | Original data | Increased 25% | £8,494 | -4% |
| Chemotherapy (no SCT) OS hazard | Original data | Decreased 25% | £9,469 | 7% |
| Chemotherapy (no SCT) PFS and OS hazards | Original data | Decreased 25% | £10,386 | 18% |
| ASCT PFS distribution | Gamma | Lognormal | £8,746 | -1% |
| ASCT OS distribution | Lognormal | Gamma | £8,840 | 0% |
| ALCL calibration for ASCT | Exclude | Include | £8,289 | -6% |
| Allo-SCT PFS distribution | Lognormal | Gamma | £8,850 | 0% |
| Allo-SCT OS distribution | Lognormal | Gamma | £8,829 | 0% |
| ALCL calibration for Allo-SCT | Exclude | Include | £8,644 | -2% |
| ALCL calibration for ASCT and Allo-SCT | Exclude | Include | £8,125 | -8% |

| Deterministic sensitivity analysis | Base case value | DSA value | ICER for brentuximab vedotin (per QALY) | % change relative to the base case* |
|---|---|---|---|---|
| Rate of stem cell transplant | Response-based (SG035-0004) | Response-based (clinical opinion) | £14,256 | 61% |
| Rate of stem cell transplant | Response-based (SG035-0004) | Equal in both arms (Mak et al.) | £8,692 | -2% |
| Proportion receiving ASCT vs. Allo-SCT | Base case (SG035-0004) | Allo-SCT = 75% | £9,561 | 8% |
| Cured time-point (years) | 5 years | 2 years | £8,955 | 1% |
| Relative dose intensity | On | Off | £8,829 | 0% |
| Chemotherapy relative dose intensity | 100% | Assumed equivalent to brentuximab | £8,843 | 0% |
| Drug wastage | Full wastage | No wastage | £8,129 | -8% |
| Cost of ASCT | Clinical expert opinion | NHS reference costs 2015-2016 | £7,973 | -10% |
| Cost of Allo-SCT | Clinical expert opinion | NHS reference costs 2015-2016 | £7,712 | -13% |
| Adverse event disutilities | Include | Exclude | £8,833 | 0% |
| Chemotherapy costs; all patients receive cheapest | Mix | ESHAP | £7,838 | -11% |
| Chemotherapy costs; all patients receive most expensive | Mix | Gem-P | £8,570 | -3% |
| Radiotherapy | 5% | 40% | £8,707 | -1% |
| *May imply no change vs. base case due to rounding | | | | |

### 5.8.3 Summary of sensitivity analyses results

The probabilistic sensitivity analysis estimated the probability that brentuximab vedotin was cost-effective was 99% at a decision threshold of £20,000 per QALY and was cost-effective with 100% certainty at £30,000 per QALY.

Moreover, none of the deterministic sensitivity analyses that were conducted yielded an ICER over £20,000 per QALY. These included assuming a 25% decrease in the PFS and OS hazards for chemotherapy (no SCT) to address the potential bias induced by the self-control comparison of PFS and unanchored indirect comparison of OS with brentuximab vedotin (no SCT).

## 5.9 Subgroup analysis

No subgroup analysis was undertaken.

## 5.10 Validation of de novo cost-effectiveness analysis

Two independent technical reviews of the cost-effectiveness model were conducted by health economists who were not involved in the model construction. This was a cell-by-cell verification process which allowed checking of all formulae and visual basic code. The reviewer provided a written summary of their interpretation in relation to each sheet to describe how to errors identified could be rectified.

## 5.11 Interpretation and conclusions of economic evidence

In the pivotal SG035-0004 trial of brentuximab vedotin in R/R sALCL,[2] 17 patients received ASCT or allo-SCT with the intent of securing a long-term remission. Moreover, the final, end of study results from this trial, following a median observation time from first dose of 71.4 months,[6] show an estimated 5-year OS rate of 60% and a median PFS of 20.0 months, demonstrating that the majority of patients achieved clinically significant durable remissions. Indeed, the authors of this recently presented 5-year follow up data concluded that a subset of patients with R/R sALCL may potentially have been cured (i.e. achieved long term survival) with single-agent brentuximab vedotin.[6] By contrast, conventional chemotherapy approaches are not curative and the potential for patients to accrue long term benefits associated with ASCT or allo-SCT is limited by the inability of standard salvage therapies to deliver a high rate of CR. On the other hand, in the SG035-0004 trial with brentuximab vedotin, objective responses were observed in 86% of patients, while 59% of patients achieved a CR.[2]

These impressive findings are replicated in the clinical outcomes predicted by this cost-effectiveness analysis. Brentuximab vedotin was predicted to enable a greater proportion of patients to receive ASCT or allo-SCT, and mean PFS and OS were significantly greater than for conventional chemotherapy, thus yielding a large incremental QALY gain of 3.56 with brentuximab vedotin. This is driven primarily by the superior PFS and OS for brentuximab vedotin (no SCT) compared to conventional chemotherapy (no SCT), and also the superior response profile of brentuximab vedotin.

Based on the strength of its clinical evidence brentuximab vedotin is highly cost-effective at decision thresholds of £20,000 and £30,000 per QALY; with a base case ICER (with PAS) of only £8,829 per QALY, which is very low for an orphan (indeed ultra-orphan) medicine. The application of a significant PAS contributes to the low ICER, although brentuximab vedotin for the treatment of patients with R/R sALCL would remain cost-effective even without the PAS. The corresponding probabilities that brentuximab vedotin is cost-effective were 99% and 100% at the £20,000 and £30,000 ICER thresholds respectively. Moreover, a variety of deterministic sensitivity analyses were conducted in order to explore uncertainty relating to structural assumptions (including the self-control and unanchored indirect comparisons of PFS and OS respectively) and aspects of the model that were largely informed by clinical

expert opinion. None of these sensitivity analyses yielded ICERs that were above the £20,000 per QALY decision threshold, reflecting the fact that the incremental QALY gains with brentuximab vedotin remain large even in scenarios that adopt more pessimistic assumptions.

One limitation of the cost effectiveness analysis is that it relies on clinical data from an open-label, single-arm trial of brentuximab vedotin in 58 patients with R/R sALCL.[2] As such, an unanchored indirect comparison was conducted with conventional chemotherapy (no SCT) for overall survival using data reported by Mak et al.,[12] which may introduce some bias in the cost-effectiveness estimates. A comparison of patient characteristics in SG035-0004 [2] and Mak et al., (2013)[12], identified age, stage III-IV disease and performance status as sources of heterogeneity, however the latter was controlled for in the base case analysis through the use of OS data for the subgroup of PTCL patients in Mak et al., (2013)[12] with performance status <2. Sensitivity analysis in which the OS hazard alone, and a combined analysis of the PFS and OS hazards, for conventional chemotherapy were decreased by 25% still yielded ICERs below £15,000 per QALY gained.

Moreover, the relatively small number of patients that are informing the PFS and OS for brentuximab vedotin (no SCT) and conventional chemotherapy (no SCT) implies some uncertainty for the long term extrapolations. However, in a condition as rare as R/R sALCL, such uncertainty is unavoidable and it can be noted that the results of the PSA indicate that this did not translate into decision uncertainty.

In conclusion, this analysis has shown that brentuximab vedotin is a highly cost-effective treatment for patients with R/R sALCL. Sensitivity analyses indicate that the cost-effectiveness results are robust and this provides added reassurance that brentuximab vedotin represents a cost-effective use of NHS resources. The existence of a significant PAS further enhances its cost-effectiveness and helps to mitigate any remaining uncertainty.

# 6. Assessment of factors relevant to the NHS and other parties

## 6.1 Budget Impact Assessment

An assessment has been made of the budget impact associated with brentuximab vedotin for the population considered in the cost-effectiveness argument:

### 6.1.1 Prevalence, incidence and estimated brentuximab vedotin use

As described in 3.1.1, anaplastic large cell lymphoma (ALCL) is a very rare malignancy, making up less than 3% of all cases of Non-Hodgkin Lymphoma (NHL).[89] Systemic disease (sALCL) is the most common and aggressive form of ALCL and accounts for approximately 88% of all ALCL cases. [90] Approximately 40% to 65% of patients with sALCL develop recurrent disease after front-line therapy and require further treatment. This would make the size of the incident r/r population potentially eligible for treatment with brentuximab vedotin approximately 66 patients per year as shown in Table 6.1 below.

**Table 6.1: Incident R/R sALCL Population in England & Wales**

| | Number of Patients |
|---|---|
| NHL 1 Year UK Prevalence | 7,591 |
| Adjusted for England & Wales Only | 6,680 |
| % of ALCL | 3% |
| sALCL | 88% |
| Total sALCL Patients in England & Wales | 147 |
| R/R sALCL in England & Wales | 66 |

According to clinical expert opinion, 60%-80% of patients with relapsed/refractory sALCL would receive brentuximab vedotin which translates to approximately forty-five patients per year.

These numbers are supported and validated by the known real world use of brentuximab vedotin in England via the national Cancer Drugs Fund (CDF) which has included brentuximab vedotin for the treatment of R/R sALCL since April 2013. Between April 2013 and March 2014, forty-four patients in England received brentuximab vedotin for sALCL through the CDF. In the following year, April 2014 to March 2015, forty-five patients in England received brentuximab vedotin for sALCL. In the latest available data from CDF notifications, capturing patient claims for the first six months of fiscal year 2015 (April 2015 to September 2015), twenty-two patients in England received brentuximab vedotin for sALCL. This figure is consistent with half-year figures from fiscal years 2013 and 2014.

As the time to relapse varies significantly from patient to patient, and there is a limited amount of data available on this very rare disease, it is difficult to estimate the pool of prevalent relapsed/refractory sALCL patients at any given time. Therefore, we consider that the most accurate and reliable estimate of the number of patients with r/r sALCL who would receive brentuximab vedotin following a positive NICE recommendation is from the known real world use through the CDF which has remained constant for r/r sALCL since the launch of brentuximab vedotin in late 2012. Takeda has confirmed with clinical experts that the use of brentuximab vedotin for patients with r/r sALCL after a positive NICE recommendation will not differ from that which has been seen via the CDF over the past 4 years.

The use of brentuximab vedotin for r/r sALCL via the CDF has already reached steady-state and, as such, the number of patients forecast to receive it is expected to remain constant over the next five years at approximately forty-five patients per year, in line with the CDF experience (Table 6.2). These figures have been applied to the budget impact forecast below.

**Table 6.2: Five year projection of brentuximab vedotin use for R/R sALCL in England & Wales**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Incident R/R sALCL Patient Pool in England & Wales | 66 | 66 | 66 | 67 | 67 |
| Expected brentuximab vedotin uptake | 68% | 68% | 68% | 68% | 68% |
| Number of Patients on brentuximab vedotin | 45 | 45 | 45 | 46 | 46 |

### 6.1.2 Costs and resource use

All costs excluding follow-up care were included in the budget impact analysis. This exclusion is not expected to have a material impact on the results given follow-up care costs represented only 4% of incremental costs in the cost-effectiveness analysis.

Post-progression therapy costs were distributed over the model time horizon based on the progression-free survival curves used in the cost-effectiveness model. For example, post-progression therapy costs for patients who enter the model in year 1 are distributed over years 1-5 based on the proportion of patients expected to experience disease progression within each year.

All resource use and unit costs were identical to the cost-effectiveness model described in Section 5. Costs were not discounted for the budget impact analysis.

### 6.1.3 Budget impact

The total costs in the current scenario (i.e. without brentuximab vedotin) and the new scenario (i.e. with brentuximab vedotin) are presented in Table 6.3 and

Table 6.4, respectively. The budget impact results take account of the PAS agreed with the Department of Health, and are presented in Table 6.5. These demonstrate the following results:

- The estimated annual budget impact after displacement of conventional chemotherapy is £1,518,367 in year 1, decreasing slightly over time to £1,430,132 in year 5. This decrease is driven by post-progression therapy costs due to differences in rates of disease progression for brentuximab vedotin compared to chemotherapy; all other costs remain constant for both treatments given the number of patients is also constant.

- The estimated total budget impact over 5 years after displacement of conventional chemotherapy is £7,295,351.

    - This is driven primarily by the costs of drug acquisition and stem cell transplant given a greater proportion of patients proceed to ASCT or Allo-SCT following salvage with brentuximab compared to chemotherapy.

    - These costs are, to an extent, offset by savings in drug administration and post-progression therapies. The latter results from the higher proportion of chemotherapy patients who are treated with brentuximab after relapse/progression.

**Table 6.3: Total costs in current scenario (without brentuximab vedotin)**

| Resource category | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Years 1-5 |
|---|---|---|---|---|---|---|
| Acquisition | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Admin | £429,542 | £429,542 | £429,542 | £429,542 | £429,542 | £2,147,710 |
| Concomitant meds | £52,697 | £52,697 | £52,697 | £52,697 | £52,697 | £263,484 |
| AEs | £102,970 | £102,970 | £102,970 | £102,970 | £102,970 | £514,850 |
| SCT | £771,103 | £771,103 | £771,103 | £771,103 | £771,103 | £3,855,517 |
| Post-progression therapies | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Total | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |

AEs, adverse events; SCT, stem cell transplant (either ASCT or allo-SCT)

**Table 6.4: Total costs in new scenario (with brentuximab vedotin, including PAS)**

| Resource category | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Years 1-5 |
|---|---|---|---|---|---|---|
| Acquisition | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Admin | £211,119 | £211,119 | £211,119 | £211,119 | £211,119 | £1,055,593 |
| Concomitant meds | £18,596 | £18,596 | £18,596 | £18,596 | £18,596 | £92,980 |
| AEs | £111,744 | £111,744 | £111,744 | £111,744 | £111,744 | £558,721 |
| SCT | £1,342,664 | £1,342,664 | £1,342,664 | £1,342,664 | £1,342,664 | £6,713,322 |
| Post-progression therapies | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Total | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| AEs, adverse events; SCT, stem cell transplant (either ASCT or allo-SCT) | | | | | | |

**Table 6.5: Budget impact (with brentuximab vedotin, including PAS)**

| Resource category | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Years 1-5 |
|---|---|---|---|---|---|---|
| Acquisition | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Admin | -£218,423 | -£218,423 | -£218,423 | -£218,423 | -£218,423 | -£1,092,116 |
| Concomitant meds | -£34,101 | -£34,101 | -£34,101 | -£34,101 | -£34,101 | -£170,504 |
| AEs | £8,774 | £8,774 | £8,774 | £8,774 | £8,774 | £43,871 |
| SCT | £571,561 | £571,561 | £571,561 | £571,561 | £571,561 | £2,857,805 |
| Post-progression therapies | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| Total | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] | £[redacted] |
| AEs, adverse events; SCT, stem cell transplant (either ASCT or allo-SCT) | | | | | | |

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**Single technology appraisal**

**Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]**

Dear Takeda

The Evidence Review Group, Aberdeen HTA group, and the technical team at NICE have looked at the submission received on 9 February 2017 from Takeda UK Ltd. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **16 March 2017** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as ********** in turquoise, and all information submitted as ********** in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sana Khan, Technical Lead (Sana.Khan@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.Yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser– Appraisals

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On behalf of:
Dr. Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

**Section A: Clarification on effectiveness data**

A1. **Priority**. Please provide a complete list of studies included in the systematic review reported in the submission (including primary and secondary references) to resolve discrepancies, in particular:

a. The 2015 systematic review states that 20 studies were included, comprising 18 full text papers and 4 conference abstracts, but only 17 full text papers and three conference abstracts were referenced. Secondary publications Coiffier et al., (2014) and Pro et al., (2014) were not listed as references.
b. The Lamarque et al., (2014) abstract is not included in the 2015 systematic review, as stated in Section 4.1.3 of the submission.
c. The Gibb et al., (2013) study is not mentioned in Section 4.1.3 of the submission or in the 2015 systematic review, but is included in the submission as retrospective case series in Section 4.9, Section 4.11.1 and Table 4.2 (page 43 of the company submission). In addition, this study includes only 5 patients with anaplastic large cell lymphoma (ALCL), which does not fulfil the eligibility criterion of 20 or more patients (Table 4.1, page 38 of the company submission).
d. Section 4.1.3 of the company submission states that 1 new full text paper is included in the submission. However, it is unclear which paper is being referred to.
e. Some references from the 2015 systematic review (Forero-Torres [2009], Mathilde [2014]) are not referenced in the submission.
f. The PRISMA flow diagram (Figure 4.1, page 39 of the company submission) states that 19 full publications and 7 abstracts were included in the submission but Table 4.2 (list of relevant non-randomised and non-controlled evidence) includes only 6 studies.

A2. Table 5.3 (page 84 of the company submission): The right hand column ("dosing source") lists studies which are not mentioned elsewhere in the company submission. Please clarify how these dosing studies were identified.

A3. The European Public Assessment Report for brentuximab vedotin (page 56) states that the inclusion criteria for trial SG035-004 specified that at US and Canadian sites, patients were to be age 12 years or older and at European sites, patients were to be

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age 18 years or older. [redacted]. Given that the population specified in the marketing authorisation is 'adults', that is age 18 years or older, please provide a commentary on whether the inclusion of patients under the age of 18 years in the SG035-004 trial would affect the generalisability of the trial results to the population specified in the marketing authorisation and to clinical practice in England.

A4. Table 5.9 (page 90 of the company submission): The response to primary therapy is listed in the Mak et al., (2013) and SG035-0004 studies. For Mak et al., the 3 probabilities sum to 101% which may be a result of a rounding error. For SG035-0004 the probabilities only sum to 93%. Please clarify whether the numbers for SG035-0004 are correct or whether there is a category missing.

**Section B: Clarification on cost-effectiveness data**

B1. **Priority.** Section 5.1, Page 77 of the company submission: It is noted that a full text paper of the cost-effectiveness study by Hux et al., (2016) (included as abstract in the company's systematic review) has been published, providing details on the modelling assumptions used (Journal of Health Economics and Outcomes Research 2016; 4(2):188-203).

a. Given that the structure of the company's economic model is similar to the structure of the economic model described in Hux et al., please comment on the reasons for the difference in the reported incremental cost effectiveness ratios (ICERs) in the company submission and that reported by Hux et al., (that is £8,829 per QALY gained in the company submission compared with £35,390 per QALY gained reported in the study by Hux et al.).

b. For progression free (PFS) and overall survival (OS), Hux et al., used data from the Canadian BC Cancer Registry on 40 patients with systemic anaplastic large cell lymphoma (sALCL) who had received first line salvage therapy between 1980 and 2012 (provided by Dr Joseph Conners, BC Cancer Agency). Given the company's involvement in this published study, please clarify why this source of patient level data was not used in the company submission to model PFS and OS for the chemotherapy treatment arm.

c. Please clarify, if possible, the overlap between the data used by Hux et al. and the data reported by Mak et al., which is used in the company submission.

B2. **Priority**. Page 41 of the company submission: The submission states that *"No formal or mixed treatment comparison was performed"*.

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a. Please clarify why a matched adjusted indirect comparison (MAIC) between the SG035-0004 trial and the Canadian registry data from Mak et al., was not attempted for OS and PFS using the variables that could be compared between the studies.

b. If a MAIC is possible, please provide the analysis and incorporate the findings in the economic model.

We note that the patient data provided for the study by Hux et al., (2016) may offer further potential for adjusted comparisons between brentuximab and chemotherapy.

B3. **Priority**. Page 94-98 of the company submission. The "mixture cure" model assumes that a proportion of the patients in the brentuximab vedotin (No stem cell transplant [SCT]) cohort have been cured, and this model has been used for both PFS and OS. However, it is noted that no cure is assumed for any patients in the chemotherapy (No SCT) cohort. The ERG's clinical advice indicates that in practice there may be a small proportion of patients who will go into long term remission following salvage chemotherapy regimens. This also seems to be reflected in the Kaplan Meier plots reported by Mak et al., and Hux et al., with a small proportion of patients surviving beyond 10 to 15 years.

Please assess the impact of incorporating a mixture cure model for OS and PFS in the chemotherapy cohort, using the data from Mak et al., or Hux et al.

B4. **Priority.** Table 5.54, page 144 of the company submission:

a. In patients who have received chemotherapy and experience post-progression survival, it appears that 80% then go on to receive brentuximab vedotin. The ERG's understanding is that the modelling incorporates the post-progression costs of this brentuximab vedotin treatment for these patients, but not the additional life year and QALY gains that might be expected (that is, the patients providing data on OS for the chemotherapy arms did not receive brentuximab vedotin in subsequent lines of treatment). The ERG considers it inappropriate to include brentuximab vedotin as a subsequent line of therapy in the chemotherapy arm in the context of the current decision problem. Please provide justification for why these costs are included, and if appropriate, remove or substitute them with the cost of chemotherapy or best supportive care (please see b below).

b. The ERG's clinical advice suggests that upon progression following salvage chemotherapy or brentuximab vedotin treatment, a substantial proportion of patients would likely receive best supportive care rather than further active treatment. However, Table 5.54 lists the post-progression therapy distribution, with 100% of patients receiving either brentuximab vedotin or

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chemotherapy. Please provide further justification for this assumption in relation to the subsequent lines of treatment actually received by the cohorts used to model OS and PFS. For example, Mak et al., reported that 57% of patients with performance status 0 or 1 who progressed following salvage therapy received one or more lines of subsequent chemotherapy. Similarly, what proportion of patients who progressed on brentuximab vedotin received chemotherapy rather than retreatment with brentuximab vedotin?

B5. **Priority**. Given the uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice, please provide an illustrative scenario analysis that incorporates all of the below:

a. data from Mak et al. or Hux et al. for chemotherapy PFS and OS,

b. adjustment for observed confounders if feasible (question B2)

c. allows a possible cure fraction for the chemotherapy as well as brentuximab. vedotin (question B3),

d. independent review facility (IRF) data (as opposed to investigator (INV) assessed data) to extrapolate PFS for brentuximab vedotin,

e. excludes or substitutes the costs of post-progression brentuximab vedotin therapy in the chemotherapy arms of the model (question B4).

B6. Page 72 of the company submission states that as a result of adverse events in 40% of the patients receiving brentuximab vedotin, 10% of doses were delayed. Please explain how this was taken into consideration in the economic model.

B7. Table 5.2, page 82 of the company submission: The time horizon of 60 years allows the model to run until the cohort age is 107. In the study by Hux et al., a 30 year time horizon was used for the base case analysis. Please provide a justification for the 60 year time horizon used in the company submission.

B8. For the base case analysis, the self-controls from the pivotal trial are used to estimate response rates and PFS for chemotherapy in the model. Please clarify in more detail whether the chemotherapies received by the self-controls are an accurate reflection of the modelled comparators for this assessment; that is are the costed treatments (Table 5.39, page 133 of the company submission) consistent with the treatments previously received by the self-controls.

B9. Page 133 of the company submission: Please clarify whether the mean time-on-treatment sourced for chemotherapy drugs is conditional on adherence and survival, or whether it is reflective of the expectation for all patients commencing treatment,

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that is, is the number of cycles for chemotherapy estimated in a way that is consistent with the approach taken for brentuximab vedotin cycles?

B10. Please provide more information on the sources of data used for adverse events in the model, particularly for chemotherapy treatments in Table 5.55, page 143 of the company submission. What methods were used to source these data and select studies if alternatives were available? Are the studies selected appropriate for the target population of this assessment?

B11. Tab “Costs”, Cell E271:272 appears to call the discounted costs from the TraceBV and TraceChemo tabs (cells: BB5: BE5) (that is, discounted costs). These costs are then eventually recycled into the respective traces in the PPS state and further discounted. Please check these cells for accuracy and make any necessary changes to avoid double discounting. It is noted, however, that because these costs are incurred in early cycles of the model, any impact on resultant ICERs will be minor.

B12. The model does not allow the combination of IRF assessment with a standard gamma parametric model for PFS.

a. Please incorporate this functionality into the model.

b. Please explain why all the parametric models explored for OS and PFS in the company submission are not incorporated in the model to enable sensitivity analysis, for example, there is no functionality to use Weibull models to extrapolate outcomes.

B13. Pages 27 and 131 of the company submission: Page 131 of the company submission states that the cost of brentuximab vedotin in the model is based on the mean number of treatment cycles patients had in SG035-0004 (8.2 cycles). Page 27 of the company submission states that the number of cycles of brentuximab vedotin used in clinical practice is likely to be less than in the SG035-0004 trial.

a. Please provide a commentary on rules used in clinical practice in England for stopping treatment with brentuximab vedotin, for example the number of cycles when maximal response would be expected, or the number of cycles when treatment would be stopped if there is no partial or complete response.

b. Please provide a scenario analysis that explores the potential effect of a stopping rule for brentuximab vedotin on the cost effectiveness analyses.

B14. Please provide a scenario analysis that explores the potential effect of removing patients under the age of 18 years in the SG035-004 trial on the cost effectiveness analyses (question A3).

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B15. Please provide ICERs for all cost effectiveness analyses using the list price of brentuximab vedotin.

# Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512] Response to clarification questions

**Submitted by Takeda UK Ltd.**

**Single Technology Appraisal (STA)**
**National Institute for Health and Care Excellence (NICE)**

Submitted 16th March 2017

# Table of Contents

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# Overview

This document contains Takeda's responses to the clarification questions from the NICE technical team and the evidence review group (ERG) that were sent to Takeda on 2nd March 2017. We have attempted to address all questions as fully as possible within the timeframe permitted (deadline of 16th March 2017). However, it has not been possible to provide a full response to questions B1c and B14:

- B1c: Please clarify, if possible, the overlap between the data used by Hux et al. and the data reported by Mak et al., which is used in the company submission.
- B14: Please provide a scenario analysis that explores the potential effect of removing patients under the age of 18 years in the SG035-004 trial on the cost effectiveness analyses (question A3).

Further detail around these responses is discussed in Section B.

# Response to clarification questions

## Section A: Clarification on clinical effectiveness data

**A1. <u>Priority. Please provide a complete list of studies included in the systematic review reported in the submission (including primary and secondary references) to resolve discrepancies, in particular:</u>**

**a. The 2015 systematic review states that 20 studies were included, comprising 18 full text papers and 4 conference abstracts, but only 17 full text papers and three conference abstracts were referenced. Secondary publications Coiffier et al., (2014) and Pro et al., (2014) were not listed as references.**

The company would like to apologise for sending the 2015 clinical systematic literature review (SLR) report and not the updated version dated 19th January 2017, as had been intended.

The updated report is attached with these responses. In the updated report, the publications by Coiffier et al. (2014)[1] and Pro et al. (2014)[2] are listed as references (see page 6 of the updated SLR report).

**b. The Lamarque et al., (2014) abstract is not included in the 2015 systematic review, as stated in Section 4.1.3 of the submission.**

The company would like to apologise for the error in the referencing of the Lamarque et al., (2014) abstract in the 2015 systematic review. The abstract is incorrectly referenced as Mathilde et al. (2014). The author's full name is Mathilde Lamarque. This error has been rectified in the updated 2017 SLR report (see Table 3.1 on page 18).

**c. The Gibb et al., (2013) study is not mentioned in Section 4.1.3 of the submission or in the 2015 systematic review, but is included in the submission**

**as retrospective case series in Section 4.9, Section 4.11.1 and Table 4.2 (page 43 of the company submission). In addition, this study includes only 5 patients with anaplastic large cell lymphoma (ALCL), which does not fulfil the eligibility criterion of 20 or more patients (Table 4.1, page 38 of the company submission).**

The company acknowledges that it is unclear why the Gibb et al. (2013)[3] study is referenced in the submission alongside studies identified by the systematic review. As correctly noted, the Gibb et al. (2013) study does not fulfil the eligibility criteria of the systematic review as it reports outcomes for less than 20 patients. However, it was felt important that this study should be presented in the submission as it reports outcomes for patients in the UK that have received brentuximab vedotin in the real world setting as part of the named patient programme (NPP). This study was hence cited as it provided supplementary, UK specific data, relevant to the NICE decision problem.

**d. Section 4.1.3 of the company submission states that 1 new full text paper is included in the submission. However, it is unclear which paper is being referred to.**

The company would like to apologise for the lack of clarity in Section 4.1.3. The company is referring to the full text paper by Lamarque et al. (2016) which is referenced in the paragraph below (Reference No. 37).

**e. Some references from the 2015 systematic review (Forero-Torres [2009], Mathilde [2014]) are not referenced in the submission.**

The company would firstly like to apologise for not sending the updated 2017 version of the systematic review report.

Secondly, the Mathilde et al. (2014) reference shown in Table 3.1 is incorrectly referenced. The correct reference for this publication is Lamarque et al. (2014). The author's full name is Mathilde Lamarque. This correct reference (an updated publication by Lamarque at al. (2016)) is shown in the updated 2017 version of the SLR report.

The Forero-Torres et al. (2009) and the Lamarque et al. (2014) references, along with others in Table 3.1 of the SLR report, are not included in the submission as they do not include the brentuximab vedotin regimen.

**f. The PRISMA flow diagram (Figure 4.1, page 39 of the company submission) states that 19 full publications and 7 abstracts were included in the submission but Table 4.2 (list of relevant non-randomised and non-controlled evidence) includes only 6 studies.**

The 19 full publications and 7 conference abstracts included in the PRISMA flow diagram on page 39 of the company submission refer to all of the publications and abstracts identified in the systematic review. The systematic review included all treatments for patients with relapsed/ refractory systemic anaplastic large cell lymphoma (R/R sALCL), not just brentuximab vedotin. Table 4.2, however, only included the six studies identified in the systematic review which relate to brentuximab vedotin, and are therefore relevant to the submission.

**A2.** **Table 5.3 (page 84 of the company submission): The right hand column ("dosing source") lists studies which are not mentioned elsewhere in the company submission. Please clarify how these dosing studies were identified.**

The dosing sources listed in Table 5.3 of the submission were based on publications cited in the National Comprehensive Cancer Network (NCCN) guidelines for PTCL[4]. These publications were selected as the systematic review of clinical efficacy (Section 4 of the submission) did not identify any studies which could inform dosing schedules for chemotherapies in R/R sALCL.

**A3.** **The European Public Assessment Report for brentuximab vedotin (page 56) states that the inclusion criteria for trial SG035-004 specified that at US and Canadian sites, patients were to be age 12 years or older and at European sites, patients were to be age 18 years or older. The clinical study report for SG035-004 (page 76) states that there were 4 patients enrolled in the trial who were aged 12-17 years. Given that the population specified in the marketing authorisation is 'adults', that is age 18 years or older, please provide a commentary on whether the inclusion of patients under the age of 18 years in the SG035-004 trial would affect the generalisability of the trial results to the population specified in the marketing authorisation and to clinical practice in England.**

There were 4 out of 58 patients (6.9%) aged 12-17 years enrolled in the SG035-004 trial. These are too small numbers to draw any conclusions from; however, the results from the 004 trial suggest that they are generalisable to the population specified in the marketing authorisation and to clinical practice in England and the inclusion of these 4 patients did not significantly influence the overall ITT results.

In general, children and young adults are affected by ALK-positive ALCL, whilst ALK-negative ALCL is more common in patients over the age of 55 years. Importantly, in the subgroups of patients with ALK-positive and ALK-negative disease, similar proportions of patients achieved objective responses with brentuximab vedotin, including CRs in at least half of the patients in both subgroups. Achieving a CR rate of 50% is clinically meaningful, especially given the poor prognosis of ALK-negative patients. Additionally, the median PFS among patients with ALK-positive disease was 14.6 months and 14.3 months in patients with ALK-negative disease, indicating that there was no difference in progression rates between the subgroups.

Furthermore, analyses of efficacy by subgroups did not reveal any subgroup of patients that did not achieve clinically meaningful antitumour activity. ORR was generally consistent among all age subgroups analysed.

**A4.** **Table 5.9 (page 90 of the company submission): The response to primary therapy is listed in the Mak et al., (2013) and SG035-0004 studies. For Mak et al., the 3 probabilities sum to 101% which may be a result of a rounding error. For SG035-0004 the probabilities only sum to 93%. Please clarify whether the numbers for SG035-0004 are correct or whether there is a category missing.**

The company acknowledges that the values for response to primary therapy presented in Table 5.9 of the submission based on Mak et al. (2013)[5] sum to 101%. The values presented in Table 5.9 align with those reported in the Mak et al. (2013) publication, and we believe the sum of 101% reflects a rounding error. The company also acknowledges that the values presented in Table 5.9 for SG035-0004 sum to 93%. This is because the best response to primary therapy was 'unknown/other' in 7% of patients in SG035-0004; a revised table is presented below.

**Table 1: Characteristics for patients in Mak et al (2013) and SG035-0004**

| **Response to primary therapy** | **Mak et al. (2013)[5]** | **SG035-0004[6]** |
|---|---|---|
| CR | 51% | 48% |
| PR/SD | 26% | 29% |
| PD | 24% | 16% |
| Unknown/other | 0% | 7% |

## Section B: Clarification on cost-effectiveness data

**B1.** **<u>Priority. Section 5.1, Page 77 of the company submission: It is noted that a full text paper of the cost-effectiveness study by Hux et al., (2016) (included as abstract in the company's systematic review) has been published, providing details on the modelling assumptions used (Journal of Health Economics and Outcomes Research 2016; 4(2):188-203).</u>**

**a.** **Given that the structure of the company's economic model is similar to the structure of the economic model described in Hux et al., please comment on the reasons for the difference in the reported incremental cost effectiveness ratios (ICERs) in the company submission and that reported by Hux et al., (that is £8,829 per QALY gained in the company submission compared with £35,390 per QALY gained reported in the study by Hux et al.).**

The company acknowledges that the publication by Hux et al. (2016)[7] evaluates the cost-effectiveness of brentuximab vedotin vs. chemotherapy for the treatment of R/R sALCL as per the cost-effectiveness analysis reported in the company submission. However, there are a number of differences between the models which will impact on the predicted ICER; these are summarised in Table 2.

**Table 2: Comparison of cost-effectiveness analyses – company submission vs. Hux et al. (2016)**

| Component | Company submission | Hux et al. (2016)* |
|---|---|---|
| Modelling approach | • The model estimates costs and health effects for the following six cohorts and weights these according to the proportion of patients in each for each treatment arm in order to estimate total costs and QALYs for the respective comparators:<br>1. Patients who only receive brentuximab vedotin<br>2. Patients who receive brentuximab vedotin followed by ASCT<br>3. Patients who receive brentuximab vedotin followed by alloSCT<br>4. Patients who only receive chemotherapy<br>5. Patients who receive chemotherapy followed by ASCT<br>6. Patients who receive chemotherapy followed by alloSCT | • The model estimates costs and health effects for brentuximab vedotin and chemotherapy overall (i.e. patients who receive alloSCT, ASCT and no SCT are modelled as a single cohort for each comparator)<br>• Outcomes associated with ASCT and alloSCT are assumed to be captured in the overall survival curves for the respective treatment arms (see below) |
| SCT modelling | • PFS and OS for ASCT and alloSCT were modelled explicitly based on data from Smith et al. (2013)[8].<br>• The associated lifetime costs and QALYs were assigned to 30% of brentuximab patients (ASCT = 14%; alloSCT = 16%) and 14% of chemotherapy patients (ASCT = 7%; alloSCT = 7%) | • Costs of alloSCT are assigned based on the assumption that 50% of brentuximab patients and 20% of chemotherapy patients receive alloSCT.<br>• Outcomes associated with ASCT and alloSCT are assumed to be captured in the overall survival curves for the respective treatment arms |
| Data-cut from SG035-0004 used to parameterise brentuximab vedotin PFS and OS | • PFS and OS data for brentuximab vedotin (no SCT) were based on 5-year follow-up data from SG035-0004 which were presented at the 58th American Society of Haematology (ASH) Annual Meeting in December 2016[9].<br>o The median follow-up was 71.4 months (range, 0.8 to 82.4). | • PFS and OS data for brentuximab were based an earlier data cut from SGN35-0004 which has shorter follow-up than the data cut used in the company submission.<br>o The median follow-up |
| Survival analysis for brentuximab PFS and OS | • Long-term PFS and OS for brentuximab vedotin (no SCT) were estimated by fitting parametric cure models to the SG035-0004 data. | • Long-term PFS and OS for brentuximab vedotin were estimated by fitting standard parametric models to the SG035-0004 data. |

| | | |
|---|---|---|
| | • These were extrapolated using general population mortality with an excess hazard of 5% for the no SCT cohort. | • These were only used for the within-trial period, following which the hazard was assumed equivalent to chemotherapy. |
| Data source for chemotherapy PFS and OS | • PFS for chemotherapy (no SCT) was based on PFS achieved with the most recent cancer-related therapy prior to brentuximab vedotin for the subgroup of 39 patients in SG035-0004 whose most recent therapy was for R/R disease.<br>• OS for chemotherapy (no SCT) was based on the subset of PTCL patients from Mak et al.[5] with PS<2 (n=47).<br>o This study reports outcomes for 89 patients with nodal PTCL who received systemic chemotherapy in the British Columbia Cancer Agency (BCCA) Lymphoid Cancer database. | • PFS and OS for chemotherapy were based on a subset of 40 patients with sALCL from the BCCA registry. |
| List price of brentuximab | • The results presented in the company submission are based on [redacted] | • The results presented are based on the BNF list price (£2,500 per 50mg vial) |
| Date | • The model has been adapted to align with the NICE scope for the appraisal based on the scoping meeting held in October 2016 | • The model built by Hux et al. (2016) was based analyses conducted in 2014 |
| *Based on manuscript; SCT, stem cell transplant; PFS, progression-free survival; OS, overall survival | | |

**b. For progression free (PFS) and overall survival (OS), Hux et al., used data from the Canadian BC Cancer Registry on 40 patients with systemic anaplastic large cell lymphoma (sALCL) who had received first line salvage therapy between 1980 and 2012 (provided by Dr Joseph Conners, BC Cancer Agency). Given the company's involvement in this published study, please clarify why this source of patient level data was not used in the company submission to model PFS and OS for the chemotherapy treatment arm.**

Mak et al (2013) was chosen as the preferred source of data for PFS and OS for chemotherapy (no SCT) as this publication was identified by the systematic review of clinical effectiveness and hence aligns with the NICE reference case which stipulates that "in general, estimates of treatment effect should be based on results of the systematic review"[10].

**c. Please clarify, if possible, the overlap between the data used by Hux et al. and the data reported by Mak et al., which is used in the company submission.**

Mak et al. (2013) reports outcomes for 153 patients (ALK-positive ALCL, n = 11; ALK-negative ALCL, n = 24; ALK status unknown, n = 1) identified in the British Columbia Cancer Agency (BCCA) Lymphoid Cancer database with nodal PTCLs who were R/R after primary therapy. Of these patients, 89 received systemic chemotherapy. The median follow-up was 4 years. None of the patients received SCT; however, 17 patients were felt to be candidates for SCT hence this dataset contains a mix of patients who were not candidates for SCT (n = 136) and those who were but did not ultimately receive SCT.

In the base case analysis, OS for chemotherapy (no SCT) is based on the subset of PTCL patients from Mak et al. with PS<2 (n=47). The model also includes the options to use PFS data for the same subset of patients, and also PFS and OS data for the subset of 17 ALCL patients from Mak et al.

The PFS and OS data used by Hux et al. is based on 40 ALCL patients in the BCCA registry who were R/R after primary therapy. The extent of overlap between these patients and those reported by Mak et al. could not be determined within the time-frame allowed for this response.

**B2. <u>Priority. Page 41 of the company submission: The submission states that *"No formal or mixed treatment comparison was performed"*.</u>**

**a. Please clarify why a matched adjusted indirect comparison (MAIC) between the SG035-0004 trial and the Canadian registry data from Mak et al., was not attempted for OS and PFS using the variables that could be compared between the studies.**

In the base case analysis, brentuximab vedotin (no SCT) and chemotherapy (no SCT) were compared by means of an unanchored indirect comparison. A MAIC was not initially explored due to the anticipated impact of the matching on the effective sample size. Specifically, in the base case analysis, PFS and OS for brentuximab (no SCT) are informed by the subset of 41 patients in the SG035-0004 trial who did not receive SCT as the first therapy following discontinuation with brentuximab. The company did not consider it appropriate to reduce this sample size further due to the anticipated increased uncertainty in long-term outcomes.

In response to this question, the company has explored the impact of matching the brentuximab vedotin (no SCT) IPD (N=41) to the characteristics which could be compared between the studies. These data are presented in Table 3.

**Table 3: Characteristics for patients in SG035-0004 and Mak et al. (2013)**

| Characteristic | Mak et al. (2013) (N=89) | SG035-0004 (no SCT) (before matching) (N=41) |
|---|---|---|
| Age (median, range) | 65 (29-86) | 55 (14-76) |
| Sex (% male) | 56% | 61% |
| Elevated lactate dehydrogenase (%) | 48% | 46% |
| Stage III-IV disease (%) | 89%* | 54% |
| Performance status ≥2 (%) | 43% | 2% |
| Response to primary therapy<br>• CR<br>• PR/SD<br>• PD<br>• Unknown/other | <br>51%<br>26%<br>24%<br>0% | <br>37%<br>22%<br>29%<br>12% |

*As reported in the Mak et al. (2013) publication; however N=76 which reflects 85% of the cohort. In the matching analysis, 85% was used.

Ten patients had missing baseline characteristics data and were excluded from the analysis. The matching analysis was conducted using the entropy weighting method described in Watson (2016)[11]. This was conducted in Stata using the 'ebalance' command using a tolerance influence level of 0.015 as per the default setting.

The algorithm did not converge when matching to all of the characteristics presented above. Upon review, the company believed this was due to the model being unable to match in terms of ECOG performance status. Specifically, only 1 patient in SG035-0004 (no SCT) had a performance status ≥2. This characteristic was hence dropped from the analysis.

The effective sample size when matching the brentuximab vedotin (no SCT) IPD to the remaining characteristics is presented in Table 4.

**Table 4: Effective sample size after matching**

| N | Minimum | Maximum | Effective sample size |
|---|---|---|---|
| 31 | 0.000001 | 9.653004 | 4.8 |

The matching analysis generated an effective sample size of 4.8 patients. The NICE Decision Support Unit (DSU) guidance[12] cites that "small effective sample sizes are an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable". In light of this, a MAIC was not pursued as a means of comparing brentuximab (no SCT) and chemotherapy (no SCT).

Of note, in the base case analysis, PFS for chemotherapy (no SCT) was modelled using PFS achieved on the most recent cancer-related systemic therapy (prior to brentuximab vedotin) for the subset of 39 patients in SG035-0004 who received this therapy in the R/R setting. This self-control comparison of PFS for brentuximab vedotin (no SCT) and chemotherapy (no SCT) adjusts for differences in baseline characteristics except for line of treatment given the internal nature of the data set (i.e. a subset of patients from SG035-0004 inform PFS for both brentuximab vedotin (no SCT) and chemotherapy (no SCT)).

In addition, for chemotherapy (no SCT), the base case analysis uses OS data from Mak et al. (2013) for the subgroup of PTCL patients with performance status <2 (n = 47). Any bias induced through differences in performance status has hence been accounted for.

**b. If a MAIC is possible, please provide the analysis and incorporate the findings in the economic model. We note that the patient data provided for the study by Hux et al., (2016) may offer further potential for adjusted comparisons between brentuximab and chemotherapy.**

Based on the effective sample size estimated in response to question B2a, a MAIC was not conducted.

**B3. Priority. Page 94-98 of the company submission. The "mixture cure" model assumes that a proportion of the patients in the brentuximab vedotin (No stem cell transplant [SCT]) cohort have been cured, and this model has been used for both PFS and OS. However, it is noted that no cure is assumed for any patients in the chemotherapy (No SCT) cohort. The ERG's clinical advice indicates that in practice there may be a small proportion of patients who will go into long term remission following salvage chemotherapy regimens. This also seems to be reflected in the Kaplan Meier plots reported by Mak et al., and Hux et al., with a small proportion of patients surviving beyond 10 to 15 years. Please assess the impact of incorporating a mixture cure model for OS and PFS in the chemotherapy cohort, using the data from Mak et al., or Hux et al.**

The parametric mixture cure models explored were all fitted in Stata using the 'strsmix' command described by Lambert (2007)[13]. Three parametric distributions (Weibull, lognormal and gamma) and three link functions for modelling the cure fraction (identity, logistic and log(-log)) are available in this command.

**PFS**

Parametric mixture cure models could not be implemented for chemotherapy (no SCT) as none of the distributions converged using any of the available link functions. In all cases, this is likely due to proximity of the proportion who are event-free beyond 10 to 15 years to the numerical limit of the cure fraction (i.e. [0,1]). This is described in more detail for the relevant datasets below.

***SG035-0004 self-control dataset***

In the base case analysis, PFS for chemotherapy (no SCT) was modelled using PFS achieved on the most recent cancer-related systemic therapy (prior to brentuximab vedotin) for the subset of 39 patients in SG035-0004 who received this therapy in the R/R setting. As

such, an attempt was first made to fit cure models to these data however none of the available distributions converged using any of the available link functions.

***Mak (2013) PS<2 dataset***

None of the available distributions converged using any of the available link functions.

***Mak (2013) ALCL dataset***

The Weibull model converged for this dataset using the identity link function, however the cure fraction coefficient was less than zero (-0.0086758) hence yielded implausible survival predictions which invalidated the model. The alternative link functions were explored however these did not rectify the issue. The lognormal and gamma distributions did not converge using any of the available link functions.

**OS**

Parametric mixture cure models could not be implemented for either the "Mak (2013) PS<2" or "Mak (2013) ALCL" datasets as none of the available distributions converged using any of the available link functions. Again, this is likely due to proximity of the proportion who are event-free beyond 10 to 15 years to the numerical limit of the cure fraction (i.e. [0,1]).

**B4. Priority. Table 5.54, page 144 of the company submission:**

**a. In patients who have received chemotherapy and experience post-progression survival, it appears that 80% then go on to receive brentuximab vedotin. The ERG's understanding is that the modelling incorporates the post-progression costs of this brentuximab vedotin treatment for these patients, but not the additional life year and QALY gains that might be expected (that is, the patients providing data on OS for the chemotherapy arms did not receive brentuximab vedotin in subsequent lines of treatment). The ERG considers it inappropriate to include brentuximab vedotin as a subsequent line of therapy in the chemotherapy arm in the context of the current decision problem. Please provide justification for why these costs are included, and if appropriate, remove or substitute them with the cost of chemotherapy or best supportive care (please see b below).**

The company recognises that the impact of brentuximab vedotin administered in the post-progression period will not be reflected in the OS curves from Mak et al. (2013) which inform OS for chemotherapy in the base case analysis, given that the patients in this study were treated in the pre-brentuximab vedotin era.

The company also recognises and agrees with the ERG that it may be inappropriate to include brentuximab vedotin as a subsequent (post-progression) therapy for patients in the chemotherapy cohorts based on the description of the comparator in the final scope, namely "established clinical management without brentuximab vedotin".

As such, the base case has been modified such that patients in the chemotherapy cohorts cannot receive brentuximab vedotin in the post-progression state. Please see our response

to Question B4b. for a complete description of the post-progression therapy distribution which has been adopted.

**b. The ERG's clinical advice suggests that upon progression following salvage chemotherapy or brentuximab vedotin treatment, a substantial proportion of patients would likely receive best supportive care rather than further active treatment. However, Table 5.54 lists the post-progression therapy distribution, with 100% of patients receiving either brentuximab vedotin or chemotherapy. Please provide further justification for this assumption in relation to the subsequent lines of treatment actually received by the cohorts used to model OS and PFS. For example, Mak et al., reported that 57% of patients with performance status 0 or 1 who progressed following salvage therapy received one or more lines of subsequent chemotherapy. Similarly, what proportion of patients who progressed on brentuximab vedotin received chemotherapy rather than retreatment with brentuximab vedotin?**

Upon reflection, the company recognises that it is inappropriate to assume that 100% of patients will receive active treatment following disease progression. In response, the company has conducted the following:

- Explored the post-progression therapy distribution received by patients in the data sources which inform OS for each model cohort
- Contacted clinical experts to elicit opinion on the post-progression therapy distribution in UK practice.

During this process, it became evident that the post-progression therapy distribution observed in SG035-0004 does not align with the feedback obtained from UK clinical experts. In light of this, the company has included separate post-progression therapy distributions in the cost-effectiveness model based on:

a) the distribution observed in the data sources informing OS in the cost-effectiveness model
b) UK clinical expert opinion.

The derivation of these distributions is discussed in the subsequent sections.

Of note, the company would like to highlight that the post-progression therapies administered in SG035-0004 include therapies (belinostat, pralatrexate, romidepsin, vorinostat) which are not licensed and therefore not used in the UK for the treatment of sALCL. The post-progression therapy distribution based on clinical expert opinion should hence be considered most reflective of the UK clinical practice and therefore most relevant to the current decision problem.

**Chemotherapy (no SCT)**

OS for chemotherapy (no SCT) is informed by Mak et al. (2013)[5] for the subset of PTCL patients with PS<2 (n=47). In this study, 57% of patients with performance status 0 or 1 who progressed following salvage therapy received one or more lines of subsequent chemotherapy.

The feedback from clinical experts was that prior to the availability of brentuximab vedotin, 40% of patients would receive best supportive care, and that the residual 60% of patients would receive single-agent palliative chemotherapy. This feedback is hence consistent with Mak et al. (2013). The post-progression therapy distributions for chemotherapy (no SCT) are presented in Table 5.

**Table 5: Chemotherapy (no SCT) post-progression therapy distribution**

| Cohort | Post-progression therapy (trial-based) | | Post-progression therapy (clinical expert opinion) | |
|---|---|---|---|---|
| | Single-agent chemotherapy | BSC* | Single-agent chemotherapy | BSC |
| Chemotherapy (no SCT) | 57% | 43% | 60% | 40% |
| BSC, best supportive care; *proportion receiving BSC assumed to be the residual of those receiving single-agent chemotherapy | | | | |

**Brentuximab vedotin (no SCT)**

OS data for brentuximab vedotin (no SCT) were taken from SG035-0004 for the subset of 41 patients who did not receive SCT. The post-progression therapy distribution from SG035-0004 is presented in Table 6.

The corresponding proportions were calculated by dividing the total number of courses of treatment administered (N) by the number of patients experiencing PD (23.14). The latter was calculated by multiplying the total number of PFS events (27) by the ratio of PD to death events observed for the ITT population (24 PD vs 4 deaths = 86%). These proportions do not sum to 100% as any given patient can receive multiple post-progression therapies.

**Table 6: Post-progression therapies in SG035-0004 – brentuximab (no SCT)**

| Therapy | No SCT cohort | |
|---|---|---|
| | N* | Proportion |
| AlloSCT | 3 | 13% |
| ASCT | 1 | 4% |
| Brentuximab vedotin | 15 | 65% |
| Single-agent chemotherapy | 8 | 35% |
| Multi-agent chemotherapy | 4 | 17% |
| Inhibitor treatments^ | 7 | 30% |
| BSC | 0 | 0% |
| *Number of courses administered – any given patient can receive multiple courses of one treatment or multiple lines of treatment; ^Belinostat, pralatrexate, romidepsin, vorinostat | | |

Notably, 65% of patients experiencing disease progression in SG035-0004 were retreated with brentuximab vedotin, and 30% received one of the following inhibitors; belinostat, pralatrexate, romidepsin, vorinostat.

In contrast, feedback from UK clinical experts indicated that retreatment with brentuximab vedotin was not currently possible, as retreatment is not routinely funded by the CDF. Moreover, none of the experts indicated that inhibitors would be used; this is likely due to these treatments not being licensed in the UK.

Of the clinical experts who were contacted; some indicated that 30% would receive single-agent chemotherapy and 10% would receive multi-agent chemotherapy; and others indicated that 20% would receive single-agent chemotherapy and 40% would receive multi-agent chemotherapy. The residual patients (60% and 40% respectively) were indicated to receive BSC by all experts.

However, the company was concerned that a higher proportion of patients receiving BSC after brentuximab (no SCT) compared to chemotherapy (no SCT) did not have clinical face validity. As such, the proportion of brentuximab patients receiving subsequent BSC was constrained to be 40% or lower. The proportion of patients receiving single-agent chemotherapy and multi-agent chemotherapy was calculated by applying the ratio of the average single-agent chemotherapy vs. multi-agent chemotherapy proportions indicated by the experts to the residual patients. The corresponding proportions are presented in Table 7.

**Table 7: Brentuximab post-progression therapy distribution based on clinical expert opinion**

| Cohort | Post-progression therapy | | |
|---|---|---|---|
| | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **BSC** |
| Brentuximab vedotin (no SCT) | 30% | 30% | 40% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | |

## SCT cohorts

Overall survival for the brentuximab + ASCT/alloSCT and chemotherapy + ASCT/alloSCT cohorts were informed by Smith et al. (2013)[8]. This study was identified by the systematic literature review and reports outcomes for 241 patients reported to the Centre for International Blood and Marrow Transplant Research (CIBMTR) between 1996 and 2006. Of these, 115 and 126 underwent ASCT alloSCT respectively.

Ideally, the post-progression therapy distribution for brentuximab + ASCT/alloSCT and chemotherapy + ASCT/alloSCT would be based on the therapies administered post-progression to patients in Smith et al. (2013)[8]; however these data were not reported.

Data on post-progression therapies were available for patients in SG035-0004 who received subsequent SCT (Table 8). These proportions were calculated as per the brentuximab (no SCT) cohort.

**Table 8: Post-progression therapies in SG035-0004 – brentuximab (SCT)**

| Therapy | SCT cohort (*N* = 17) | |
|---|---|---|
| | N* | Proportion |
| AlloSCT | 0 | 0% |
| ASCT | 0 | 0% |
| Brentuximab vedotin | 2 | 39% |
| Single-agent chemotherapy | 2 | 39% |
| Multi-agent chemotherapy | 0 | 0 |
| Inhibitor treatments^ | 1 | 19% |
| BSC | 0 | 0% |
| *Number of courses administered – any given patient can receive multiple courses of one treatment or multiple lines of treatment; ^Belinostat, pralatrexate, romidepsin, vorinostat | | |

However, use of these data to cost post-progression treatments for the SCT cohorts was not considered to be appropriate given Smith et al. (2013) reports outcomes for patients in the CIBMTR between 1996 and 2006, hence prior to the availability of brentuximab vedotin or inhibitor treatments.

In light of this, the post-progression therapy distribution for the SCT cohorts was assumed to be equal to chemotherapy (no SCT) for the trial-based scenario. These data are presented in Table 9.

**Table 9: SCT post-progression therapy distribution – trial-based**

| Cohort | Post-progression therapy | |
|---|---|---|
| | Single-agent chemotherapy | BSC* |
| Brentuximab + ASCT | 57% | 43% |
| Brentuximab + alloSCT | 57% | 43% |
| Chemotherapy + ASCT | 57% | 43% |
| Chemotherapy + alloSCT | 57% | 43% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care; *proportion receiving BSC assumed to be the residual of those receiving single-agent chemotherapy | | |

Of the clinical experts who were contacted, the following feedback was elicited:

- **Clinical expert 1:** 75% of patients on brentuximab + ASCT would receive multi-agent chemotherapy and the residual 25% patients would receive BSC.
- **Clinical expert 2:** 75% of patients on brentuximab vedotin + ASCT/alloSCT would receive multi-agent chemotherapy, and the residual 25% would receive single-agent chemotherapy.
- **Clinical expert 3:** 30% of patients on brentuximab vedotin + ASCT would receive single-agent chemotherapy, 30% would receive multi-agent chemotherapy, and the

residual 40% would receive BSC. In addition, 30% of patients on brentuximab vedotin + alloSCT would receive single-agent chemotherapy, 10% would receive multi-agent chemotherapy, and the residual 60% would receive BSC.

- **Clinical expert 4**: 30% of patients on brentuximab vedotin + ASCT would receive single-agent chemotherapy and 10% would receive multi-agent chemotherapy. No information was provided for the proportion receiving BSC for this cohort or for brentuximab + alloSCT.

The clinical experts did not provide feedback relating to the post-progression therapy distribution for chemotherapy + ASCT/alloSCT. This was hence assumed to be equal to chemotherapy (no SCT) as per the trial-based analysis.

As per the brentuximab (no SCT) cohort, the company was concerned that a higher proportion of patients receiving BSC after brentuximab (SCT) compared to chemotherapy (SCT) did not have clinical face validity. As such, the proportion of patients receiving BSC was constrained to be 40% or lower. The proportion of patients receiving single-agent chemotherapy and multi-agent chemotherapy was calculated as per the brentuximab vedotin (no SCT) cohort.

The post-progression therapy distribution based on clinical expert feedback is presented in Table 10.

**Table 10: SCT post-progression therapy distribution - clinical expert opinion**

| Cohort | Post-progression therapy | | |
|---|---|---|---|
| | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **BSC** |
| Brentuximab + ASCT | 22% | 38% | 40% |
| Brentuximab + alloSCT | 24% | 36% | 40% |
| Chemotherapy + ASCT | 60% | 0% | 40% |
| Chemotherapy + alloSCT | 60% | 0% | 40% |

AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care

The post-progression therapy distributions for each cohort are summarised in Table 11 and Table 12 for the trial-based and clinical opinion analyses respectively.

**Table 11: Trial-based post-progression therapy distribution**

| Cohort | Post-progression therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Brentuximab vedotin** | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **Inhibitors** | **AlloSCT** | **ASCT** | **BSC** |
| Brentuximab vedotin (no SCT) | 65% | 35% | 17% | 30% | 13% | 4% | 0% |
| Brentuximab + ASCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Brentuximab + alloSCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Chemotherapy (no SCT) | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Chemotherapy + ASCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Chemotherapy + alloSCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | | | | | |

**Table 12: Clinical expert opinion post-progression therapy distribution**

| Cohort | Post-progression therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Brentuximab vedotin** | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **Inhibitors** | **AlloSCT** | **ASCT** | **BSC** |
| Brentuximab vedotin (no SCT) | 0% | 30% | 30% | 0% | 0% | 0% | 40% |
| Brentuximab + ASCT | 0% | 22% | 38% | 0% | 0% | 0% | 40% |
| Brentuximab + alloSCT | 0% | 24% | 36% | 0% | 0% | 0% | 40% |
| Chemotherapy (no SCT) | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| Chemotherapy + ASCT | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| Chemotherapy + alloSCT | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | | | | | |

## Post-progression therapy costs

The total costs for each of the therapies are summarised in Table 13. As per the original company submission, post-progression therapy costs for brentuximab vedotin and multi-

agent chemotherapy comprised drug acquisition, drug administration, concomitant medications and adverse events. GDP was chosen to cost multi-agent chemotherapy as this was cited by all clinical experts. GDP is associated with the second highest total costs of all the chemotherapy regimens included in the model. The costs of alloSCT and ASCT included the costs of transplant and adverse events respectively.

Gemcitabine was chosen to cost single-agent chemotherapy as this was cited by all of the clinical experts who were contacted regarding post-progression therapies. The corresponding regimen (1200 mg/m$^2$ on days 1, 8 and 15 every 28 days for a maximum of 6 cycles) was taken from Zinzani et al. (2010)[14].

Given none of the inhibitors administered in SG035-0004 (belinostat, pralatrexate, romidepsin, vorinostat) are licensed in the UK, it was not considered appropriate to include the associated costs in the analysis. These patients were therefore assumed to accrue the cost of multi-agent chemotherapy.

**Table 13: Post-progression therapy costs**

| Therapy | Total cost |
|---|---|
| AlloSCT | £111,551 |
| ASCT | £52,737 |
| Brentuximab vedotin | £46,937 |
| Single-agent chemotherapy | £11,610 |
| Multi-agent chemotherapy | £12,310 |
| Inhibitor treatments | £12,310 |
| BSC | £0 |

The corresponding cost-effectiveness results based on the trial-based and clinical expert opinion post-progression therapy distributions are presented in Table 14 and Table 15 respectively. The increases observed compared to the base case ICER presented in the original company submission are due to the increase in incremental post-progression therapy costs resulting from the modifications to the post-progression therapy distribution.

**Table 14: Cost-effectiveness results using the trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | £106,590 | 9.53 | 5.15 | £69,235 | 6.18 | 3.56 | £19,451 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 15: Cost-effectiveness results using the clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | £83,508 | 9.53 | 5.15 | £45,779 | 6.18 | 3.56 | £12,861 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

All results in this document are presented using the within-trial post-progression therapy distribution and the clinical expert opinion post-progression therapy distribution separately.

**B5. <u>Priority. Given the uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice, please provide an illustrative scenario analysis that incorporates all of the below:</u>**

Results are presented for each scenario individually (to illustrate the impact of each based on the revised post-progression therapy distributions), then as combined scenarios in Table 20 and Table 21 for the trial-based and clinical expert opinion post-progression therapy distributions respectively.

**a. data from Mak et al. or Hux et al. for chemotherapy PFS and OS,**

PFS in this scenario is based on data from Mak et al. for the subgroup of PTCL patients with performance status <2 (*n* = 47) in order to align with the data used for OS in the base case. The corresponding cost-effectiveness results based on the trial-based and clinical expert opinion post-progression therapy distributions are presented in Table 16 and Table 17 respectively.

**Table 16: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,722 | 3.35 | 1.87 | - | - | - | - |
| Brentuximab | £106,590 | 9.53 | 5.15 | £69,868 | 6.18 | 3.29 | £21,245 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 17: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,063 | 3.35 | 1.87 | - | - | - | - |
| Brentuximab | £83,508 | 9.53 | 5.15 | £46,445 | 6.18 | 3.29 | £14,123 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

In relation to the phrasing of the question, specifically "uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice", the company would like to highlight that use of the Mak et al. data for PFS for chemotherapy (no SCT) introduces an additional potential source of bias relative to the base case in which a self-control comparison is conducted. However, the company recognises the extent to which the chemotherapies administered in the self-control dataset align with Mak et al. could not be determined (see response to question B8).

**b. adjustment for observed confounders if feasible (question B2)**

This scenario has not been conducted based on the effective sample size estimated in response to question B2a.

**c. allows a possible cure fraction for the chemotherapy as well as brentuximab. vedotin (question B3),**

This scenario has not been conducted given parametric cure models could not be fitted to the data for chemotherapy (see response to question B3).

**d. independent review facility (IRF) data (as opposed to investigator (INV) assessed data) to extrapolate PFS for brentuximab vedotin,**

This scenario has been conducted using the IRF assessed data for both response and PFS for brentuximab vedotin in order to retain consistency across endpoints. The corresponding cost-effectiveness results based on the within-trial and clinical expert opinion post-progression therapy distributions are presented in Table 18 and Table 19 respectively.

**Table 18: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | £109,800 | 9.54 | 4.06 | £73,138 | 6.25 | 2.50 | £29,265 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 19: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | £80,717 | 9.54 | 4.06 | £43,680 | 6.25 | 2.50 | £17,478 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

In relation to the phrasing of the question, specifically “uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice”, the company would like to highlight that the use of the IRF data introduces additional potential sources of bias relative to the base case due to the following:

- The IRF data is less comparable to the PFS with the last therapy received prior to SG035-0004 entry which informed PFS for chemotherapy (no SCT) in the base case as the latter is based on an investigator assessment
- Moreover, the IRF data has shorter follow-up relative to the INV data (maximum follow-up; 40 months per IRF vs. 76 months per INV) hence may induce more uncertainty in the long term extrapolations of PFS

**e. excludes or substitutes the costs of post-progression brentuximab vedotin therapy in the chemotherapy arms of the model (question B4).**

This scenario has been conducted using the post-progression therapy distributions presented in Table 5 and Table 7. The cost-effectiveness results for this are presented in Table 14 and Table 15 respectively.

The corresponding cost-effectiveness results based on the within-trial and clinical expert opinion post-progression therapy distributions for scenarios a-e combined are presented in Table 20 and Table 21 respectively.

**Table 20: Cost-effectiveness results for combined scenarios - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,023 | 3.29 | 1.83 | - | - | - | - |
| Brentuximab | £109,800 | 9.54 | 4.06 | £73,777 | 6.25 | 2.23 | £33,146 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 21: Cost-effectiveness results for combined scenarios - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,365 | 3.29 | 1.83 | - | - | - | - |
| Brentuximab | £80,717 | 9.54 | 4.06 | £44,352 | 6.25 | 2.23 | £19,927 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**B6. Page 72 of the company submission states that as a result of adverse events in 40% of the patients receiving brentuximab vedotin, 10% of doses were delayed. Please explain how this was taken into consideration in the economic model.**

Given treatment costs were calculated based on the mean number of cycles observed for the SCT and no SCT cohorts in SG035-004, and were adjusted based on the observed relative dose intensity for each cohort, no adjustment for delayed doses was made.

**B7. Table 5.2, page 82 of the company submission: The time horizon of 60 years allows the model to run until the cohort age is 107. In the study by Hux et al., a 30 year time horizon was used for the base case analysis. Please provide a justification for the 60 year time horizon used in the company submission.**

The time horizon used in the company submission was selected to ensure that all relevant differences in costs and outcomes were captured; hence this emerged based on the parametric extrapolations used in the analysis. Specifically, the time horizon was selected as the point at which OS for all cohorts had reached 0% (rounded to zero decimal places). Given parametric cure models were used to model OS for all cohorts excluding chemotherapy (no SCT), this time point reflects maximum survival for the general population based on the mean starting age in the model (47.7 years) and incorporating the cohort-specific excess hazards applied in the base case (see Table 5.21 of the original company submission).

The time point at which OS predicted by the model reaches 0% (rounded to zero decimal places) in both treatment arms is 53.11 years. A scenario analysis was therefore conducted adopting a time horizon of 53.11 years; the corresponding cost-effectiveness results based on the within-trial and clinical expert opinion post-progression therapy distributions are

presented in Table 22 and Table 23 respectively. This modification has an immaterial impact on the ICERs relative to those presented in response to question B4b.

**Table 22: Cost-effectiveness results based on 53.11 year time horizon - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | £106,590 | 9.53 | 5.15 | £69,235 | 6.18 | 3.56 | £19,454 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 23: Cost-effectiveness results based on 53.11 year time horizon - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | £83,508 | 9.53 | 5.15 | £45,779 | 6.18 | 3.56 | £12,863 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**B8. For the base case analysis, the self-controls from the pivotal trial are used to estimate response rates and PFS for chemotherapy in the model. Please clarify in more detail whether the chemotherapies received by the self-controls are an accurate reflection of the modelled comparators for this assessment; that is are the costed treatments (Table 5.39, page 133 of the company submission) consistent with the treatments previously received by the self-controls.**

The chemotherapies administered to the patients in the self-control dataset are summarised in Table 24. Unfortunately, it was unknown which regimen was used for 67% of the 39 patients in SG035-0004 whose most recent therapy was for R/R disease. As such, the extent to which these align with the regimens which were used to estimate acquisition and administration costs for chemotherapy in the cost-effectiveness analysis cannot be determined.

**Table 24: Most recent cancer-related therapy for R/R disease prior to SG035-0004**

| Reported Name of Drug regimen or Therapy | N | % |
|---|---|---|
| CHOP | 3 | 7.7 |
| ICE | 9 | 23.1 |
| Other | 26 | 66.7 |
| R-CHOP | 1 | 2.6 |
| CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; R-CHOP, rituximab + CHOP; ICE, ifosfamide, carboplatin, etoposide | | |

However, feedback from the clinical expert survey performed (Section 5.3.8 of the company submission) was that the chemotherapy regimens used in practice are not expected to differ with regards to efficacy. Moreover, scenario analyses assuming that all patients receive the most and least expensive regimen (Gem-P and ESHAP, respectively) only varied the ICER by 3% and 10% respectively compared to the base case. Therefore, the inability to align acquisition and administration costs for chemotherapy with the regimens which informed the PFS curve for the self-control dataset is not expected to have a material impact on the cost-effectiveness results.

**B9. Page 133 of the company submission: Please clarify whether the mean time-on-treatment sourced for chemotherapy drugs is conditional on adherence and survival, or whether it is reflective of the expectation for all patients commencing treatment, that is, is the number of cycles for chemotherapy estimated in a way that is consistent with the approach taken for brentuximab vedotin cycles?**

A summary of the data used to estimate time on treatment for the chemotherapy regimens is provided in Table 25.

**Table 25: Chemotherapy time on treatment data**

| Regimen | Definition of data point used for time on treatment | Is the impact of survival on time on treatment captured? | Is the impact of adherence on time on treatment captured? | Source |
|---|---|---|---|---|
| ICE | Number of cycles planned to be administered, as per treatment program reported in publication | No | No | Zelenetz (2003)[15] |
| ESHAP | Mid-point of range (6-8 cycles) reported in publication | No | Cannot be determined based on publication | Vellasquez (1994)[16] |
| DHAP | Mid-point of range (6-8 cycles) of cycles planned to be administered, as per treatment program reported in publication | No | No | Vellasquez (1988)[17] |
| GDP | Median | Yes | Cannot be determined based on publication | Dong (2013)[18] |
| Gem-P | N/A | N/A | N/A | Assumed equivalent to GDP |
| N/A, not applicable | | | | |

**B10. Please provide more information on the sources of data used for adverse events in the model, particularly for chemotherapy treatments in Table 5.55, page 143 of the company submission. What methods were used to source these data and select studies if alternatives were available? Are the studies selected appropriate for the target population of this assessment?**

The rates of adverse events for patients on brentuximab vedotin were based on the treatment-related adverse events (TRAEs) which occurred in the ITT population of the SG035-0004 trial.

Adverse event rates for the chemotherapy regimens were obtained from the studies used to inform dosing schedules. These sources were based on publications cited in the National Comprehensive Cancer Network (NCCN) guidelines for PTCL[4] (see response to question A2).

The study which informed the dosing schedule for ICE (Zelenetz et al. [2003])[15] did not report adverse event rates. Therefore, adverse event rates for ICE were based on Mikesch et al. (2013)[19]; a retrospective analysis of 31 patients with R/R aggressive PTCL who underwent DexaBEAM or ICE as salvage therapy prior to HDT and ASCT. This study was identified by a targeted search.

**B11. Tab "Costs", Cell E271:272 appears to call the discounted costs from the TraceBV and TraceChemo tabs (cells: BB5: BE5) (that is, discounted costs). These costs are then eventually recycled into the respective traces in the PPS state and further discounted. Please check these cells for accuracy and make any necessary changes to avoid double discounting. It is noted, however, that because these costs are incurred in early cycles of the model, any impact on resultant ICERs will be minor.**

PPS therapy costs have been double-discounted intentionally. The discounting which is calculated in cells BB5:BE5 in the TraceBV and TraceChemo tabs reflects time elapsing from initiation to discontinuation of treatment. These are then discounted back to $t = 0$ in the model to reflect the time at which patients enter the PPS state (which differs across treatment arms) and therefore begin to accrue the associated costs.

As such, no changes have been made to this component of the model.

**B12. The model does not allow the combination of IRF assessment with a standard gamma parametric model for PFS.**

**a. Please incorporate this functionality into the model.**

An overlay of the Kaplan-Meier and the parametric curves to demonstrate within-trial fit are presented in Figure 1; the corresponding AIC and BIC statistics are presented in Table 26.

**Table 26: AIC and BIC statistics and 99% PFS estimates for brentuximab vedotin (no SCT) PFS per IRF**

| | Exponential | Weibull | Lognormal | Log-logistic | Gamma |
|---|---|---|---|---|---|
| 99% PFS (years) | 5.6 | 7.3 | 15.3 | 27.5 | NR |
| AIC | 134.126 | 134.543 | 128.350 | 130.207 | 127.226 |
| BIC | 135.839 | 137.970 | 131.777 | 133.634 | 132.367 |
| AIC rank | 4 | 5 | 2 | 3 | 1 |
| BIC rank | 4 | 5 | 1 | 3 | 2 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reached; PFS, progression-free survival | | | | | |

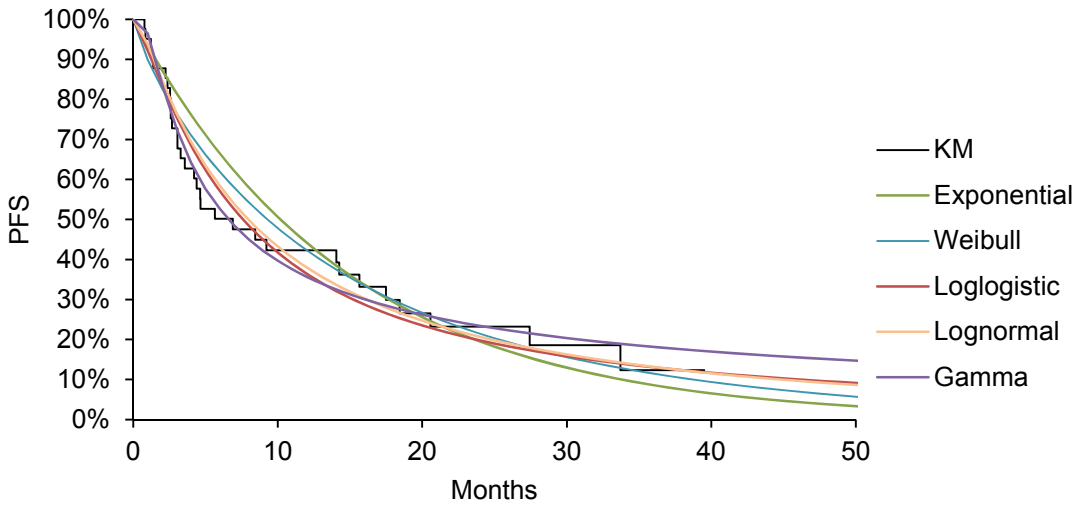


**Figure 1: Standard parametric models for brentuximab (no SCT) for PFS per IRF**

Based on this assessment, the lognormal and gamma models could both be considered the most appropriate model. However notably, the gamma model had not reached 1% by 60 years, although these outcomes would not be realised due to the competing risk of general population mortality. As such, both the lognormal and gamma models have been incorporated in the cost-effectiveness model to provide alternative predictions of long term PFS. The corresponding cost-effectiveness results per IRF are presented in Table 27 and Table 28 respectively based on the within-trial post-progression therapy distribution, and Table 29 and Table 30 respectively based on the clinical expert opinion post-progression therapy.

**Table 27: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | £111,768 | 9.54 | 3.54 | £75,107 | 6.25 | 1.98 | £37,864 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 28: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | £109,540 | 9.54 | 3.89 | £72,879 | 6.25 | 2.33 | £31,332 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 29: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | £80,988 | 9.54 | 3.54 | £43,951 | 6.25 | 1.98 | £22,157 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 30: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | £80,682 | 9.54 | 3.89 | £43,644 | 6.25 | 2.33 | £18,764 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**b. Please explain why all the parametric models explored for OS and PFS in the company submission are not incorporated in the model to enable sensitivity analysis, for example, there is no functionality to use Weibull models to extrapolate outcomes.**

The suitability of each parametric model for each dataset was assessed using the methods described in NICE DSU technical support document (TSD) 14[20] (see Table 5.11 of the company submission). This assessment was used to identify models that provided a good fit to the observed data and clinically and biologically plausible extrapolations. In line with TSD 14, models which did not satisfy both of these criteria were not considered in the cost-effectiveness model.

For a number of endpoints, all of the parametric models provided a very similar satisfactory within trial fit hence it was not deemed necessary to incorporate all of these models. Rather, the model which minimised the AIC and BIC was selected for the base case analysis, and a second model was selected for the sensitivity analysis to either provide an alternative estimate of the cure fraction (for cure models) or long term extrapolation (for standard models).

**B13. <u>Pages 27 and 131 of the company submission: Page 131 of the company submission states that the cost of brentuximab vedotin in the model is based on the mean number of treatment cycles patients had in SG035-0004 (8.2 cycles). Page 27 of the company submission states that the number of cycles of brentuximab vedotin used in clinical practice is likely to be less than in the SG035-0004 trial.</u>**

**a. Please provide a commentary on rules used in clinical practice in England for stopping treatment with brentuximab vedotin, for example the number of**

**cycles when maximal response would be expected, or the number of cycles when treatment would be stopped if there is no partial or complete response.**

Clinical experts with experience of treating R/R sALCL in England have provided some guidance regarding the existence of and nature of stopping rules applied in clinical practice for brentuximab vedotin in patients with R/R sALCL. The consistent response from the clinical experts is that patients receive 3-4 cycles of brentuximab vedotin, at which point a PET scan will be performed. If the patient has not achieved either a partial response (PR) or a complete response (CR) based on the PET scan, then they will stop treatment with brentuximab vedotin. Almost all patients who are going to achieve an objective response (PR or CR) will do so by cycle 4. Furthermore, a stopping rule for patients who have failed to reach an objective response after 4 cycles would also be consistent with NICE appraisal ID722 on brentuximab vedotin in R/R Hodgkin lymphoma.

**b. Please provide a scenario analysis that explores the potential effect of a stopping rule for brentuximab vedotin on the cost effectiveness analyses.**

In SG035-0004, PET scans were conducted at cycles 4 and 7; no additional PET scanning was required beyond cycle 7 unless clinically indicated. As such and in order to reflect clinical expert opinion, a scenario analysis was conducted in which it was assumed that patients who did not have a PR or CR by cycle 4 would discontinue treatment.

For the investigator-assessed responses, only 1 patient in the no SCT cohort who did not have CR or PR by cycle 4 received more than 4 cycles of brentuximab vedotin. For the IRF-assessed responses, only 1 patient in the SCT cohort who did not have CR or PR by cycle 4 received more than 4 cycles of brentuximab vedotin. This is summarised in Table 31.

**Table 31: Brentuximab vedotin exposure**

| Parameter | No SCT cohort (*N* = 41) | | SCT cohort (*N* = 17) | |
|---|---|---|---|---|
| | IRF | Investigator | IRF | Investigator |
| Number of patients that did not have CR or PR by cycle 4 | 8 | 10 | 1 | 0 |
| Number of patients that did not have CR or PR by cycle 4 and that received more than 4 cycles of brentuximab | 0 | 1 | 1 | 0 |
| Number of cycles administered beyond cycle 4 to patients that did not have CR or PR by cycle 4 | 0 | 3 | 3 | 0 |
| SCT, stem cell transplant; IRF, independent review facility | | | | |

To inform this scenario, the mean cycles and mean relative dose intensity (RDI) for the no SCT and SCT cohorts were recalculated excluding drug administered to each of these patients beyond cycle 4. The corresponding mean cycles and RDI are summarised in Table 32.

**Table 32: Mean cycles and RDI based on cycle 4 stopping rule**

| Parameter | No SCT cohort (*N* = 41) | | | | SCT cohort (*N* = 17) | | | |
|---|---|---|---|---|---|---|---|---|
| | IRF | | Investigator | | IRF | | Investigator | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Number of cycles | 7.98 | 5.26 | 7.90 | 5.29 | 8.59 | 3.74 | 8.76 | 3.58 |
| RDI | 94.49% | 11.18% | 94.49% | 11.18% | 94.59% | 12.23% | 94.59% | 12.23% |
| SCT, stem cell transplant; SD, standard deviation; RDI, relative dose intensity; IRF, independent review facility | | | | | | | | |

The corresponding cost-effectiveness results using the investigator-assessed data and the within-trial and clinical expert opinion post-progression therapy distributions are presented in in Table 33 and Table 34 respectively.

**Table 33: Cost-effectiveness results based on cycle 4 stopping rule – trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | £105,884 | 9.53 | 5.15 | £68,529 | 6.18 | 3.56 | £19,252 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 34: Cost-effectiveness results based on cycle 4 stopping rule – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | £82,986 | 9.53 | 5.15 | £45,257 | 6.18 | 3.56 | £12,714 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

It should be noted that clinical outcomes have not been modified for this scenario. However, these are not expected to differ with the stopping rule given the impact on exposure relative to the safety set analysis in SGN035-0004 is minor.

**B14. <u>Please provide a scenario analysis that explores the potential effect of removing patients under the age of 18 years in the SG035-004 trial on the cost effectiveness analyses (question A3).</u>**

As per the response to question A3, 4 out of 58 patients enrolled in SG035-004 were aged <18 years; 2 patients were in the no SCT cohort and 2 patients were in the SCT cohort.

In order to explore the effect of removing patients under the age of 18 years in the SG035-004 trial on cost-effectiveness, the following analyses would need to be conducted excluding these patients:

- Brentuximab (no SCT)
    - Response
    - PFS – parametric cure modelling
    - OS – parametric cure modelling
    - Exposure
    - Safety
    - Patient characteristics (gender, starting age)
    - Time to transplant
        - AlloSCT
        - ASCT
    - Post-progression therapies
- Chemotherapy (no SCT)
    - Response
    - PFS – standard parametric modelling

It was not feasible to conduct, implement in the cost-effectiveness model, validate and complete reporting for these analyses within the time frame available for this response. However, the company plans to conduct these analyses and provide the revised cost-effectiveness model and associated write-up of results as soon as possible.

B15. **Please provide ICERs for all cost effectiveness analyses using the list price of brentuximab vedotin.**

Results for all of the analyses presented in this document using the list price for brentuximab are presented below.

**Table 35: Cost-effectiveness results using the trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 36: Cost-effectiveness results using the clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 37: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,722 | 3.35 | 1.87 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.29 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 38: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,063 | 3.35 | 1.87 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.29 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 39: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.06 | [redacted] | 6.25 | 2.50 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 40: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin – clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.06 | [redacted] | 6.25 | 2.50 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 41: Cost-effectiveness results for combined scenarios - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,023 | 3.29 | 1.83 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.06 | [redacted] | 6.25 | 2.23 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 42: Cost-effectiveness results for combined scenarios - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,365 | 3.29 | 1.83 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.06 | [redacted] | 6.25 | 2.23 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 43: Cost-effectiveness results based on 53.11 year time horizon - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 44: Cost-effectiveness results based on 53.11 year time horizon - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 45: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.54 | [redacted] | 6.25 | 1.98 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 46: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.89 | [redacted] | 6.25 | 2.33 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 47: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.54 | [redacted] | 6.25 | 1.98 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 48: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.89 | [redacted] | 6.25 | 2.33 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 49: Cost-effectiveness results based on cycle 4 stopping rule – trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 50: Cost-effectiveness results based on cycle 4 stopping rule – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.59 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.15 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

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# Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

## Adverse event disutilities question (received from NICE on 20/03/2017; response provided by Takeda on 22/3/2017)

"As we understand, these are the disutilities associated with adverse events. However, in the deterministic analysis they appear to be incorporated into the QALY calculations with a positive rather than a negative sign. When the probabilistic mode is switched on, the sign is negative as it should be. Could you please look at this and correct it accordingly in any resulting analysis as an erratum to the clarification response?"

**Response from Takeda**

In response to this question from the ERG, Takeda provides the following response:

The company has reviewed the cost-effectiveness model submitted to NICE on 16/03/2017 and acknowledges that the ERG has correctly identified an error in the implementation of disutilities associated with adverse events. The company would like to apologise for this. This error has now been rectified.

Revised responses to the relevant ERG clarification questions sent on 16/03/2017 following rectification of this error are presented below. **Within this response document, changes in results or accompanying text relative to the version sent on 16/03/2017 have been highlighted in red text. The company would like to highlight and reassure both NICE and the ERG that the rectification of this error has had an immaterial impact on the cost effectiveness results, relative to those presented in the responses sent previously on 16/03/2017.**

**B4. Priority. Table 5.54, page 144 of the company submission:**

**b. The ERG's clinical advice suggests that upon progression following salvage chemotherapy or brentuximab vedotin treatment, a substantial proportion of patients would likely receive best supportive care rather than further active treatment. However, Table 5.54 lists the post-progression therapy distribution, with 100% of patients receiving either brentuximab vedotin or chemotherapy. Please provide further justification for this assumption in relation to the subsequent lines of treatment actually received by the cohorts used to model OS and PFS. For example, Mak et al., reported that 57% of patients with performance status 0 or 1 who progressed following salvage therapy received one or more lines of subsequent chemotherapy. Similarly, what proportion of patients who progressed on brentuximab vedotin received chemotherapy rather than retreatment with brentuximab vedotin?**

Upon reflection, the company recognises that it is inappropriate to assume that 100% of patients will receive active treatment following disease progression. In response, the company has conducted the following:

- Explored the post-progression therapy distribution received by patients in the data sources which inform OS for each model cohort
- Contacted clinical experts to elicit opinion on the post-progression therapy distribution in UK practice.

During this process, it became evident that the post-progression therapy distribution observed in SG035-0004 does not align with the feedback obtained from UK clinical experts. In light of this, the company has included separate post-progression therapy distributions in the cost-effectiveness model based on:

a) the distribution observed in the data sources informing OS in the cost-effectiveness model
b) UK clinical expert opinion.

The derivation of these distributions is discussed in the subsequent sections.

Of note, the company would like to highlight that the post-progression therapies administered in SG035-0004 include therapies which are not licensed in the UK (belinostat, pralatrexate, romidepsin, vorinostat). The post-progression therapy distribution based on clinical expert opinion could hence be considered most reflective of the current decision problem.

**Chemotherapy (no SCT)**

OS for chemotherapy (no SCT) is informed by Mak et al. (2013)[1] for the subset of PTCL patients with PS<2 (n=47). In this study, 57% of patients with performance status 0 or 1 who progressed following salvage therapy received one or more lines of subsequent chemotherapy.

The feedback from clinical experts was that prior to the availability of brentuximab vedotin, 40% of patients would receive best supportive care, and that the residual 60% of patients would receive single-agent palliative chemotherapy. This feedback is hence consistent with Mak et al. (2013). The post-progression therapy distributions for chemotherapy (no SCT) are presented in Table 1.

**Table 1: Chemotherapy (no SCT) post-progression therapy distribution**

| Cohort | Post-progression therapy (trial-based) | | Post-progression therapy (clinical expert opinion) | |
|---|---|---|---|---|
| | Single-agent chemotherapy | BSC* | Single-agent chemotherapy | BSC |
| Chemotherapy (no SCT) | 57% | 43% | 60% | 40% |
| BSC, best supportive care; *proportion receiving BSC assumed to be the residual of those receiving single-agent chemotherapy | | | | |

**Brentuximab vedotin (no SCT)**

OS data for brentuximab vedotin (no SCT) were taken from SG035-0004 for the subset of 41 patients who did not receive SCT. The post-progression therapy distribution from SG035-0004 is presented in Table 2.

The corresponding proportions were calculated by dividing the total number of courses of treatment administered (N) by the number of patients experiencing PD (23.14). The latter was calculated by multiplying the total number of PFS events (27) by the ratio of PD to death events observed for the ITT population (24 PD vs 4 deaths = 86%). These proportions do not sum to 100% as any given patient can receive multiple post-progression therapies.

**Table 2: Post-progression therapies in SG035-0004 – brentuximab (no SCT)**

| **Therapy** | **No SCT cohort** | |
|---|---|---|
| | **N*** | **Proportion** |
| AlloSCT | 3 | 13% |
| ASCT | 1 | 4% |
| Brentuximab vedotin | 15 | 65% |
| Single-agent chemotherapy | 8 | 35% |
| Multi-agent chemotherapy | 4 | 17% |
| Inhibitor treatments^ | 7 | 30% |
| BSC | 0 | 0% |
| *Number of courses administered – any given patient can receive multiple courses of one treatment or multiple lines of treatment; ^Belinostat, pralatrexate, romidepsin, vorinostat | | |

Notably, 65% of patients experiencing disease progression in SG035-0004 were retreated with brentuximab vedotin, and 30% received one of the following inhibitors; belinostat, pralatrexate, romidepsin, vorinostat.

In contrast, feedback from UK clinical experts indicated that retreatment with brentuximab vedotin was not currently possible, as retreatment is not routinely funded by the CDF. Moreover, none of the experts indicated that inhibitors would be used; this is likely due to these treatments not being licensed in the UK.

Of the clinical experts who were contacted; 1 indicated that 30% would receive single-agent chemotherapy and 10% would receive multi-agent chemotherapy; and a second indicated that 20% would receive single-agent chemotherapy and 40% would receive multi-agent chemotherapy. The residual patients (60% and 40% respectively) were indicated to receive BSC by both experts. The remaining 2 experts did not provide feedback on this component.

However, the company was concerned that a higher proportion of patients receiving BSC after brentuximab (no SCT) compared to chemotherapy (no SCT) did not have clinical face validity. As such, the proportion of brentuximab patients receiving subsequent BSC was constrained to be 40% or lower. The proportion of patients receiving single-agent chemotherapy and multi-agent chemotherapy was calculated by applying the ratio of the

average single-agent chemotherapy vs. multi-agent chemotherapy proportions indicated by the experts to the residual patients. The corresponding proportions are presented in Table 3.

**Table 3: Brentuximab post-progression therapy distribution based on clinical expert opinion**

| Cohort | Post-progression therapy | | |
|---|---|---|---|
| | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **BSC** |
| Brentuximab vedotin (no SCT) | 30% | 30% | 40% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | |

**SCT cohorts**

Overall survival for the brentuximab + ASCT/alloSCT and chemotherapy + ASCT/alloSCT cohorts were informed by Smith et al. (2013)[2]. This study was identified by the systematic literature review and reports outcomes for 241 patients reported to the Centre for International Blood and Marrow Transplant Research (CIBMTR) between 1996 and 2006. Of these, 115 and 126 underwent ASCT alloSCT respectively.

Ideally, the post-progression therapy distribution for brentuximab + ASCT/alloSCT and chemotherapy + ASCT/alloSCT would be based on the therapies administered post-progression to patients in Smith et al. (2013)[2]; however these data were not reported.

Data on post-progression therapies were available for patients in SG035-0004 who received subsequent SCT (Table 4). These proportions were calculated as per the brentuximab (no SCT) cohort.

**Table 4: Post-progression therapies in SG035-0004 – brentuximab (SCT)**

| Therapy | SCT cohort (*N* = 17) | |
|---|---|---|
| | N* | Proportion |
| AlloSCT | 0 | 0% |
| ASCT | 0 | 0% |
| Brentuximab vedotin | 2 | 39% |
| Single-agent chemotherapy | 2 | 39% |
| Multi-agent chemotherapy | 0 | 0 |
| Inhibitor treatments^ | 1 | 19% |
| BSC | 0 | 0% |
| *Number of courses administered – any given patient can receive multiple courses of one treatment or multiple lines of treatment; ^Belinostat, pralatrexate, romidepsin, vorinostat | | |

However, use of these data to cost post-progression treatments for the SCT cohorts was not considered to be appropriate given Smith et al. (2013) reports outcomes for patients in the CIBMTR between 1996 and 2006, hence prior to the availability of brentuximab vedotin or inhibitor treatments.

In light of this, the post-progression therapy distribution for the SCT cohorts was assumed to be equal to chemotherapy (no SCT) for the trial-based scenario. These data are presented in Table 5.

**Table 5: SCT post-progression therapy distribution – trial-based**

| Cohort | Post-progression therapy | |
|---|---|---|
| | Single-agent chemotherapy | BSC* |
| Brentuximab + ASCT | 57% | 43% |
| Brentuximab + alloSCT | 57% | 43% |
| Chemotherapy + ASCT | 57% | 43% |
| Chemotherapy + alloSCT | 57% | 43% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care; *proportion receiving BSC assumed to be the residual of those receiving single-agent chemotherapy | | |

Of the clinical experts who were contacted, the following feedback was elicited:

- **Clinical expert 1:** 75% of patients on brentuximab + ASCT would receive multi-agent chemotherapy and the residual 25% patients would receive BSC.

- **Clinical expert 2:** 75% of patients on brentuximab vedotin + ASCT/alloSCT would receive multi-agent chemotherapy, and the residual 25% would receive single-agent chemotherapy.
- **Clinical expert 3:** 30% of patients on brentuximab vedotin + ASCT would receive single-agent chemotherapy, 30% would receive multi-agent chemotherapy, and the residual 40% would receive BSC. In addition, 30% of patients on brentuximab vedotin + alloSCT would receive single-agent chemotherapy, 10% would receive multi-agent chemotherapy, and the residual 60% would receive BSC.
- **Clinical expert 4**: 30% of patients on brentuximab vedotin + ASCT would receive single-agent chemotherapy and 10% would receive multi-agent chemotherapy. No information was provided for the proportion receiving BSC for this cohort or for brentuximab + alloSCT.

The clinical experts did not provide feedback relating to the post-progression therapy distribution for chemotherapy + ASCT/alloSCT. This was hence assumed to be equal to chemotherapy (no SCT) as per the trial-based analysis.

As per the brentuximab (no SCT) cohort, the company was concerned that a higher proportion of patients receiving BSC after brentuximab (SCT) compared to chemotherapy (SCT) did not have clinical face validity. As such, the proportion of patients receiving BSC was constrained to be 40% or lower. The proportion of patients receiving single-agent chemotherapy and multi-agent chemotherapy was calculated as per the brentuximab vedotin (no SCT) cohort.

The post-progression therapy distribution based on clinical expert feedback is presented in Table 6.

**Table 6: SCT post-progression therapy distribution - clinical expert opinion**

| Cohort | Post-progression therapy | | |
|---|---|---|---|
| | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **BSC** |
| Brentuximab + ASCT | 22% | 38% | 40% |
| Brentuximab + alloSCT | 24% | 36% | 40% |
| Chemotherapy + ASCT | 60% | 0% | 40% |
| Chemotherapy + alloSCT | 60% | 0% | 40% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | |

The post-progression therapy distributions for each cohort are summarised in Table 7 and Table 8 for the trial-based and clinical opinion analyses respectively.

**Table 7: Trial-based post-progression therapy distribution**

| Cohort | Post-progression therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Brentuximab vedotin** | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **Inhibitors** | **AlloSCT** | **ASCT** | **BSC** |
| Brentuximab vedotin (no SCT) | 65% | 35% | 17% | 30% | 13% | 4% | 0% |
| Brentuximab + ASCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Brentuximab + alloSCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Chemotherapy (no SCT) | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Chemotherapy + ASCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| Chemotherapy + alloSCT | 0% | 57% | 0% | 0% | 0% | 0% | 43% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | | | | | |

**Table 8: Clinical expert opinion post-progression therapy distribution**

| Cohort | Post-progression therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Brentuximab vedotin** | **Single-agent chemotherapy** | **Multi-agent chemotherapy** | **Inhibitors** | **AlloSCT** | **ASCT** | **BSC** |
| Brentuximab vedotin (no SCT) | 0% | 30% | 30% | 0% | 0% | 0% | 40% |
| Brentuximab + ASCT | 0% | 22% | 38% | 0% | 0% | 0% | 40% |
| Brentuximab + alloSCT | 0% | 24% | 36% | 0% | 0% | 0% | 40% |
| Chemotherapy (no SCT) | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| Chemotherapy + ASCT | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| Chemotherapy + alloSCT | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSC, best supportive care | | | | | | | |

**Post-progression therapy costs**

The total costs for each of the therapies are summarised in Table 9. As per the original company submission, post-progression therapy costs for brentuximab vedotin and multi-agent chemotherapy comprised drug acquisition, drug administration, concomitant medications and adverse events. GDP was chosen to cost multi-agent chemotherapy as this was cited by all clinical experts. GDP is associated with the second highest total costs of all the chemotherapy regimens included in the model. The costs of alloSCT and ASCT included the costs of transplant and adverse events respectively.

Gemcitabine was chosen to cost single-agent chemotherapy as this was cited by all of the clinical experts who were contacted regarding post-progression therapies. The corresponding regimen (1200 mg/m$^2$ on days 1, 8 and 15 every 28 days for a maximum of 6 cycles) was taken from Zinzani et al. (2010)[3].

Given none of the inhibitors administered in SG035-0004 (belinostat, pralatrexate, romidepsin, vorinostat) are licensed in the UK, it was not considered appropriate to include the associated costs in the analysis. These patients were therefore assumed to accrue the cost of multi-agent chemotherapy.

**Table 9: Post-progression therapy costs**

| Therapy | Total cost |
|---|---|
| AlloSCT | £111,551 |
| ASCT | £52,737 |
| Brentuximab vedotin | £46,937 |
| Single-agent chemotherapy | £11,610 |
| Multi-agent chemotherapy | £12,310 |
| Inhibitor treatments | £12,310 |
| BSC | £0 |

The corresponding cost-effectiveness results based on the trial-based and clinical expert opinion post-progression therapy distributions are presented in Table 10 and Table 11 respectively. The increases observed compared to the base case ICER presented in the original company submission are due to the increase in incremental post-progression therapy costs resulting from the modifications to the post-progression therapy distribution.

**Table 10: Cost-effectiveness results using the trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | £106,590 | 9.53 | 5.12 | £69,235 | 6.18 | 3.56 | £19,470 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 11: Cost-effectiveness results using the clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | £83,508 | 9.53 | 5.12 | £45,779 | 6.18 | 3.56 | £12,873 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**B5. Priority. Given the uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice, please provide an illustrative scenario analysis that incorporates all of the below:**

**a. data from Mak et al. or Hux et al. for chemotherapy PFS and OS,**

PFS in this scenario is based on data from Mak et al. for the subgroup of PTCL patients with performance status <2 (*n* = 47) in order to align with the data used for OS in the base case. The corresponding cost-effectiveness results based on the trial-based and clinical expert opinion post-progression therapy distributions are presented in Table 12 and Table 13 respectively.

**Table 12: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,722 | 3.35 | 1.83 | - | - | - | - |
| Brentuximab | £106,590 | 9.53 | 5.12 | £69,868 | 6.18 | 3.29 | £21,267 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 13: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,063 | 3.35 | 1.83 | - | - | - | - |
| Brentuximab | £83,508 | 9.53 | 5.12 | £46,445 | 6.18 | 3.29 | £14,137 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

In relation to the phrasing of the question, specifically “uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice”, the company would like to highlight that use of the Mak et al. data for PFS for chemotherapy (no SCT) introduces an additional potential source of bias relative to the base case in which a self-control comparison is conducted. However, the company recognises the extent to which the chemotherapies administered in the self-control dataset align with Mak et al. could not be determined (see response to question B8).

**d. independent review facility (IRF) data (as opposed to investigator (INV) assessed data) to extrapolate PFS for brentuximab vedotin,**

This scenario has been conducted using the IRF assessed data for both response and PFS for brentuximab vedotin in order to retain consistency across endpoints. The corresponding cost-effectiveness results based on the within-trial and clinical expert opinion post-progression therapy distributions are presented in Table 14 and Table 15 respectively.

**Table 14: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | £109,800 | 9.54 | 4.02 | £73,138 | 6.25 | 2.50 | £29,296 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 15: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | £80,717 | 9.54 | 4.02 | £43,680 | 6.25 | 2.50 | £17,496 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

In relation to the phrasing of the question, specifically “uncertainties arising from the lack of comparative data for brentuximab vedotin compared with the range of salvage chemotherapies used in current practice”, the company would like to highlight that the use of the IRF data introduces additional potential sources of bias relative to the base case due to the following:

- The IRF data is less comparable to the PFS with the last therapy received prior to SG035-0004 entry which informed PFS for chemotherapy (no SCT) in the base case as the latter is based on an investigator assessment
- Moreover, the IRF data has shorter follow-up relative to the INV data (maximum follow-up; 40 months per IRF vs. 76 months per INV) hence may induce more uncertainty in the long term extrapolations of PFS

**e. excludes or substitutes the costs of post-progression brentuximab vedotin therapy in the chemotherapy arms of the model (question B4).**

This scenario has been conducted using the post-progression therapy distributions presented in Table 1 and Table 3. The cost-effectiveness results for this are presented in Table 10 and Table 11 respectively.

The corresponding cost-effectiveness results based on the within-trial and clinical expert opinion post-progression therapy distributions for scenarios a-e combined are presented in Table 16 and Table 17 respectively.

**Table 16: Cost-effectiveness results for combined scenarios (Mak et al. PTCL patients with performance status <2 (n = 47) for chemotherapy (no SCT) PFS and brentuximab vedotin (no SCT) IRF assessment) - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,023 | 3.29 | 1.80 | - | - | - | - |
| Brentuximab | £109,800 | 9.54 | 4.02 | £73,777 | 6.25 | 2.22 | £33,186 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 17: Cost-effectiveness results for combined scenarios (Mak et al. PTCL patients with performance status <2 (n = 47) for chemotherapy (no SCT) PFS and brentuximab vedotin (no SCT) IRF assessment) - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,365 | 3.29 | 1.80 | - | - | - | - |
| Brentuximab | £80,717 | 9.54 | 4.02 | £44,352 | 6.25 | 2.22 | £19,951 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**B7. Table 5.2, page 82 of the company submission: The time horizon of 60 years allows the model to run until the cohort age is 107. In the study by Hux et al., a 30 year time horizon was used for the base case analysis. Please provide a justification for the 60 year time horizon used in the company submission.**

The time horizon used in the company submission was selected to ensure that all relevant differences in costs and outcomes were captured; hence this emerged based on the parametric extrapolations used in the analysis. Specifically, the time horizon was selected as the point at which OS for all cohorts had reached 0% (rounded to zero decimal places). Given parametric cure models were used to model OS for all cohorts excluding chemotherapy (no SCT), this time point reflects maximum survival for the general population based on the mean starting age in the model (47.7 years) and incorporating the cohort-specific excess hazards applied in the base case (see Table 5.21 of the original company submission).

The time point at which OS predicted by the model reaches 0% (rounded to zero decimal places) in both treatment arms is 53.11 years. A scenario analysis was therefore conducted adopting a time horizon of 53.11 years; the corresponding cost-effectiveness results based on the within-trial and clinical expert opinion post-progression therapy distributions are presented in Table 18 and Table 19 respectively. This modification has an immaterial impact on the ICERs relative to those presented in response to question B4b.

**Table 18: Cost-effectiveness results based on 53.11 year time horizon - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | £106,590 | 9.53 | 5.12 | £69,235 | 6.18 | 3.56 | £19,473 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 19: Cost-effectiveness results based on 53.11 year time horizon - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | £83,508 | 9.53 | 5.12 | £45,779 | 6.18 | 3.56 | £12,875 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**B12. The model does not allow the combination of IRF assessment with a standard gamma parametric model for PFS.**

**a. Please incorporate this functionality into the model.**

An overlay of the Kaplan-Meier and the parametric curves to demonstrate within-trial fit are presented in Figure 1; the corresponding AIC and BIC statistics are presented in Table 20.

**Table 20: AIC and BIC statistics and 99% PFS estimates for brentuximab vedotin (no SCT) PFS per IRF**

| | Exponential | Weibull | Lognormal | Log-logistic | Gamma |
|---|---|---|---|---|---|
| 99% PFS (years) | 5.6 | 7.3 | 15.3 | 27.5 | NR |
| AIC | 134.126 | 134.543 | 128.350 | 130.207 | 127.226 |
| BIC | 135.839 | 137.970 | 131.777 | 133.634 | 132.367 |
| AIC rank | 4 | 5 | 2 | 3 | 1 |
| BIC rank | 4 | 5 | 1 | 3 | 2 |
| AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reached; PFS, progression-free survival | | | | | |

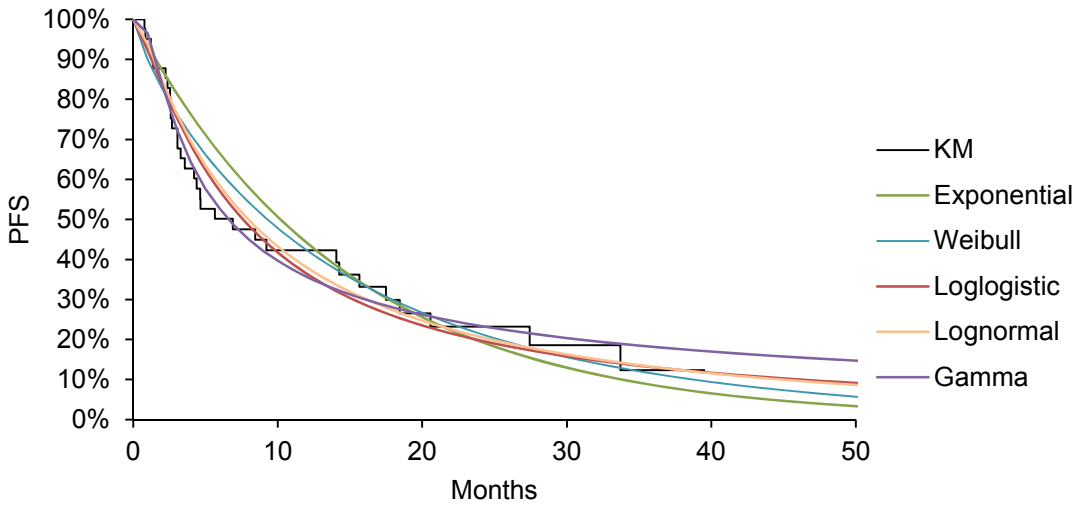


**Figure 1: Standard parametric models for brentuximab (no SCT) for PFS per IRF**

Based on this assessment, the lognormal and gamma models could both be considered the most appropriate model. However notably, the gamma model had not reached 1% by 60 years, although these outcomes would not be realised due to the competing risk of general population mortality. As such, both the lognormal and gamma models have been incorporated in the cost-effectiveness model to provide alternative predictions of long term PFS. The corresponding cost-effectiveness results per IRF are presented in Table 21 and Table 22 respectively based on the within-trial post-progression therapy distribution, and Table 23 and Table 24 respectively based on the clinical expert opinion post-progression therapy.

**Table 21: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | £111,768 | 9.54 | 3.51 | £75,107 | 6.25 | 1.98 | £37,915 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 22: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | £109,540 | 9.54 | 3.85 | £72,879 | 6.25 | 2.32 | £31,368 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 23: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | £80,988 | 9.54 | 3.51 | £43,951 | 6.25 | 1.98 | £22,187 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 24: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | £80,682 | 9.54 | 3.85 | £43,644 | 6.25 | 2.32 | £18,785 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**B13. Pages 27 and 131 of the company submission: Page 131 of the company submission states that the cost of brentuximab vedotin in the model is based on the mean number of treatment cycles patients had in SG035-0004 (8.2 cycles). Page 27 of the company submission states that the number of cycles of brentuximab vedotin used in clinical practice is likely to be less than in the SG035-0004 trial.**

**b. Please provide a scenario analysis that explores the potential effect of a stopping rule for brentuximab vedotin on the cost effectiveness analyses.**

In SG035-0004, PET scans were conducted at cycles 4 and 7; no additional PET scanning was required beyond cycle 7 unless clinically indicated. As such and in order to reflect

clinical expert opinion, a scenario analysis was conducted in which it was assumed that patients who did not have a PR or CR by cycle 4 would discontinue treatment.

For the investigator-assessed responses, only 1 patient in the no SCT cohort who did not have CR or PR by cycle 4 received more than 4 cycles of brentuximab vedotin. For the IRF-assessed responses, only 1 patient in the SCT cohort who did not have CR or PR by cycle 4 received more than 4 cycles of brentuximab vedotin. This is summarised in Table 25.

**Table 25: Brentuximab vedotin exposure**

| **Parameter** | **No SCT cohort (*N* = 41)** | | **SCT cohort (*N* = 17)** | |
|---|---|---|---|---|
| | **IRF** | **Investigator** | **IRF** | **Investigator** |
| Number of patients that did not have CR or PR by cycle 4 | 8 | 10 | 1 | 0 |
| Number of patients that did not have CR or PR by cycle 4 and that received more than 4 cycles of brentuximab | 0 | 1 | 1 | 0 |
| Number of cycles administered beyond cycle 4 to patients that did not have CR or PR by cycle 4 | 0 | 3 | 3 | 0 |
| SCT, stem cell transplant; IRF, independent review facility | | | | |

To inform this scenario, the mean cycles and mean relative dose intensity (RDI) for the no SCT and SCT cohorts were recalculated excluding drug administered to each of these patients beyond cycle 4. The corresponding mean cycles and RDI are summarised in Table 26.

**Table 26: Mean cycles and RDI based on cycle 4 stopping rule**

| **Parameter** | **No SCT cohort (*N* = 41)** | | | | **SCT cohort (*N* = 17)** | | | |
|---|---|---|---|---|---|---|---|---|
| | **IRF** | | **Investigator** | | **IRF** | | **Investigator** | |
| | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| Number of cycles | 7.98 | 5.26 | 7.90 | 5.29 | 8.59 | 3.74 | 8.76 | 3.58 |
| RDI | 94.49% | 11.18% | 94.49% | 11.18% | 94.59% | 12.23% | 94.59% | 12.23% |
| SCT, stem cell transplant; SD, standard deviation; RDI, relative dose intensity; IRF, independent review facility | | | | | | | | |

The corresponding cost-effectiveness results using the investigator-assessed data and the within-trial and clinical expert opinion post-progression therapy distributions are presented in in Table 27 and Table 28 respectively.

**Table 27: Cost-effectiveness results based on cycle 4 stopping rule – trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | £105,884 | 9.53 | 5.12 | £68,529 | 6.18 | 3.56 | £19,271 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 28: Cost-effectiveness results based on cycle 4 stopping rule – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | £82,986 | 9.53 | 5.12 | £45,257 | 6.18 | 3.56 | £12,727 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

It should be noted that clinical outcomes have not been modified for this scenario. However, these are not expected to differ with the stopping rule given the impact on exposure relative to the safety set analysis in SGN035-0004 is minor.

**B15. Please provide ICERs for all cost effectiveness analyses using the list price of brentuximab vedotin.**

Results for all of the analyses presented in this document using the list price for brentuximab are presented below.

**Table 29: Cost-effectiveness results using the trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 30: Cost-effectiveness results using the clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 31: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,722 | 3.35 | 1.83 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.29 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 32: Cost-effectiveness results using data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS – clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,063 | 3.35 | 1.83 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.29 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 33: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.02 | [redacted] | 6.25 | 2.50 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 34: Cost-effectiveness results using IRF-assessed data for response and PFS for brentuximab vedotin – clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.02 | [redacted] | 6.25 | 2.50 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 35: Cost-effectiveness results for combined scenarios (Mak et al. PTCL patients with performance status <2 (n = 47) for chemotherapy (no SCT) PFS and brentuximab vedotin (no SCT) IRF assessment) - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,023 | 3.29 | 1.80 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.02 | [redacted] | 6.25 | 2.22 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 36: Cost-effectiveness results for combined scenarios (Mak et al. PTCL patients with performance status <2 (n = 47) for chemotherapy (no SCT) PFS and brentuximab**

**vedotin (no SCT) IRF assessment) - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,365 | 3.29 | 1.80 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 4.02 | [redacted] | 6.25 | 2.22 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 37: Cost-effectiveness results based on 53.11 year time horizon - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 38: Cost-effectiveness results based on 53.11 year time horizon - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 39: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.51 | [redacted] | 6.25 | 1.98 | [redacted] |

| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years |
|---|

**Table 40: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - trial-based post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £36,661 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.85 | [redacted] | 6.25 | 2.32 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 41: Cost-effectiveness results based on standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.51 | [redacted] | 6.25 | 1.98 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 42: Cost-effectiveness results based on standard gamma model for brentuximab vedotin (no SCT) PFS per IRF - clinical expert opinion post-progression therapy distribution – without PAS**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,037 | 3.29 | 1.53 | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | 3.85 | [redacted] | 6.25 | 2.32 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 43: Cost-effectiveness results based on cycle 4 stopping rule – trial-based post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,354 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Table 44: Cost-effectiveness results based on cycle 4 stopping rule – clinical expert opinion post-progression therapy distribution**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | £37,729 | 3.35 | 1.56 | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | 5.12 | [redacted] | 6.18 | 3.56 | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

## References


1. Mak VH. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;**31**(16):1970-76.
2. Smith SMB. Hematopoietic cell transplantation for systemic mature T-cell non-hodgkin lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;**31**(25):3100-09.

3. Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Annals of oncology : official journal of the European Society for Medical Oncology 2010;**21**(4):860-3.

**NHS England submission into the NICE appraisal for the use of brentuximab in systemic anaplastic large cell lymphoma May 2017**

1. Brentuximab is licensed in adult patents with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

2. The main phase 2 study of brentuximab in relapsed/refractory sALCL was in heavily pretreated patients: median of 2 previous lines of treatment (range 1-6), 62% were refractory to 1st line treatment, 22% had never responded to any chemotherapy and 26% had failed an autologous stem cell transplant (SCT).

3. The place of brentuximab in treatment in the Cancer Drugs Fund has been as 2nd line treatment. It has been in the CDF for over 5 years and there remains an application rate to the CDF of about 45 patients/year.

4. Responses to brentuximab occur quickly and thus the small minority that fail to respond have their treatment stopped early. The complete remission rate is high and is achieved relatively quickly and thus treatment is usually stopped after 4-6 cycles of treatment. Those patients having brentuximab as a potential bridge to transplant and who then respond will usually proceed swiftly to SCT and thus have fewer rather than more cycles of therapy. The mean number of cycles was 8 in the phase II study and NHS England considers that the mean cycle number will be less in practice in England.

5. Assessment of response in the brentuximab trial by investigator review was slightly higher than by independent review. NHS England would recommend that the investigator-assessed figures are more clinically relevant as assessment of response is not just on the CT or PET/CT scans but also includes assessment of symptoms and the findings from clinical examination. Only the assessment of scans is subject to independent review.

6. The main significant toxicity is neurological, mainly a sensory neuropathy and one which usually improves after discontinuation of treatment. Since the number of cycles given in England is less than in the phase Ii study, the long term problems of brentuximab neuropathy is likely to be less than reported.

7. The comparator chemotherapy for brentuximab is mainly the combination of gemcitabine, dexamethasone and cisplatin or the combination of dexamethasone, high dose cytarabine and cisplatin. The latter is more inconvenient to patients as it requires greater time in hospital.

8. NHS England notes the data from a series of patients treated between 1976 and 2010 for relapsed peripheral T cell non-Hodgkin's lymphoma (Mak et al). ALCL made up 23% of the 153 patients in all in this study and only 58% of the whole group had been treated with chemotherapy. Of the 36 patients with ALCL, only 17 had received chemotherapy, the median PFS being 1.8 mo and OS 3.0 mo. The PFS and OS curves extending over 20 years published in this Mak paper showed that a small but definite proportion of ALCL patients were salvaged at the time of the study despite the fact that only a half of these

patients had received chemotherapy. There is likely to be great heterogeneity between the Mak et al and brentuximab phase II populations of patients.

9. NHS England notes that the Mak paper was clear that the outcomes were generally poor in ALCL for systemic therapy given after 1st or 2nd line treatment. The clear tail and plateauing on the PFS and OS curve for brentuximab in the phase II study are noteworthy and occur at much higher survival levels than those observed in the Mak paper. NHS England thus regards the benefits of brentuximab to be a step change in the management of relapsed/refractory sALCL.

10. Although brentuximab has been in the Cancer Drugs Fund for 5 years for the treatment of sALCL in both adults and children, NHS England does not regard brentuximab as being the current standard of care of this population of relapsed/refractory sALCL patients in England. NHS England only regards treatments as standard of care in England when they are funded by baseline commissioning (and in the case of this indication of brentuximab if and when NICE recommends it as being clinically and cost effective).

11. The license for brentuximab is limited to adults. Relapsed/refractory sALCL is seen in patients aged less than 18 years and there is no biological reason why any NICE recommendation as to the clinical and cost effectiveness of brentuximab for relapsed/refractory sALCL would not be valid in paediatric and teenager populations. If NICE recommends the use of brentuximab in sALCL within its marketing authorisation, NHS England would potentially wish to routinely commission its use in patients of less than 18 years in age, subject to NHS England ascertaining the impact of such a decision on currently running clinical trials.

[redacted]

5 May 2017

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name:**
**Dr Christopher P Fox,**
**MBChB(Hons) MRCP FRCPath PhD**
**Consultant Haematologist**
**Lymphoma MDT lead**
[redacted]

**Name of your organisation**

[redacted]

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
  - **YES. LARGE REGIONAL AND REFERRAL CLINICAL PRACTICE. CHAIR OF NOTTINGHAMSHIRE LYMPHOMA MDT AND T CELL LYMPHOMA RESEARCH LEAD, N.U.H**
  - **MEMBER OF UK NCRI T CELL WORKING PARTY, CORE MEMBER OF NCRI HIGH-GRADE SUBGROUP AND NCRI LYMPHOMA CLINICLA STUDIES GROUP**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
  - **YES, SEE ABOVE. ALSO MAJOR RECRUITER AS A PRINCIPAL INVESTIGATOR TO THE ECHELON2 CLINICAL TRIAL**

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **SEE ABOVE**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

**Systemic anaplastic T cell lymphoma (sALCL) in adults is a rare disease. This sub-group of mature peripheral T cell lymphomas can be further delineated by expression (or not) of the Alk protein. It is now clear that there is significant clinical and biological heterogeneity particularly within Alk-negative sALCL.**

**The most commonly employed first-line therapy in the UK for sALCL is CHOP (or CHOEP) chemotherapy. Some patients receive first-line consolidation with high-dose chemotherapy (most commonly BEAM) and autologous stem cell support.**

**Unfortunately the majority of patients with sALCL are destined to experience relapsed or refractory disease. Such patients represent a major area of unmet clinical need, typically experiencing a short overall survival following relapse with a lack of clear consensus or strong evidence base on which to recommend second line therapies. Conventional salvage chemotherapy (e.g. ICE) is employed, followed by either autologous or allogeneic stem cell transplantation; determined by clinician and patient preference influenced by a number of factors (e.g. patient age and fitness, nature and response to prior therapy(ies), donor availability and clinical trial options)**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**Clinical guidelines for peripheral T cell lymphomas (including ALCL) were published in 2013: http://www.b-s-h.org.uk/media/15665/haem-onc-dearden-management-of-mature-t-cell-and-nk-cell-neoplasms.pdf**

**The antibody drug conjugate Brentuximab Vedotin (BV) has been the most widely studied novel agent in sALCL. An analysis of patients treated in the early phase II study, after observation of almost 3 years demonstrated a median duration of response for CR patients of 26.3 months, and 16 (47%) of 34 remained in remission (Pro B et al. Blood. 2013;122(21). Abstract 1809.)**

**Clinical experience of BV as a treatment for relapsed/refractory sALCL in the UK has been possible through NHSE's Cancer Drug Fund for relapsed/refractory ALCL.**

**In addition, a number of UK sites participated in the ECHELON-2 phase 3 RCT (NCT01777152), which compared standard CHOP to CHP and brentuximab vedotin in newly diagnosed CD30+ PTCLs. This trial closed to recruitment in 2016 and results are awaited.**

**Clinical experience has been that this agent is very well tolerated with a limited side-effect profile usually manageable with dose reductions or delays. Typically, patients with r/r sALCL have been treated (through the CDF funding approval) with BV at relapse/progression with, broadly speaking, 2 strategies in mind (according to individual patient and disease characteristics and guided by regional lymphoma MDT discussion)**

**1. BV as a first salvage therapy as a bridge to consolidation with either autologous or allogeneic stem cell transplantation. In this setting, response assessment with PET-CT imaging would typically be performed after 4 doses of BV administered on a 21 day cycle.**

**2. BV as a first salvage therapy without the intention to consolidate with stem cell transplantation but the intention to deliver 16 cycles of BV supported evidence of ongoing response and tolerability.**

**Based on available evidence and clinical experience for this patient group with unmet clinical need, I would strongly support access to BV for patients with relapsed/refractory sALCL. I consider the development of this targeted therapy to represent an unprecedented and major step-change in the management of patients with r/r sALCL.**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

**Please see above statement.**

**- Early response assessment would typically would involve a PET-CT scan; lack of response (or progression) after 4 cycles of BV would be an indication to change therapy.**

**- Very well tolerated drug. It would be unusual for a patient to prematurely discontinue BV because of toxicity or tolerability concerns.**

**Equality and Diversity**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

**NA**

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

**Already funded through NHSE CDF so unlikely to have significant implementation issues.**

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Patient/carer expert statement (STA)

## Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

## *1. About you*

**Your name:** Marcus Williams
**Name of your nominating organisation:** Leukaemia Care
**Do you know if your nominating organisation has submitted a statement?**

No, Leukaemia Care have not submitted a statement.

☒ Yes ☐ No

**Do you wish to agree with your nominating organisation's statement?**

Not applicable. Leukaemia Care have not submitted a statement.

☐ Yes ☒ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

**Are you:**

- a patient with the condition?

☒ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?

☐ Yes ☒ No

**Do you have experience of the treatment being appraised?**

☒ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

## *2. Living with the condition*

**What is your experience of living with the condition as a patient or carer?**

As the patient, the initial experience of the condition was excruciatingly painful and immeasurably frightening. The pain was so severe and quality of life so poor that I would have welcomed the choice of euthanasia. Post pain relief, the physical side effects of treatment were hugely unpleasant. With little or no certainties of a positive outcome the mental effects were a constant challenge.

## *3. Current practice in treating the condition*

**Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.**

I believe the naïve, knee-jerk, answer is that as the patient you want the best possible outcome. You want a fast acting treatment with minimal, preferably no, side effects with the high potential for a positive outcome and a disease-free future.

In reality, the world isn't a wish granting factory. So, which is more important? Primarily, and rather selfishly I would like treatment to provide a lasting cure, enabling an enduring quality of life. Speed of treatment, particularly in terms of pain/discomfort relief is probably of equal importance, but you can't necessarily have the former without the latter. In reality, the trade-off is the inevitability of treatment side effects.

**What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?**

In terms of NHS care, the staff and facilities at Wigan Royal Albert Infirmary and The Christie are largely faultless. All staff perform to highly commendable level given well publicised constraints.

My specific experience of treatments were:

1. Chemoptherapy:

- First-line, two cycles of CHOP
- Second-line, one cycle of DHAP
- Followed by several cycles of Brentuximab Vedotin

2. 40Gy of radiotherapy.

3. Allogenic Stem Cell Transplant with 1 weeks Fludarabine, Melphalan and Campath conditioning.

4. Post-transplant treatment for:

- Grade 2 gastro intestinal and skin Graft versus Host Disease (GvHD)
- Recurrent infections as a consequence of immunosuppression
- Hypoadrenalism
- Hypothyroidism

From personal experience, traditional, standard chemotherapy is not especially pleasant, particularly the pre-Stem Cell Transplant conditioning, but traditional, standard radiotherapy to the head is particularly brutal. As are the GvHD specific side effects of the Stem Cell Transplant.

Which treatment did I prefer? Brentuximab Vedotin, without exception. Why? Owing to its significant effectiveness combined with its limited and mild side effects. Side effects being fatigue and neuropathy, specifically of the fingers.

## *4. What do you consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

**Please list the benefits that you expect to gain from using the treatment being appraised.**

My primary expectation was an increased survival outcome through the treatment of Brentuximab Vedotin.

Other, secondary benefits include:

- Relatively straight forward administration by intravenous infusion
- Treatment as an out-patient on a day unit
- Less time spent in a hospital environment
- Rapid visible reduction of physical symptoms, specifically drenching sweats and tumour mass
- Sustained reduction of symptom related pain and corresponding analgesia
- Improved mental health and associated quality of life

**Please explain any advantages that you think this treatment has over other NHS treatments in England.**

In simple terms, it works. I don't believe that I would be alive today had I not received Brentuximab Vedotin.

My disease was recurrent after initial treatment. In June 2014 I had failed two lines of traditional, standard chemotherapy. Brentuximab Vedotin represented my third line, targeted treatment. Without it I was looking at six to twelve weeks' life expectancy via palliative care (radiotherapy), given the aggressive nature of the Lymphoma. Brentuximab Vedotins effectiveness was astonishing. The most powerful tool I have to demonstrate this is a personal daily photo diary relating to the days before and after the initial administration of Brentuximab Vedotin on 1 July 2014. The speed at which my tumours shrank was miraculous. I would be delighted to share these with the committee.

The key advantages Brentuximab Vedotin has over other NHS treatments include:

- The positive outcome of my condition
- Access to future stages of treatment, specifically a Stem Cell Transplant
- More benign side effects compared with more traditional, standard treatments

- Rapid and sustained reduction in physical symptoms
- Significant contribution to sustained pain relief and reduction in pain relief medication
- Improved mental outlook, specifically hope for the first time
- Overall improved quality of life

**If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.**

Except for information available in the public domain, specifically that relating to former Christie Hospital patient Ian Brooks, I am not aware of any other patient who has received Brentuximab Vedotin.

http://www.dailymail.co.uk/health/article-2567455/Cancer-patients-lethal-70-tumours-disappear-just-two-WEEKS-thanks-pioneering-treatment.html

## *5. What do you consider to be the disadvantages of the treatment being appraised?*

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

The only minor side effects of Brentuximab Vedotin I experienced was fatigue and neuropathy, specifically of the fingers. I also experienced a handful of hours flu like symptoms following my initial intravenous infusion. This turned out to be an isolated occurrence and was not repeated after subsequent infusions.

**Please list any concerns you have about current NHS treatments in England.**

None that I am aware of.

**Please list any concerns you have about the treatment being appraised.**

None that I am aware of.

**If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.**

None that I am aware of.

## *6. Patient population*

**Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.**

With the exception of those in similar circumstances likely to benefit, I do not believe that I am sufficiently medically aware to comment.

**Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.**

Again, I do not believe that I am sufficiently medically aware to comment.

## *7. Research evidence on patient or carer views of the treatment*

**Are you familiar with the published research literature for the treatment?**

☐ Yes ☒ No

**If you answered 'no', please skip the rest of section 7 and move on to section 8.**

**Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.**

**Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?**

**If the treatment being appraised is already available in the NHS, are**

**there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?**

**Are you aware of any relevant research on patient or carer views of the condition or existing treatments?**

☐ Yes ☐ No

**If yes, please provide references to the relevant studies.**

## *8. Equality*

**NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.**

None that I am aware of, but again, I do not believe that I am sufficiently medically aware to comment.

## *9. Other issues*

**Do you consider the treatment to be innovative?**

☒ Yes ☐ No

**If yes, please explain what makes it significantly different from other treatments for the condition.**

I understand Brentuximab Vedotin to be a targeted therapy that selectively targets protein on the surface of cancer cells, where it sticks and delivers a drug that kills the cell. In my opinion this is what leads me to interpret that it is an innovative treatment.

**Is there anything else that you would like the Appraisal Committee to consider?**

Every society is judged by how it treats it's least fortunate amongst them.

## *10. Key messages*

**In no more than 5 bullet points, please summarise the key messages of your submission.**

- I had the great fortune to be in the right place at the right time. A positive outcome of this appraisal is the significant potential to support increased survival outcomes for similarly relapsed or refractory systemic anaplastic large cell lymphoma patients.
- The traditional, standard chemotherapy treatments were, in my case, ineffective and the side effects more severe than was the experience with Brentuximab Vedotin.
- Brentuximab Vedotin can be administered to Out Patients by intravenous infusion in around an hour, compared with hospital admission for other forms of treatment such as DHAP.
- My experience emphasises the significance of new and innovative treatments for the benefit of patients.
- Approved use of Brentuximab Vedotin will send a powerful message to the research and development community, encouraging them to discover other new, innovative, possibly targeted therapies for the future.

# Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma


**Produced by** Aberdeen HTA Group

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**Rider on responsibility for report**

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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**Contribution of authors**

Dwayne Boyers, Elisabet Jacobsen acted as health economists; critiqued and reviewed the cost-effectiveness evidence, checked and re-analysed the economic model, and carried out further sensitivity analyses. Moira Cruickshank acted as the systematic reviewer; wrote the background chapter, critiqued the company's definition of the decision problem, and clinical effectiveness methods. David Cooper acted as statistician; critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Cynthia Fraser acted as information scientist; critiqued the methods used for identifying relevant studies and conducted additional searches. Dominic Culligan acted as clinical expert; provided clinical advice and general guidance. Graham Scotland acted as project lead for this appraisal; contributed to the critique and review of the cost effectiveness methods, and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

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## List of tables

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## List of abbreviations

| | |
|---|---|
| **ADC** | Antibody drug conjugate |
| **AE** | Adverse event |
| **AIC** | Akaike information criterion |
| **ALK** | Alpha lymphoma kinase |
| **ALK-** | Alpha lymphoma kinase negative |
| **ALK+** | Alpha lymphoma kinase positive |
| **ALCL** | Anaplastic large cell lymphoma |
| **AlloSCT** | Allogeneic stem cell transplant |
| **ASCT** | Autologous stem cell transplant |
| **BIC** | Bayesian information criterion |
| **BNF** | British National Formulary |
| **BSA** | Body surface area |
| **BSC** | Best supportive care |
| **BV** | Brentuximab vedotin |
| **CDF** | Cancer drugs fund |
| **CHOP** | Cyclophosphamide, Hydroxydaunomycin, Oncovin®, Prednisolone |
| **CI** | Confidence interval |
| **CR** | Complete remission |
| **CS** | Company's submission |
| **CT** | Computed tomography |
| **DOR** | Duration of response |
| **ECOG** | Eastern Cooperative Oncology Group |
| **EFS** | Event free survival |
| **EMA** | European Medicines Agency |
| **EQ-5D** | EuroQol five dimensions |
| **ERG** | Evidence review group |
| **GCSF** | Granulocyte-colony stimulating factor |
| **HDC** | High-dose chemotherapy |
| **HL** | Hodgkin lymphoma |
| **HRG** | Healthcare resource groups |

| | |
|---|---|
| **HRQoL/ HRQL** | Health-related quality of life |
| **ICER** | Incremental cost effectiveness ratio |
| **INV** | Investigator |
| **IPI** | International prognostic index |
| **IRF** | Independent review facility |
| **ITT** | Intention to treat |
| **KM** | Kaplan Meier |
| **LY** | Life year |
| **MMAE** | Monomethyl auristatin E |
| **NHL** | Non-Hodgkin lymphoma |
| **NPP** | Named patient programme |
| **ORR** | Objective response rate |
| **OS** | Overall survival |
| **PAS** | Patient access scheme |
| **PD** | Progressive disease |
| **PET** | Positron emission tomography |
| **PET-CT** | Positron emission tomography-computed tomography |
| **PFS** | Progression free survival |
| **PPS** | Post-progression survival |
| **PR** | Partial remission |
| **PSS** | Personal social services |
| **PTCL** | Peripheral T-cell lymphoma |
| **PTCL NOS** | Peripheral T-cell lymphoma not otherwise specified |
| **QALY** | Quality adjusted life year |
| **RCT** | Randomised controlled trial |
| **RDI** | Relative dose intensity |
| **R/R** | Relapsed or refractory |
| **SAE** | Serious adverse event |
| **sALCL** | Systemic anaplastic large cell lymphoma |
| **SD** | Stable disease |
| **SLR** | Systematic literature review |
| **SPC/ SmPC** | Summary of product characteristics |

| | |
|---|---|
| **TEAE** | Treatment-emergent adverse event |
| **TTO** | Time-trade off |
| **VB** | Visual basic |

# 1 Summary

Anaplastic large cell lymphoma (ALCL) is a rare, aggressive peripheral T-cell lymphoma which occurs most commonly in children and young people. The two main types are systemic ALCL (sALCL) and primary cutaneous ALCL. There are two distinct subtypes of sALCL: ALK-positive and ALK-negative. Patients with ALK-positive ALCL tend to be younger than those diagnosed with ALCL-negative disease, and there are more males than females with both types. The prognosis of ALK-positive ALCL is better than that of ALK-negative disease, with significantly longer failure-free survival and overall survival then ALK-negative patients. Standard front-line treatment has traditionally been multi-agent chemotherapy but up to two-thirds of patients developed recurrent disease, and a proportion are refractory. There has been no standard treatment for recurring or refractory (R/R) sALCL and the outcome for these patients has been, in general, very poor.

Brentuximab vedotin (Adcetris®, Takeda UK Ltd, Taastrup, Denmark) is a CD-30 directed antibody-drug conjugate, which consists of an antibody against a cancer cell marker, covalently linked to a drug that kills the target cell. The mechanism of action involves the active drug's attachment to the antibody, which seeks out cancer cells. The linker binds the drug to the cancer cells, where it is internalised into the cells. The microtubule network is disrupted, leading to cell cycle arrest and apoptosis of the cell. Non-randomised single-arm trials and Named Patient Programmes have shown high rates of objective response with an acceptable safety profile. Brentuximab vedotin has had conditional authorisation in the EU since October 2012 and has become adopted as the standard of care for R/R sALCL in the UK, with funding from the Cancer Drugs Fund in England and via independent funding requests in Scotland and Wales.



## *1.1 Critique of the decision problem in the company submission*

The NICE scope for this appraisal considered the clinical and cost-effectiveness of brentuximab vedotin within its licensed indication for the treatment of R/R sALCL. The decision problem addressed in the company's submission was consistent with the NICE final scope.

### *1.2 Summary of clinical effectiveness evidence submitted by the company*

The company did not conduct any meta-analyses as only non-randomised single-arm studies were identified in the systematic review.

The company's clinical effectiveness evidence focused upon the Phase II, open-label, single-arm, multi-centre trial by Pro et al 2012, examining the efficacy and safety of brentuximab vedotin in patients with relapsed or recurrent sALCL after treatment failure of at least one prior therapy. The primary outcome was objective response rate, defined as the proportion of patients with complete response or partial response, as determined by an independent review facility. Objective response rate was 86% (range across included studies: 60% to 100%); complete remission rate was 59% (range across included studies: 48% to 63%); partial remission rate was 28% (range across included studies: 29% to 50%).

Adverse events were common. Every patient in the Pro et al 2012 study experienced at least one adverse event. Overall, the most common adverse events of any grade were peripheral sensory neuropathy, nausea, fatigue and pyrexia. The most common adverse events of grade 3 or above were neutropenia, thrombocytopenia, peripheral sensory neuropathy and anaemia. There were some cases of adverse events leading to treatment discontinuation or dose delays. No deaths were attributable to brentuximab vedotin.



### *1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted*

The company's systematic review identified the prospective interventional study by Pro et al 2012 and further identified two retrospective studies (Gopal 2014, Chihara 2015) and three named patient programmes (Gibb 2013, Lamarque 2016, Pellegrini 2016) involving use of brentuximab vedotin in patients with R/R sALCL. The study by Gibb et al 2103 included only five participants with ALCL, which did not fulfil the company's relevant eligibility criterion (i.e. at least 20 patients with ALCL). At clarification, the company justified the study's inclusion with the explanation that that the study reports outcomes for the UK which are relevant to the decision problem. The ERG agrees that the Gibb et al 2013 study reports relevant UK-specific outcomes but is of the opinion that this study should not have been included in the company's submission as it does not fulfil the eligibility criteria.

The ERG considers Pro et al 2012 an appropriate source of evidence for the efficacy of brentuximab vedotin and that due to the condition and the data available, the correct approach was taken.

As there is no standard comparator and no available comparative evidence, the ERG are satisfied that the data from Mak et al 2013 provides the only realistic option for making an indirect comparison with the efficacy of chemotherapy. The ERG agree with the decision to use a subset of Mak et al. 2013 participants (performance status <2) to inform OS for chemotherapy, but remain concerned about observed (age, stage of disease) and unobserved heterogeneity that may bias unadjusted comparisons in favour of brentuximab vedotin. With respect to the use of historical response data - for a subset of patients enrolled in the SG035-0004 - to model response rates and PFS for salvage chemotherapy, the ERG have concerns about potential bias relating to the exclusion of any long-term responders (to salvage chemotherapy) from this source of data.

### *1.4. Summary of cost-effectiveness evidence submitted by the company*

The company submitted a *'de novo'* partitioned-survival model to "*assess the cost-effectiveness of brentuximab vedotin compared to established clinical management without brentuximab vedotin for the treatment of patients with R/R s ALCL".* Six cohorts were modelled according to assumptions regarding progression to stem cell transplantation following each treatment. Three cohorts were modelled for brentuximab vedotin (No SCT (71%), + ASCT (14%), +allo-SCT (16%)) and 3 for chemotherapy (No SCT (86%), + ASCT (7%), + allo-SCT (7%)).

Progression free survival (PFS), post-progression survival (PPS) and death were modelled. Health state occupancy is based on the area under the modelled PFS and OS curves. Costs, life years and QALYs for a 48 year old were accrued on a weekly basis, discounted continuously at a rate of 3.5% per annum, over a 60 year time horizon according to the proportion of the modelled cohorts in each state. An NHS perspective on costs was adopted.

Model cost-effectiveness results are driven primarily by differences in treatment effectiveness in the 'No SCT' cohorts. Brentuximab vedotin PFS was based on data

observed in the SG035-0004 study, per investigator (INV) assessment, max follow up: 76 months in the base case, or per independent review facility (IRF) assessment, max follow up: 40 months as a sensitivity analysis. Per INV data show a long plateau on the Kaplan Meier curves. Therefore mixture cure models were used for PFS in the base case analysis. Per IRF assessment showed substantially poorer outcomes for brentuximab vedotin, with insufficient evidence (perhaps due to insufficient follow up) to determine the plausibility of long-term remission. OS data for brentuximab were extrapolated from data observed from the SG035-0004 study and similar cure assumptions were applied. The base case analysis of chemotherapy PFS was informed using internal self-control data from the single arm, open label, non-randomised SG035-0004 study for a subset of 39/58 (67%) of patients who had previously had a salvage chemotherapy for R/R disease. This inherently excludes any long term remissions following chemotherapy. With the respect to OS on chemotherapy, a subgroup of patients with PTCL, PS < 2, reported by Mak et al. was used. The same source was considered as a sensitivity analysis for PFS. It was assumed that chemotherapy would not be curative with subsequent stem cell transplant, therefore standard parametric survival models were used for both PFS and OS in the chemotherapy cohort. PFS and OS data for SCT adopted a similar approach to brentuximab vedotin, assuming mixture cure models due to the plateaus observed in the KM curves. Data from a single study were used for both ASCT and AlloSCT and the treatment effectiveness of SCT was not dependent upon the initial salvage therapy (brentuximab vedotin or chemotherapy). In all cases, an additional 5% excess mortality risk was applied to general population life-table estimates to model long-term survival in those assumed to be cured.

Utility data were sourced from a single study (Swinburn et al.) that elicited time trade-off values for health state vignettes describing CR, PR, SD and PD. Additional utility decrements, based on clinical expert opinion, were applied to general population norms to reflect the fact long term cancer survivors may not regain full utility. Utility data associated with adverse events had minimal impact on the model.

Costs included drug acquisition, administration, concomitant medications, SCT treatment, follow up care and post progression therapy. Modelled costs were sensitive to the number of treatment cycles on brentuximab vedotin and a judgement is required

regarding the most appropriate number for routine clinical practice in the UK. The base case analysis in the company's original submission assumed that 80% of patients treated with chemotherapy would receive brentuximab vedotin in a subsequent line of treatment. Given that this was in breach of the NICE scope for the appraisal, and inconsistent with the treatment effectiveness data used for chemotherapy (i.e. OS data from an era prior to the availability of brentiximab vedotin) the company provided a revised analysis with alternative distributional assumptions for post-progression therapy ('trial based', as observed in SG035-0004 and 'expert based', following revised consultation with clinical experts). The ERG prefer the use of the 'trial based' analysis for its consistency with the observed outcome data in SG035-0004.

The original submission predicted additional costs for brentuximab vedotin of [redacted], additional life years of [redacted] and additional QALYs of [redacted] over chemotherapy. The ICER was £8,829. After adopting the revised 'trial based' post progression therapy distribution, and correction of a technical error, the ICER increased to £19,470 per QALY gained after response to clarification queries. The probabilistic ICER was £19,034 per QALY gained, with a probability of cost effectiveness of 58%, 83% and 100% at a willingness to pay per QALY gained of £20k, £30k and £50k respectively. The ICER was most sensitive to assumptions surrounding the source of data for brentuximab vedotin PFS (IRF vs INV) and extrapolation models applied. An exploratory analysis using per IRF data for PFS, with a standard (log normal) model for brentuximab vedotin in the No SCT cohort, increased the ICER to £37,915 per QALY gained. This serves to illustrate the uncertainty surrounding the base case results.

### *1.5 Summary of the ERG's critique of cost effectiveness evidence.*

The ERG considers the submitted model to be generally of good quality, with an appropriate model structure. The ERG agrees with the use of a partitioned survival model, and acknowledges that significant effort has gone into modelling the bridge to SCT and incorporating best available data in the model. Whilst the ERG notes the paucity of available data for sALCL and the difficulties this presents for economic modelling, there are a number of concerns with some of the parameter estimates and assumptions used, particularly relating the choice of survival data used for chemotherapy in the model. A judgement call will be required to determine which

parameter inputs and data sources are most appropriate in the UK setting. The ERG considers that the key areas of uncertainty for a decision maker relate to:

- The true rate of stem cell transplantation following brentuximab vedotin or chemotherapy is unclear. The higher the rate of SCT following brentuximab vedotin, the higher the resultant ICER. This is due to progression to a high cost treatment for minimal additional survival gain over that achieved with brentuximab without SCT.
- The method of assessment used to gauge progression in brentuximab vedotin. The use of longer term INV data are indicative of cure. However, the likely less biased per IRF data report a higher proportion progressing with no evidence of cure (albeit at a shorter follow up).
- A related point of uncertainty is therefore whether it is appropriate to use a mixture cure model for brentuximab vedotin, but not for chemotherapy, given the conflicting evidence from per INV and per IRF assessment.
- The model is sensitive to the costs of brentuximab vedotin and the most appropriate number of cycles in the model (observed in trial: 8 cycles; expert opinion: 4-6 cycles; scheduled dosage: 16 cycles).
- The distribution of post-progression therapy. The ERG considers the initial model (assuming 80% of chemotherapy patients receive brentuximab vedotin) to be outwith the scope of the appraisal. However, a judgement call is required as to whether the revised 'trial based' distribution or 'expert based' distribution is most appropriate. The ERG takes the view that the former should be preferred.
- The appropriateness of using Swinburn et al as a source of utility, based on health state vignettes with emotionally charged, condition specific language. The ERG offers an alternative source (Doorduijn et al) based on EQ-5D data in an older population in Belgium / Netherlands, which does not differentiate by clinical response. As such the alternative source provides utilities only for progressed and non-progressed disease.

### *1.6 ERG commentary on the robustness of evidence submitted by the company*

#### 1.6.1 Strengths

In general, the methods used in the clinical and cost-effectiveness sections were appropriate. The economic model was well structured and made good use of the limited data available. The use of a partitioned survival model is a key strength of the company's submission.

#### 1.6.2 Weaknesses and areas of uncertainty

Uncertainty regarding the choice of data sources in the model to estimate PFS and OS gains for brentuximab vedotin versus chemotherapy:

- The use of per INV vs per IRF data for brentuximab vedotin PFS
- The use of mixture cure models for brentuximab vedotin vs. standard models for chemotherapy
- The use of internal self-control data from SG035-0004 to model chemotherapy PFS when alternative data from Mak et al were available.

Additionally, substantial uncertainty exists regarding the most appropriate distribution of post progression therapy for patients who fail treatment on either brentuximab vedotin or chemotherapy. There is a challenge to incorporate both real world use of the drug (where brentuximab vedotin is used at a number or points in the treatment pathway) vs. the NICE scope for the appraisal which requires brentuximab vedotin be removed for the comparator arm.

### *1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG*

In light of the above outlined uncertainties, the ERG conducted a number of further sensitivity analyses and re-ran deterministic and probabilistic analyses on the company's revised model (after clarification). In particular, the ERG note the impact of multi-variate sensitivity analyses on the ICER.

The ERG found that the ICER was particularly sensitive to the time horizon employed in the model and the discount rate applied, with substantial variation in the ICER depending on values selected in the model. Whilst great uncertainty exists in the modelling process over the longer term, the ERG acknowledges that the company's

approach adheres to the NICE reference case with regards to time horizon and discounting.

The model was particularly sensitive to additional ERG exploratory analyses around assumptions regarding the treatment effectiveness (PFS and OS) for brentuximab vedotin relative to chemotherapy. This applies particularly to the extrapolated PFS data for brentuximab vedotin and chemotherapy under optimistic and pessimistic assumptions *(See Figure 9).* The ERG's preferred base case analysis uses Kaplan Meier data from Mak et al. for chemotherapy PFS instead of the internal self-controls from SG035-0004, applied to the company's 'trial based' distribution of post-progression therapy. The associated ICER was £21,336 per QALY gained (probabilistic ICER: £20,720). The probability that brentuximab vedotin is cost-effective under the ERG's preferred base case assumptions is 53%, 78% and 99% at a willingness to pay for a QALY gain of £20,000, £30,000 and £50,000 respectively.

The ERG considers that an exploratory analysis using the more conservative IRF data for PFS and standard parametric models for both PFS and OS, and avoiding the use of self-control data for chemotherapy (i.e. using Mak et al data for both OS and PFS) in the No SCT cohorts, presents a plausible and more conservative estimate of the ICER (£38,927). A worst case scenario, combining this analysis with the further assumption that rates of progression to SCT are equal following both treatments (at 20% overall) pushes the ICER to £50,190 per QALY gained. Further uncertainty relates the magnitude of the survival benefit for brentuximab vedotin versus chemotherapy, which is based on an unadjusted naïve indirect comparison between independent single arm studies with heterogeneous cohorts. Reducing the hazard of progression and mortality in the chemotherapy arm, significantly increases the ICER for brentuximab vedotin.

# 2 Background

Lymphoma is the most common type of blood cancer. It occurs when immune system cells called lymphocytes grow and multiply uncontrollably. The two main types of lymphocytes are B lymphocytes (B cells) and T lymphocytes (T cells). Cancerous lymphocytes can migrate around the body to the lymph nodes, spleen, bone marrow, blood, or other organs, and form tumours. There are two principal types of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[1]

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of clinically aggressive NHLs that develop from mature T-cells of post-thymic origin.[2-4] Peripheral T-cell lymphomas account for around 12-15% of all NHLs in Western populations.[4, 5] Two of the most common types of PTCL are peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and anaplastic large cell lymphoma (ALCL).[2]

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is the most prevalent subtype of PTCL, representing up to one-third of PTCL diagnoses and 4% of NHL diagnoses in general.[6] It tends to be aggressive, is of variable morphology and phenotype, and relapse is common:[7, 8] PTCL-NOS has been described as a "wastebasket" category of aggressive nodal lymphomas.[7] Patients commonly present with generalised lymphadenopathy, often with nodal or extranodal disease and involvement of the skin, intestine, spleen, liver or bone marrow.[7, 9-13] Diagnosis of PTCL-NOS is based on a tissue biopsy, commonly of a lymph node.[7]

Anaplastic large cell lymphoma (ALCL) was first described in 1985 as a lymphoma with large anaplastic (or "bizarre") pleomorphic cells with strong and consistent expression of CD30.[14-17] The cell surface antigen CD30 is a member of the tumour necrosis receptor superfamily and is expressed by classical HL and ALCL (Fanale 2012). Anaplastic large cell lymphoma occasionally occurs in people with a history of previous lymphoma but mainly develops in primary form.[18, 19]

Anaplastic large cell lymphoma is a rare disease which occurs most commonly in children, representing around 40% of all NHL diagnoses in paediatric populations and

2% to 5% of all adult NHL cases.[16, 19, 20] The disease is classed as 'orphan' as it is below the threshold for orphan designation in the European Union of 5 people in 10,000.[21] Anaplastic large cell lymphoma is more common in males than in females, with a ratio of 3:1 reported.[22]

Anaplastic large cell lymphoma has been classified into two distinct forms: primary cutaneous ALCL and systemic ALCL (sALCL), classifications which have been confirmed in the 2016 revision of the WHO classification of lymphoid neoplasms.[23, 24] Primary cutaneous ALCL is out with the scope of this appraisal, which will focus upon sALCL henceforth.

Systemic ALCL often presents as an aggressive stage III to IV disease, commonly with systemic symptoms and extranodal involvement, in particular, skin, bone, soft tissue, liver, spleen, lung and bone marrow.[15, 18, 22, 25] In addition, patients frequently present with B symptoms (i.e. fever, night sweats, weight loss > 10%).[15, 25, 26]

The 2016 WHO classification of lymphoid neoplasms[23, 24] also confirmed the further distinction of sALCL into ALK-negative and ALK-positive forms, based on the expression of the anaplastic lymphoma kinase (ALK) protein (a receptor tyrosine kinase, which is normally expressed by neural tissues).[27, 28] Gene expression profiling studies have demonstrated that the ALK-negative ALCL signature is similar to that of ALK-positive ALCL and different from other natural killer/T-cell lymphomas. The distinction of ALK-positive and ALK-negative ALCL is important because of clinical and prognostic differences.[7, 23] Patients diagnosed with ALK-positive ALCL tend to be younger than those diagnosed with ALK-negative disease, with more males than females evident in each type.[4, 15, 22, 25] The higher proportion of males is particularly noticeable in those with ALK-positive ALCL and especially in the 35 years or younger age group.[22]

The prognosis of ALK-positive ALCL is better than that of ALK-negative disease, with significantly longer failure-free survival and overall survival reported for patients with ALK-positive ALCL. Both ALK-positive ALCL and ALK-negative ALCL have superior survival over PTCL-NOS.[4, 15, 25, 29, 30]

The standard front-line treatment for aggressive lymphomas, including ALCL, is considered to be CHOP (cyclophosphamide, doxorubicin, vincristine [Oncovin®], prednisone) or CHOP-type multi-agent chemotherapy. Of all the PTCLs, only ALK-positive ALCL tends to respond positively to CHOP (or other anthracycline-based regimens).[4, 31-34] In general, ALK-positive ALCL benefits from chemotherapy more than ALK-negative disease.[18, 31]

A review of 138 patients with sALCL between 1997 and 2010 (46% ALK-positive, 54% ALK-negative) reported that the most common regimen was ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by sequential consolidation with methotrexate, ifosfamide, etoposide and cytarabine (plus high dose chemotherapy and ASCT for some patients). The outcomes of people with ALK-positive disease were superior to those with ALK-negative disease.[25]

Up to around two-thirds of patients with sALCL develop recurrent disease following front-line chemotherapy.[4, 15] In the absence of brentuximab vedotin, treatment options for these patients, or for those refractory to front-line chemotherapy, depend on individual patient characteristics. High-dose chemotherapy (HDC) with autologous SCT is recommended for people with relapsed chemotherapy-sensitive disease who are eligible for transplant. For patients who have relapsed after HDC with autologous SCT, or who are not eligible for that combination, options are generally limited to non-curative treatments including GDP or DHAP. Single-agent alkylator-based regimens may be an option for people who are older and/or unfit. Prior to the introduction of brentuximab vedotin, there was a need for less toxic treatments for these patients and, in general, for R/R sALCL, a disease for which there was no standard treatment and poor outcomes.[15, 31, 33, 35-37]

Brentuximab vedotin (Adcetris®, Takeda UK Ltd, Taastrup, Denmark) is a CD30-directed antibody-drug conjugate (ADC).[26] Antibody-drug conjugates are a novel class of drugs for the selective treatment of cancer, consisting of an antibody against a cancer cell marker, covalently linked to a drug that kills the target cell.[38, 39] There are three components of brentuximab vedotin: (1) antibody (cAC10chimeric anti-human CD30 monoclonal antibody), (2) linker (a protease-cleavable linker composed of a maleimidocaproyl attachment group, a valine-citrulline dipeptide and a spacer), and

(3) drug (monomethyl auristatin E [MMAE], a pentapeptide consisting of methyl valine, valine, dolaisoleuine, dolaproine, and norephedrine).[40] The mechanism of action involves a multi-step process, beginning with the drug's attachment to the antibody, which seeks out cancer cells. The linker binds the drug to the cancer cells, where it is internalised into the cells and disrupts the microtubule network, leading to cell cycle arrest and apoptosis of the cell.[26, 32, 38]

The European Commission granted conditional marketing authorisation on 25-10-2012[41] for brentuximab vedotin for treating adult patients with relapsed or refractory CD30+ Hodgkin lymphoma after autologous stem cell transplant or after at least two previous therapies when ASCT or multi-agent chemotherapy is not a treatment option, and for the treatment of adult patients with relapsed or refractory sALCL. Conditions of the marketing authorisation include continued follow-up of patients in study SG035-0003 and in study SG035-004 (including sub-analysis of patients ≥ 100 kg), and a Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500), including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).

An abstract published in May 2015 of the MA25101 PASS reported that 62 patients were recruited between June 2013 and January 2015, of which 18 (29%) had R/R sALCL. Adverse events were not reported separately for patients with R/R sALCL. Adverse events were reported in 45/62 (73%) of patients. The most common AEs were peripheral neuropathy (n=18), infections (n=14) and neutropenia (n=13). There were grade 3 or above AEs in 24/62 (39%) patients, the most common being infections (n=8), neutropenia (n=6) and peripheral neuropathy (n=2). Seven patients (11%) reported grade 4 toxicities, including infection (n=4), progression with sepsis (n=2), neutropenia (n=2), thrombocytopenia (n=1) and tumour lysis syndrome (n=1, sALCL patient). There were SAEs in 21/62 (34%) patients, including 11 patients with drug-related SAEs; the most common were infection (n=9) and peripheral neuropathy (n=4). Two patients discontinued brentuximab vedotin, one due to grade 5 multi-organ failure, and one due to grade 3 left pleural effusion and grade 5 bronchopneumonia. There were 4 on-study deaths in total, due to pneumonia (n=3) and disease progression (n=1). The study authors concluded that the severity and frequency of reported toxicities are consistent with the known safety profile of

brentuximab vedotin, which is manageable and tolerable in the conditionally approved indications. The final study report of MA25101 is due in December 2018.

The company's submission appropriately refers to The British Committee for Standards in Haematology guidelines for management of mature T-cell and NK-cell neoplasms, which makes the following recommendations for ALCL:[42]

- The International Prognostic Index (IPI) has predictive value in ALCL but ALK positivity is the most important prognostic factor
- Patients with limited stage ALCL and no adverse prognostic features by IPI should be treated with four cycles of CHOP chemotherapy and involved field radiography
- All other patients should be entered into a clinical trial or receive six to eight cycles of CHOP chemotherapy
- Patients with ALK-negative ALCL should be treated as for peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
- Primary cutaneous ALCL (ALK-negative) should be managed with local excision +/- radiotherapy and chemotherapy reserved for those patients with systemic disease (note: primary cutaneous ALCL is out with the scope of this appraisal)
- At relapse, patients should receive platinum-based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemo-sensitive disease should be considered for transplant.

These guidelines do not specify treatment for recurrent disease.



### *2.1 Critique of company's description of underlying health problems*

The company's description of sALCL in terms of histology, prognosis and prevalence appears accurate and appropriate to the decision problem. The ERG further notes that some young, fit patients with ALK-negative disease would be considered for autograft in first remission. This option subsequently appears in the company's simplified treatment pathway (reproduced below; Figure 1).

### *2.2 Critique of company's overview of current service provision*

Figure 1 presents the company's simplified treatment pathway for sALCL, indicating where brentuximab vedotin is currently licensed. The company does not specify the origin or development of the pathway. The ERG agrees that the company's simplified pathway is representative of current clinical practice and appropriately highlights that there are several points at which brentuximab vedotin can be used, depending on the clinician's choice of salvage regimens. The ERG suggests the addition of GDP to the list of salvage regimens as it is increasingly used in the UK for a wide range of relapsed aggressive lymphomas. It should be noted that the company included GDP as relevant salvage therapy in their economic model.

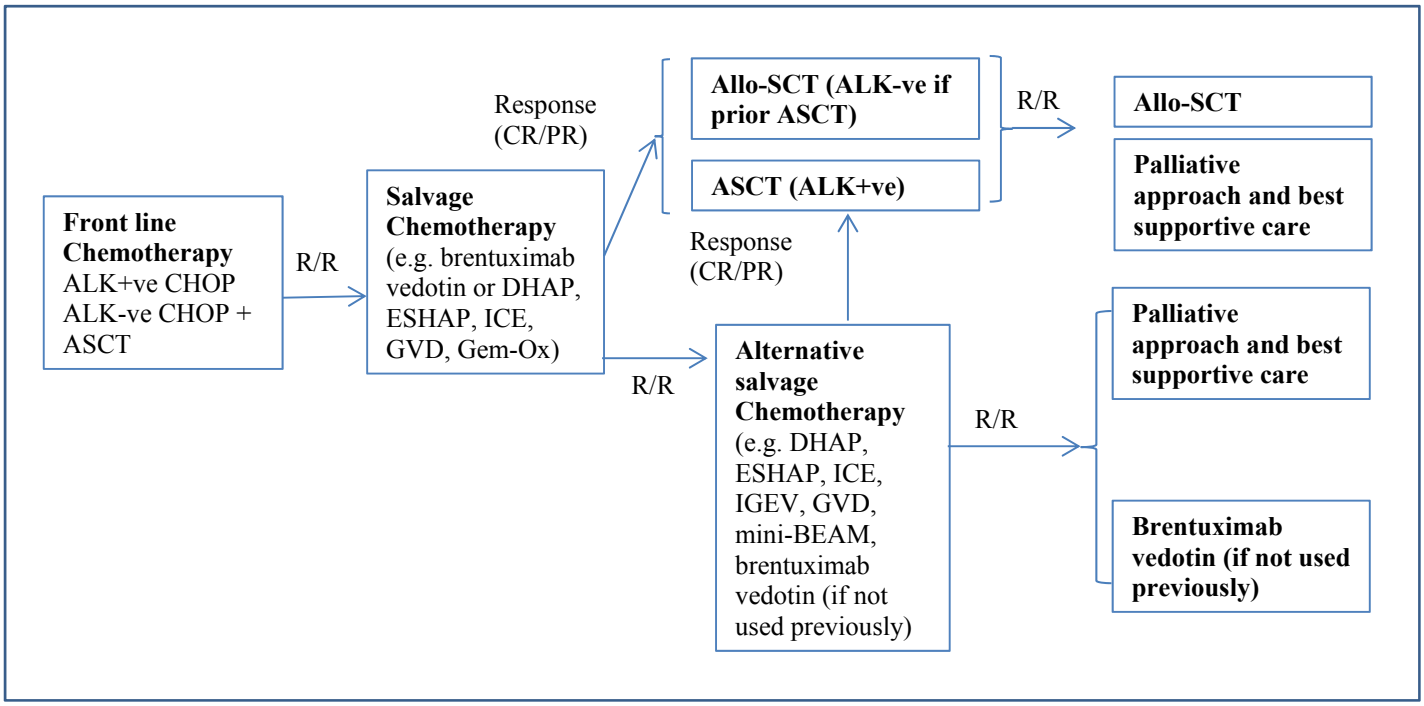



**Figure 1 Company's simplified treatment pathway in sALCL, showing where brentuximab vedotin is licensed for use (reproduced from Figure 3.1 of the company's submission)**

The company's submission states that brentuximab vedotin has been adopted as the standard of care for R/R sALCL in the UK, and has been available via the national Cancer Drugs Fund in England since April 2013, and via individual patient treatment requests or individual funding requests in Scotland and Wales. The National Cancer Drugs Fund List (version 1.22; dated 21st March 2017) lists as an indication for brentuximab "*relapsed or refractory systemic anaplastic large cell lymphoma*". The

company's submission reported that 44 patients received brentuximab vedotin for R/R sALCL via the CDF between April 2013 and March 2014, 45 patients between April 2014 to March 2015 and 22 patients between April 2015 and September 2015. The company concluded that use of brentuximab vedotin via the CDF has reached steady-state and the number of patients is expected to remain consistent with these figures. The company further stated that brentuximab vedotin has become established as the standard of care in the UK and that any changes in service provision and management will have already occurred. The ERG agrees that this is the situation as it currently stands. Therefore, no change in service provision would be anticipated and no impact upon the NHS in England for use of brentuximab vedotin within the pathway proposed in Figure 1.

The Scottish Medicine Consortium (SMC) accepted brentuximab vedotin in September 2014 for restricted use within NHS Scotland for treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma.[43] The SMC document states that "*brentuximab is also indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). SMC cannot recommend use in sALCL as the company did not include evidence for use in this indication in its submission*". Brentuximab vedotin is not recommended for use within NHS Wales for the treatment of adult patients with relapsed or refractory sALCL as the company did not supply clinical or cost effectiveness data.[44]

Hospital Episode Statistics data for England for the year April 2015 to March 2016 [45]reported 512 admissions equating to 547 finished consultant episodes and 1277 bed days for 'anaplastic large cell lymphoma, ALK-positive' (code C84.6) and 457 admissions equating to 478 finished consultant episodes and 828 bed days for 'anaplastic large cell lymphoma, ALK-negative' (code C84.7). Corresponding outpatient data for the same period showed 27 and 33 outpatients attendances, respectively. However, primary diagnosis is not a mandated field in the outpatient dataset and reporting of these data is poor.

# 3 Critique of company's definition of decision problem

### *3.1 Population*

Both the NICE final scope and the company's submission specify the population for this appraisal as "*people with relapsed or refractory systemic anaplastic large cell lymphoma*".

The company's submission focuses upon the evidence of one trial,[46] a Phase II, open-label, single-arm, multi-centre study which examines the efficacy and safety of brentuximab vedotin in patients with relapsed or recurrent sALCL after treatment failure of at least one prior therapy (front-line chemotherapy; CHOP or multi-agent chemotherapy regimens) with curative intent. The study CSR reported an inclusion criterion of age greater than or equal to 18 years, with a codicil that patients of at least 12 years could be enrolled at US and Canadian sites.

### *3.2 Intervention*

Brentuximab vedotin is a potent CD30-directed ADC, a class of drugs which facilitate the provision of a cytotoxic drug to a target malignant cell.[32, 46] The lymphocyte activation marker CD30 is a member of the tumour necrosis family and is highly expressed on the cell surface in anaplastic large cell lymphoma, while its expression on healthy cells is limited to activated T and B cells.[14, 47-49] Brentuximub vedotin comprises three elements: the chimeric monoclonal antibody cAC10 specific for CD30; the potent cytotoxic antitubulin agent monomethyl auristatin E (MMAE); and a stable valine-citrulline dipeptide linker, acting as the protease-cleavage site attaching MMAE to cAC10.[26, 50] The mechanism of action of brentixumab vedotin involves, first, the CD30 receptor binding to the surface of malignant cells. The brentixumab vedotin-CD30 complex is then internalised and carried to lysosomes, where MMAE is released, disrupting the microtubule network and leading to cell apoptosis.[26]

Brentuximab vedotin (Adcetris®, Takeda Pharma, Taastrup, Denmark) is formulated as a powder for concentrate for solution for infusion. Each vial contains 50mg of brentuximab vedotin and, after reconstitution, each ml contains 5mg of brentuximab

vedotin. The recommended dose is 1.8mg/kg administered as an intravenous infusion over 30 minutes every three weeks. The recommended starting dose for the retreatment of patients with relapsed or refractory Hodgkin lymphoma or sALCL who have previously responded to treatment with brentuximab vedotin is 1.8mg/kg administered as an intravenous infusion over 30 minutes every three weeks. Alternatively, treatment may be started at the last tolerated dose. If the patient's weight is more than 100kg, the dose calculation should use 100kg. Brentuximab vedotin should be administered under the supervision of a physician experienced in the use of anti-cancer agents. Complete blood counts should be monitored prior to infusion of each dose of brentuximab vedotin. Patients should be monitored during and after infusion. Treatment should be continued until disease progression or unacceptable toxicity. Patients with relapsed or refractory Hodgkin lymphoma or sALCL who achieve stable disease or better should receive a minimum of eight cycles and up to a maximum of 16 cycles (approximately one year). Listed in the summary of product characteristics is that combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity. The summary of product characteristics reports that no data are currently available for the safety and efficacy of brentuximab vedotin in people aged less than 18 years, or people aged 65 years or older.[51]

Adcetris® is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma:

1. Following autologous stem cell transplant or
2. Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

Adcetris® is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.
Adcetris® is indicated for the treatment of adult patients with relapsed or refractory sALCL.[51]

Adcetris® was designated as an orphan medicinal product for the treatment of ALCL on 15-01-2009 by the European Commission.[52]

A tabulated list of adverse reactions to Adcetris® is presented in Table 1. Adverse reactions are listed under frequency categories of: Very common (≥1/10), common

(≥1/100 to < 1/10), uncommon (≥1/1000 to < 1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), and not known (cannot be estimated from the available data).

**Table 1 Adverse reactions to Adcetris® (reproduced from Table 3 of Summary of Product Characteristics)**

| **System organ class** | **Adverse reactions** |
|---|---|
| **Infections and infestations** | |
| Very common | Infection, upper respiratory tract infection |
| Common | Sepsis/septic shock, herpes zoster, pneumonia, herpes simplex |
| Uncommon | Oral candidiasis, pneumocystis jiroveci pneumonia, staphylococcal bacteraemia |
| Frequency not known | Progressive multifocal leukoencephalopathy |
| Blood and lymphatic system disorders | |
| Very common | Neutropenia |
| Common | Anaemia, thrombocytopenia |
| Frequency not known | Febrile neutropenia |
| **Immune system disorders** | |
| Frequency not known | Anaphylactic reaction |
| **Metabolism and nutrition disorders** | |
| Common | Hyperglycaemia |
| Uncommon | Tumour lysis syndrome |
| **Nervous system disorders** | |
| Very common | Peripheral sensory neuropathy, peripheral motor neuropathy |
| Common | Dizziness, demyelinating polyneuropathy |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common | Cough, dyspnoea |

| System organ class | Adverse reactions |
|---|---|
| **Gastro-intestinal disorders** | |
| Very common | Diarrhoea, nausea, vomiting, constipation, abdominal pain |
| Uncommon | Pancreatitis acute |
| Hepatobiliary disorders | |
| Common | Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased |
| **Skin and subcutaneous tissue disorders** | |
| Very common | Alopecia, pruritus |
| Common | Rash |
| Rare | Stevens-Johnson syndrome/toxic epidermal necrolysis |
| Musculoskeletal and connective tissue disorders | |
| Very common | Myalgia, arthralgia |
| Common | Back pain |
| **General disorders and administration site conditions** | |
| Very common | Fatigue, chills, pyrexia, infusion-related reactions |
| **Investigations** | |
| Very common | Weight decreased |

### *3.3 Comparators*

In line with the NICE final scope, the company's submission specifies '*established clinical management without brentuximab vedotin'* as the comparator for this appraisal. In UK clinical practice, this equates to salvage chemotherapy regimens on their own or with ASCT or allo-SCT. Current commonly used salvage chemotherapy regimens identified by the company's survey of clinical experts are ICE (ifosfamide,

carboplatin, etoposide), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), DHAP (dexamethasone, high-dose cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin) and Gem-P (gemcitabine, methylprednisolone, cisplatin). The ERG clinical expert agrees that these are the predominant regimens in current UK clinical practice. The ERG notes that the comparator, as specified for this appraisal (‘*established clinical management without brentuximab vedotin’*), could potentially include supportive care for the small proportion of patients for whom chemotherapy is not suitable due to its toxicity.

### *3.4 Outcomes*

The outcomes addressed in the company’s submission were overall survival, progression-free survival, objective response rate, complete response rate, rate of stem cell transplantation (autologous and allogeneic), adverse effects of treatment and health-related quality of life. These outcomes are in line with the NICE final scope.

The primary endpoint of the SG035-0004 trial, reported by Pro et al 2012,[46] was objective response rate, defined as proportion of patients with complete response or partial response, as determined by an independent review facility (IRF) (Seattle Genetics CSR).

### *3.5 Other relevant factors*

The company stated that their economic analysis was in line with the NICE reference case and Guide to the Methods of Technology Appraisal [53] with the main output of the analysis being cost per QALY gained. This differed from the NICE final scope in that the perspective of the NHS was taken and PSS costs were not considered. The ERG is satisfied that this approach is justified in the specified context. In addition, the economic analysis included modelling of the following cohorts:

- Brentuximab vedotin (no SCT)
- Brentuximab vedotin + ASCT
- Brentuximab vedotin + allo-SCT
- Chemotherapy (no SCT)
- Chemotherapy + ASCT
- Chemotherapy + allo-SCT

The ERG agrees that these cohorts are appropriate to address the NICE final scope requirement that the economic analysis should model stem cell transplant further down the treatment pathway if the evidence allowed.

Table 2 details the NICE final scope and the decision problem addressed by the company and includes both the company's and the ERG's comments.

The company note that sALCL is designated orphan status, and based on stage of disease (R/R sALCL) it meets the ultra-orphan medicine definition (prevalence of less than 1 in 50,000 persons). The company note that they do not wish for the medicine to be considered at this time for the application of NICE's end of life criteria. Based on the undiscounted life expectancy in the comparator arm of the company's model (mean 4.64 years), the drug may not meet the criteria for the population with R/R sALCL as a whole. It could however potentially be relevant for cohorts not intended for SCT.

**Table 2 Comparison of NICE final scope and decision problem addressed by the company**

| | Final scope issued by NICE | Decision problem addressed in the submission | Comments from the company | Comments from the ERG |
|---|---|---|---|---|
| **Population** | People with relapsed or refractory sALCL | People with relapsed or refractory sALCL | None | None |
| **Intervention** | Brentuximab vedotin | Brentuximab vedotin | None | None |
| **Comparators** | Established clinical management without brentuximab vedotin | Established clinical management without brentuximab vedotin | None | None |
| **Outcomes** | • Overall survival<br>• Progression-free survival<br>• Objective response rate<br>• Complete response rate<br>• Rate of stem cell transplantation (autologous or allogeneic)<br>• Adverse effects of treatment<br>• Health-related quality of life | • Overall survival<br>• Progression-free survival<br>• Objective response rate<br>• Complete response rate<br>• Rate of stem cell transplantation (autologous or allogeneic)<br>• Adverse effects of treatment<br>• Health-related quality of life | None | None |
| **Economic analysis** | The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY.<br>The reference case stipulates that the time horizon for | The analysis performed is in line with the NICE reference case and Guide to the Methods of Technology Appraisal (2013).<br>The main output of the economic | Using cost per QALY gained as per decision problem, but from the perspective of the NHS. No PSS costs have been considered | The ERG considers the company's approach to be justified |

| | Final scope issued by NICE | Decision problem addressed in the submission | Comments from the company | Comments from the ERG |
|---|---|---|---|---|
| | estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and PSS perspective | analysis is the cost per QALY gained | | |
| **Subgroups** | Not applicable | Not applicable | None | None |
| **Special considerations** | If the evidence allows, the economic analysis should model stem cell transplantation further down the treatment pathway.<br>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator | The economic analysis includes modelling of the following cohorts;<br>• Brentuximab vedotin + ASCT<br>• Brentuximab vedotin + allo-SCT<br>• Chemotherapy<br>• Chemotherapy + ASCT<br>• Chemotherapy + allo-SCT | None | The ERG considers these cohorts appropriate to the NICE final scope |

# 4 Clinical effectiveness

## *4.1 Critique of the methods of review(s)*

### 4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The search strategies are provided in Appendix 2 of the CS. The major relevant databases: MEDLINE and MEDLINE In Process (Ovid), EMBASE (Ovid), CENTRAL and PUBMED (for publications ahead of print) were searched for publications written in the English language. No date restrictions were applied. The searches were originally undertaken on 18th January 2011 and then updated on 18th June 2012, 13th July 2015 and 17th November 2016. The same strategies were used on each occasion. A manual search of the following most recent conference proceedings was also carried out: American Society of Hematology, European Haematology Association and the International Conference on Malignant Lymphoma.

The strategies were designed to retrieve all publications about relapsed or refractory systemic anaplastic large cell lymphoma. For MEDLINE and EMBASE, two search facets were combined using the Boolean operator AND : anaplastic large cell lymphoma and recurrence or salvage therapy while in CENTRAL, search terms related to anaplastic large cell lymphoma without further restriction. No study design or intervention restrictions were imposed while studies of animals only were excluded.

The search strategies comprised both appropriate controlled vocabulary (MeSH and EMTREE) and free text terms and are considered to be sensitive enough to identify relevant studies on relapsed or refractory systemic anaplastic large cell lymphoma with any intervention and any outcome.

### 4.1.2 Inclusion criteria

The inclusion criteria used in the company's systematic review of clinical evidence are presented in Table 3.

**Table 3 Inclusion criteria used in the company's systematic review of clinical effectiveness (reproduced from Table 4.1 of company's submission)**

| Clinical effectiveness | Inclusion criteria |
|---|---|
| **Population** | Patients with R/R sALCL |
| **Interventions/ Comparators** | No restrictions by intervention were imposed |
| **Outcomes** | Response, overall survival, progression-free survival, adverse events |
| **Study design** | All study designs were considered with the exception of study protocols or conference abstracts (unless they were identified from the conference proceeding search):<br>RCTs<br>Non-randomised studies: prospective interventional, prospective observational studies or retrospective studies<br>Studies must have included 20 or more patients with R/R sALCL<br>Only studies in the English language were included |

Note. R/R sALCL: relapsed or refractory systemic anaplastic large cell lymphoma; RCT: randomised controlled trial

The company's systematic review was an update of reviews conducted in 2011, 2012 and 2015. The 2015 update, conducted by Icon PLC, was included in the reference pack supplied to the ERG by the company in the original submission. At clarification, the company stated that the 2015 systematic review had been sent in error, and the up-to-date 2017 version was provided to the ERG.

The company's 2017 systematic review included 22 studies, of which five investigated the use of brentuximab vedotin in adults.[46, 54-57] An additional report of the data reported by Lamarque et al 2014 was also included.[58] The Lamarque et al 2014 abstract was originally referred to as Mathilde 2014 in the 2015 systematic review. At clarification, the company explained that the abstract had been incorrectly referenced, with the author's first name ('Mathilde') being used as the reference point rather than the last name ('Lamarque'). The Lamarque et al 2014[57] abstract reports data from 65 participants of the French named patient programme (NPP), whilst the

Lamarque et al 2016 full text paper reports data from 56 participants from the same programme.[58] As there is undoubtedly some overlap in participants of these two publications, the Lamarque et al 2016 full text version is being treated as the primary report for the purposes of this assessment due to being published in full text form and, therefore, providing a more complete description of the study.

The 2017 systematic review reported that seven of the 22 included studies involved children or adolescent populations. However, the ERG noted that the study by Gross et al 2010[59] also recruited exclusively children and adolescents, giving a total of eight studies of those populations.[59-65] Of the remaining nine studies investigating adult populations, interventions included anti-CD30 monoclonal antibodies other than brentuximab vedotin;[66] single agent chemotherapy;[67] autologous stem cell transplant;[68, 69] allogeneic stem cell transplant;[70] high dose therapy plus autologous stem cell transplant;[71] a variety of unspecified treatments;[72] autologous or allogeneic stem cell transplant;[73] myeloablative conditioning plus allogeneic stem cell transplant or reduced-intensity conditioning plus allogeneic stem cell transplant.[74] Three studies[46, 66, 67] were prospective interventional studies and the remaining studies were retrospective.

The study by Gibb[75] was included as one of the six relevant studies in the company's systematic review, despite not being included in the 2015 systematic review and the fact that only five patients with sALCL were included in the study. At clarification, the company agreed that the eligibility criteria were not fulfilled by the sample size and justified its inclusion as follows:

> "*it was felt important that this study should be presented in the submission as it reports outcomes for patients in the UK that have received brentuximab vedotin in the real world setting as part of the named patient programme (NPP). This study was hence cited as it provided supplementary, UK specific data, relevant to the NICE decision problem.*"

The ERG agrees that the Gibb study[75] reports relevant UK-specific outcomes but is of the opinion that it should not be included in the submission. The study does not fulfil the eligibility criteria of the company's systematic review and including it for

subjective reasons violates the principles of integrity and reproducibility of systematic reviews, as set out in commonly used guidance documents.[76, 77]

The company also identified three abstracts reporting follow-up data of the Pro et al 2012 study .[78-80] As these abstracts report follow-up data from the original Pro et al 2012 study, they will be considered as secondary publications for the purposes of this assessment.

In summary, the company's 2017 systematic review update identified a total of 22 studies of the relevant population, of which five studies involved brentuximab vedotin and were included as relevant studies in the company's submission.[46, 54-56, 58] The study by Gibb[75] was subsequently included by the company, giving the six relevant studies included in the company's submission (with a total of 10 publications, including four secondary reports).

### 4.1.3 Critique of data extraction

The company did not specify whether the methods of their systematic review of clinical effectiveness were based on published guidance. Abstracts and full text papers were screened for eligibility by two experienced systematic reviewers with any disagreements resolved by arbitration by a third reviewer. The ERG considers these methods appropriate. The processes of title screening, data extraction and the number of reviewers involved were not detailed in the submission.

The company's systematic review of clinical effectiveness included six studies published in ten papers, which they described as relevant.[46, 54-58, 75, 78-80] One study was prospective interventional in design[46] two were retrospective studies[54, 55] and three were named patient programmes (NPP).[56, 58, 75] Two studies were published only as abstracts[54, 56] and four as full text papers.[46, 55, 58, 75]

The study by Gopal[55] was a retrospective analysis of seven brentuximab vedotin studies between 2006 and 2012. The trial reported by Pro[46] was one of the seven studies. Thus, there is likely to be some overlap in participants between the studies.[46, 55]

### 4.1.4 Quality assessment

The company did not specify the source of the items used to critically appraise the included non-randomised studies (Table 4.6 of company submission). The ERG questions the validity of some of the items used by the company. For example, the ERG considers the critical appraisal item "*Were outcome measures reliable? Were all clinically relevant outcome measures assessed?*" questionable for several reasons. First, the definition of reliability in this context is unclear. It could signify, for example, consistency over time, or internal consistency of the outcome measures themselves. Second, the item consists of two separate questions but only one answer, which makes interpretation problematic. The ERG considers the item "*Are the study results internally valid?*" potentially inappropriate for assessing the included studies, as internal validity is relevant only in studies investigating a causal relationship.[77] In addition, it is unclear to the ERG how the items "*Was selection bias minimised?*" and "*Did the analysis include an intention-to-treat analysis*?" were applied in the included studies. These items appear more relevant to comparative studies, but all the studies included in the submission were non-comparative in design.

The submission stated that a complete quality assessment for each non-randomised study and NPP were included in Appendix 3, but this was not evident in the submission. Table 4.6 of the submission details assessment of the study by Pro et al 2012[46] and summary assessments of the retrospective case series studies[54, 55] and the named patient programmes.[56, 58, 75]

The ERG agrees with the company's assessments (Table 4.6 of submission) that all the included studies involve populations relevant for this appraisal, that all participants were accounted for at study end and that the studies' findings are externally valid. The settings of the majority of included studies appear to reflect UK clinical practice, in the dosage, frequency and number of cycles of brentuximab vedotin, and that it is administered intravenously in an outpatient setting.[46, 55, 56, 58, 75] The abstract of the study by Chihara[54] does not report this information and, therefore, it is unclear if this study reflects UK practice.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical effectiveness evidence using the CRD criteria. Results are shown in Table 4.

**Table 4 Quality assessment of the company's systematic review of clinical effectiveness evidence**

| CRD quality item | Yes/No/Unclear |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? | Yes |
| 2. Is there evidence of a substantial effort to search for all of the relevant research? | Yes |
| 3. Is the validity of included studies adequately assessed? | Unclear |
| 4. Are sufficient details of the individual studies presented? | No |
| 5. Are the primary studies summarised appropriately? | No |

#### 4.1.5 Evidence synthesis

The company did not conduct any meta-analyses as only non-randomised single-arm studies were identified in the systematic review.

### *4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)*

The submission identified six studies considered by the company to be relevant to the decision problem.[46, 54-56, 58, 75] All six studies investigated the use of brentuximab vedotin in people with relapsed or refractory ALCL.

The main focus of the submission was the Phase II, prospective, open-label, single-arm study reported by Pro et al 2012,[46] with survival data at 3 years,[80] 4 years[78] and 5 years[79] also reported. The company justified the inclusion of a study of this design due to the rarity of the disease for which there were no licensed therapies or consistent standards of care at the protocol stage of the study. In addition, the company liaised with the EMA and FDA who agreed that there was no standard comparator at the time. The ERG agrees that conducting an RCT would be almost impossible due to the rarity of the condition and acknowledges that deciding on a single comparator treatment would be contentious.

Two of the six studies were retrospective case series. The study by Gopal[55] was a retrospective analysis of patients from seven previous trials of brentuximab vedotin in

people with CD30-positive lymphomas, including the trial by Pro et al.[46] Chihara[54] reported a retrospective analysis of patients with refractory or relapsed ALCL initially diagnosed between 1999 and 2014. The remaining three studies were retrospective studies of Named Patient Programmes (NPP) conducted in the UK in 2010/2011,[75] France between 2011 and 2014,[58] and Italy between 2012 and 2014.[56]

Table 5 presents study characteristics of the six included studies.

**Table 5 Characteristics of the six studies included in the company submission**

| Study ID | Country (no of centres) | Main inclusion criteria | Main exclusion criteria | Intervention | No of patients with ALCL/ total sample size | Primary outcome (with response criteria) | Safety outcomes |
|---|---|---|---|---|---|---|---|
| **Prospective interventional studies** | | | | | | | |
| Pro 2012[46, 78-80] | USA (15 centres, 43/58 participants), France (3 centres, 8/58 participants), Canada (2 centres, 3/58 participants), Belgium (1 centre, 1/58 participants), UK (1 centre, 3/58 participants) | Patients with relapsed or refractory sALCL after treatment failure of at least 1 prior therapy with curative intent; age ≥12 years (USA) or ≥18years (other countries); ECOG status of 0 or 1 | Pregnancy; previous allogeneic SCT | Brentuximab vedotin 1.8mg/kg intravenously once every 3 weeks over 30 minutes on outpatient basis for maximum 16 cycles | 58/58 | Objective response rate per independent review (response criteria: Cheson 2007) | Incidence of AEs, coded using MedDRA and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events |
| **Retrospective studies** | | | | | | | |
| Gopal 2014[55] | USA, Canada, Europe (multi-centre) | Patients with histologically confirmed CD30-positive disease, beyond first remission or | Patients enrolled in a hepatic/renal impairment arm of a brentuximab vedotin pharmacokinetics | At least one dose of single-agent brentuximab vedotin (≥1.2mg/kg | 22/40 | Outcomes reported: Adverse events, complete remission, | Incidence of AEs, coded according to MedDRA and graded using the |

| Study ID | Country (no of centres) | Main inclusion criteria | Main exclusion criteria | Intervention | No of patients with ALCL/ total sample size | Primary outcome (with response criteria) | Safety outcomes |
|---|---|---|---|---|---|---|---|
| | | refractory to frontline chemotherapy, aged ≥ 60 years, enrolled in studies of single-agent brentuximab vedotin in the treatment of relapsed or refractory CD30-positive lymphomas | study; patients with cutaneous ALCL (unless it had transformed to sALCL) | every 3 weeks), with the exception of dose escalation trial by Younes 2010 (≥0.6mg/ kg every week) | | partial remission, stable disease, progressive disease, long term survival (response criteria: Cheson 2007) | National Cancer Institute's Common Terminology Criteria for Adverse Events; physical examination findings; vital signs and routine lab tests |
| Chihara 2015[54] | Not reported | Patients with ALCL who experienced disease progression or relapse after first line and subsequent therapy; initially diagnosed between 1999 and 2014 | Not reported | Not reported | 176/176 | Progression free survival, overall survival | Not reported |

| Study ID | Country (no of centres) | Main inclusion criteria | Main exclusion criteria | Intervention | No of patients with ALCL/ total sample size | Primary outcome (with response criteria) | Safety outcomes |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| **Named Patient Programmes** | | | | | | | |
| Gibb 2013[75] | UK (1 centre) | All patients presenting between December 2010 and August 2011 with either Hodgkin lymphoma, ALCL or CD30-positive T-cell lymphoma refractory to at least 2 lines of chemotherapy or autotransplant, a positive PET-CT scan and deemed suitable for systemic therapy | Previous allogeneic transplant, severe myelosuppression, active infection, significant hepatic or renal dysfunction | Brentuximab vedotin 1.8mg/kg (capped at 100kg body weight), administered in 250mL of 0.9% saline intravenously over 30 minutes every 3 weeks | 5/24 | Objective response rates, subsequent allogeneic SCT rate, progression free survival, overall survival (response criteria: Cheson 2007) | Toxicity, graded by the Common Terminology Criteria for Adverse Events |
| Lamarque 2016 [Lamarque 2014][57, 58] | France (no of centres not reported) | Patients with a confirmed diagnosis of peripheral T-cell | Not reported | Brentuximab vedotin as monotherapy (reported in | 24/56 | Outcomes reported: Complete response, | Adverse events |

| Study ID | Country (no of centres) | Main inclusion criteria | Main exclusion criteria | Intervention | No of patients with ALCL/ total sample size | Primary outcome (with response criteria) | Safety outcomes |
|---|---|---|---|---|---|---|---|
| | | lymphoma between March 2011 and January 2014, treated with brentuximab vedotin, who were relapsed or refractory during the NPP in France | | Table 4.2 of company submission as 1.8mg/kg every 3 weeks) | | partial response, stable disease, progressive disease, progression free survival, objective response rate | |
| Pellegrini 2016[56] | Italy (no of centres not reported) | Patients with relapsed or refractory, histologically documented CD30+ sALCL between November 2012 and July 2014 | Not reported | Brentuximab vedotin 1.8mg/kg every 3 weeks for a maximum of 16 cycles | 40/40 | Best response | Toxicity |

Note. sALCL: systemic anaplastic large cell lymphoma; ECOG: Eastern Cooperative Oncology Group; SCT: stem cell transplant; PET-CT: positron emission tomography-computed tomography; ALCL: anaplastic large cell lymphoma; AE: adverse events

Funding from Takeda Pharmaceuticals[55] or other links to Takeda Pharmaceuticals[46, 54, 56, 75] were reported by five of the six studies. Lamarque stated there were no conflicts of interest and funding information was not reported.[58]

Median number of cycles of brentuximab vedotin received by participants ranged from 5.5 (range 1-13[75]) to 6 (range 1-16[58]), 7 (range 1-16[46]) or 7.5 (range 1-22[55]). Two studies did not report this information.[54, 56]

The six studies included a total of eight participants in the UK (3 in Pro[46] and 5 in Gibb[75]).

Table 6 reports baseline demographics and disease characteristics of participant in the six studies included in the company's review of clinical effectiveness.

The company submission presents demographics for three studies only.[46, 55, 75] The remaining studies do report demographic data and the company does not explain their omission from the submission.

**Table 6 Baseline demographics and disease characteristics of the six included studies**

| | Pro 2012 [46] (n=58) | Gopal 2014[55] (n=40; ALCL=22)[a] | Chihara 2015[54] (n=176) | Gibb 2013 [75](n=24; ALCL=5)[b] | Lamarque 2016[58] (n=56; ALCL=24)[c] | Pellegrini 2016[56] (n=40) |
|---|---|---|---|---|---|---|
| **Patient characteristics** | | | | | | |
| **Age, years, median (range)** | 52 (14-76) | 66 (60-82) | 50 (18-89) | 41.5 (21-78) | 58 (19-83) | NR |
| **Sex, n (%)** | | | NR | | | NR |
| Male | 33 (57) | 26 (65) | | 11 (46) | 37 (66) | |
| Female | 25 (43) | 14 (35) | | 13 (54) | 19 (34) | |
| **Race, n (%)** | | | NR | NR | NR | NR |
| Asian | 1 (2) | 1 (3) | | | | |
| Black or African American | 7 (12) | 4 (10) | | | | |
| White | 48 (83) | 34 (85) | | | | |
| Other | 2 (3) | 1 (3) | | | | |
| **ECOG status, n (%)** | | | NR | NR | NR | NR |
| 0 | 19 (33) | 13 (33) | | | | |
| 1 | 38 (66) | 25 (63) | | | | |
| 2 | 1 (2)[d] | 2 (5) | | | | |
| **ALK status, n (%)** | | | | | | |
| Positive | 16 (28) | NR | 74 (42) | 2 (40) | 9 (38) | 22 (55) |
| Negative | 42 (72) | 18 | 102 (58) | 0 | 15 (62) | 18 (45) |
| Unknown | 0 | NR | 0 | 3 (60) | 0 | 0 |
| **Disease characteristics** | | | | | | |
| **Disease diagnosis, n (%)** | | | | | | |
| ALCL | 58 (100) | 22 (55) | 176 (100) | 5 (21) | 24 (43) | 40 (100) |
| | 0 | 16 (40) | 0 | 18 (75) | 0 | 0 |

| | **Pro 2012 [46] (n=58)** | **Gopal 2014[55] (n=40; ALCL=22)[a]** | **Chihara 2015[54] (n=176)** | **Gibb 2013 [75](n=24; ALCL=5)[b]** | **Lamarque 2016[58] (n=56; ALCL=24)[c]** | **Pellegrini 2016[56] (n=40)** |
|---|---|---|---|---|---|---|
| Hodgkin lymphoma<br>Other CD30+ lymphoma subtype | 0 | 2 (5) | 0 | 1 (4) | 32 (57) | 0 |
| **Baseline B symptoms, n (%)** | 17 (29) | NR | NR | NR | NR | NR |
| **No of prior chemotherapy regimens, median (range)** | 2 (1-6) | NR | NR | 3 (2-8) | 3 (1-8) | NR |
| **Prior SCT, n (%)** | 15 (26) autologous | 12 (35)[f] autologous or allogeneic | NR | 8 (33) autologous | 8 (14) autologous;<br>3 (5) allogeneic | 13 (33) autologous |
| **Prior radiotherapy, n (%)** | 26 (45) | NR | NR | 10 (42) | NR | NR |
| **No response to most recent treatment, n (%)** | 13 (22) | NR | NR | 17 (71) | NR | NR |
| **Disease status relative to most recent treatment, n (%)**<br>Refractory<br>Relapsed | <br>29 (50)<br>29 (50) | <br>11/26 (42)[g]<br>NR | NR | NR | <br>32 (57)<br>23 (41) | <br>24 (60)<br>16 (40) |

Note. [a]Data for group aged 60 years or older. This includes people with diagnoses other than ALCL; [b]Data reported for all 24 participants, of whom 5 had ALCL; [c]Reported for all 56 participants reported in the full text Lamarque 2016 publication, of whom 24 had ALCL; [d]Enrolled in violation; [e]18/19 patients with a known ALK status were confirmed to be ALK-negative; [f]Data for 34 treatment courses available; [g]Data not available for all patients in analysis set;

ECOG: Eastern Cooperative Oncology Group; ALK: anaplastic lymphoma kinase; SCT: stem cell transplant; NR: not reported

Median age of participants in the trial by Gibb (41.5 years)[75] was lower than the other trials (albeit this was for the total sample of 24 participants, of which only five had ALCL). Gopal reported a median age of 66 years for the group aged at least 60 years and median age of 32 years for the group aged under 60 years.[55] Three trials reported median ages in the sixth decade of life.[46, 54, 58] One trial did not report participants' age.[56]

The ALK status of participants varied across studies. Participants were mainly ALK-negative in two of the studies (72% ALK-negative/28% ALK-positive;[46] 62% ALK-negative/38% ALK-negative[58]) but more balanced across ALK-positive and ALK-negative status in two further studies (42% ALK-positive/58% ALK-negative;[54] 55% ALK-positive, 45% ALK-negative[56]). In the study by Gibb,[75] two participants were ALK-positive and three were of unknown ALK status. Gopal reported that 18 of the 19 participants (of a total of 40 participants) with known ALK status were ALK-negative. [55]

Participants had received prior autologous transplants in the trials by Pro (26%), Gibb (33%) and Pellegrini (33%).[46, 56, 75] Two trials reported that participants had received prior autologous or allogeneic transplants.[55, 58] Chihara did not report this information.[54]

The main evidence regarding adverse events in the company's submission is provided by the study by Pro.[46]. The studies by Gopal, Gibb and Lamarque also reported adverse events.[55, 58, 75]

Pellegrini reported that brentuximab vedotin was well tolerated and the toxicity profile (which was mainly neurological, rarely required treatment reduction or interruption and always reversed completely after completion of treatment) was similar to the published data. [56]

Table 7 presents details of adverse events occurring in at least 20% of participants in the studies included in the company submission.

The data reported for adverse events of all grades in over 20% of participants reported by Gopal, Gibb and Lamarque[55, 58, 75] are broadly in line with the Pro study[46] but with some exceptions. Among AEs of any grade, Lamarque reported neutropenia and anaemia in 42% and 51% of participants, respectively.[58] This is substantially higher than the 21% for neutropenia[46], and 25% for neutropenia and 30% for anaemia[55] reported in other studies. In addition, Gopal reported a number of adverse events in over 20% of participants, for example, dyspnoea, headache, decreased appetite dizziness, vomiting, cough, URTI and arthralgia.[55] However, these data subsume the entire study population, of which only around half (of the ≥60 years' old group) had a diagnosis of ALCL (22/40; 55%). Similarly, Lamarque et al 2016 reported that 37% of the entire sample of 56 participants experienced thrombocytopenia and 29% had infections; only 24/56 participants (43%) had ALCL.

Adverse events of grade 3 or higher were reported separately by three studies.[46, 55, 75] In the Pro study,[46] the most common adverse events of grade 3 or higher were neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%) and anaemia (7%). Similarly, Gopal[55] reported a total of 28 participants (70%) in the over 60 age group with a grade 3 or higher treatment-emergent adverse event. These included neutropenia (25%), anaemia (20%), peripheral sensory neuropathy (15%), fatigue (10%) and thrombocytopenia (10%). Gibb reported a total of nine grade 3/4 adverse events.[75] Three of the nine events were neurotoxicity which stabilised following dose reduction. There were three septic deaths in patients with very advanced disease and associated poor performance status. Two of the events were sepsis and one was a sub-acute bowel obstruction believed to have been caused by something other than the brentuximab vedotin treatment.

**Table 7 Adverse events of any grade in at least 20% of participants from the six studies included in the company submission**

| Adverse event (of any grade in ≥20% patients) | Pro 2012 [46] (n=58) | Gopal 2014 [55] | | Chihara 2015 [54](n=176) | Gibb 2013 [75] (n=24; ALCL=5) | Lamarque 2016 [58](n=56; ALCL=24) | Pellegrini 2016 [56](n=40) |
|---|---|---|---|---|---|---|---|
| | | ≥60 yrs (n=40; ALCL = 22) | <60yrs (n=326; ALCL = 272) | | | | |
| Peripheral sensory neuropathy | 24 (41%) | 24 (60%) | 150 (46%) | NR | NR | 20 (53%) | NR |
| Nausea | 23 (40%) | 15 (38%) | 135 (41%) | NR | NR | - | NR |
| Fatigue | 22 (38%) | 23 (58%) | 140 (43%) | NR | NR | - | NR |
| Pyrexia | 20 (34%) | 11 (28%) | 111 (34%) | NR | NR | - | NR |
| Diarrhoea | 17 (29%) | 10 (25%) | 99(30%) | NR | NR | - | NR |
| Rash | 14 (24%) | 8 (20%) | 39 (12%) | NR | NR | - | NR |
| Constipation | 13 (22%) | 8 (20%) | 59 (18%) | NR | NR | - | NR |
| Neutropenia | 12 (21%) | 10 (25%) | 67 (21%) | NR | NR | 15 (42%) | NR |
| Anaemia | - | 12 (30%) | 34 (10%) | NR | NR | 19 (51%) | NR |
| Dyspnoea | - | 9 (23%) | 52 (16%) | NR | NR | - | NR |
| Headache | - | 9 (23%) | 73 (22%) | NR | NR | - | NR |
| Decreased appetite | - | 8 (20%) | 50 (15%) | NR | NR | - | NR |
| Dizziness | - | 8 (20%) | 29 (12%) | NR | NR | - | NR |
| Vomiting | - | 8 (20%) | 65 (20%) | NR | NR | - | NR |
| Cough | - | 6 (15%) | 66 (20%) | NR | NR | - | NR |
| URTI | - | 4 (10%) | 102 (31%) | NR | NR | - | NR |

| **Adverse event (of any grade in ≥20% patients)** | **Pro 2012 [46] (n=58)** | **Gopal 2014 [55]** | | **Chihara 2015 [54](n=176)** | **Gibb 2013 [75] (n=24; ALCL=5)** | **Lamarque 2016 [58](n=56; ALCL=24)** | **Pellegrini 2016 [56](n=40)** |
|---|---|---|---|---|---|---|---|
| | | **≥60 yrs (n=40; ALCL = 22)** | **<60yrs (n=326; ALCL = 272)** | | | | |
| Arthralgia | - | 3 (8%) | 68 (21%) | NR | NR | - | NR |
| Thrombocytopenia | - | - | - | NR | NR | 14 (37%) | NR |
| Infection | - | - | - | NR | NR | 10 (29%) | NR |
| Deaths within 30 days of last BV administration | 6 (10%)[a] | NR[b] | NR[b] | NR | NR | NR | NR |
| AEs leading to treatment discontinuation | 14 (24%) | 13 (33%) | 55 (17%) | NR | NR | 5 (9%) | NR |
| AEs leading to dose delays | 23 (40%) | 20 (50%) | 140 (43%) | NR | NR | 11 (19%)[c] | NR |

Note. ALCL: anaplastic large cell lymphoma; URTI: upper respiratory tract infection; BV: brentuximab vedotin; AE: adverse event; NR: not reported

[a]None of these deaths were attributed to the study drug

[b]One patient (with ALCL) died within 30 days of last administration of study drug, but it is unclear whether the patient was ≥60 years old or <60 years of age. The death was not attributed to the study drug or disease

[c]Doses reduced due to toxicity (not dose delays)

Sixteen serious adverse events in 11 patients related to brentuximab vedotin were reported by Pro.[46] Two of these events were grade 4 (neutropenia, tumour flare), 12 were grade 3 (vomiting, diarrhoea, 2 urinary tract infection, pneumonia, pulmonary embolism, peripheral sensory neuropathy, peripheral motor neuropathy, myositis, constipation, demyelinating polyneuropathy, tumour lysis syndrome) and two were grade 2 (retinal vein occlusion, neuralgia). Three of these events led to treatment discontinuation (retinal vein occlusion, peripheral sensory neuropathy, demyelinating polyneuropathy).(SG035-0004 CSR)

Two studies reported deaths within 30 days of last administration of brentuximab vedotin; Pro reported six deaths[46] and Gopal reported one death.[55] None of the deaths were attributable to the study drug.

The group aged at least 60 years in the Gopal[55] study experienced a higher incidence of adverse events leading to treatment discontinuation (33%) than the group aged under 60 years in the same study (17%) or participants in the studies by Pro (24%) or Lamarque (9%).[46, 58]

Table 8 presents the relevant results reported by the studies included in the company's submission.

**Table 8 Relevant results reported by included studies**

| Study ID | Median OS | Median PFS | ORR | CR | PR | SD | PD |
|---|---|---|---|---|---|---|---|
| **Pro 2012[46] (n=58)** | Not reached | 13.3 mo | 50/58 (86%) | 33/58 (57%)[a] | 17/58 (29%)[a] | 3/58 (5%) | 5/58 (9%) |
| **Gopal 2014[55] (n=22)** | Not reached | 15.6 mo | 22/22 (100%) | 11/22 (50%) | 11/22 (50%) | 0/22 (0%) | 0/22 (0%) |
| **Chihara 2015[54] (n=176)** | ALK-pos: 47.3/6.1 mo; ALK-neg: 10.8/5.8 mo[b] | ALK-pos: 5.2 mo/2.3 mo; ALK-neg: 3.0/2.0 mo[b] | NR | NR | NR | NR | NR |
| **Gibb 2013[75] (n=5)** | NR | NR[c] | 3/5 (60%) | 3/5 (60%) | NR | NR | 1/5 (20%) |
| **Lamarque 2016[58] (n=24)** | NR | 10.5 mo | 15/24 (63%) | 15/24 (63%) | NR | 1/24 (4%) | 7/24 (29%) |
| **Pellegrini 2016 [56](n=40)** | NR | NR[d] | 25/40 (63%)[e] | 19/40 (48%)[f] | 12/40 (30%)[f] | NR | NR |

**Note.** [a]Company's submission reports CR as 34/58 (59%) and PR as 16/58 (28%); [b]After 1st/2nd salvage therapy, respectively; [c]Gibb et al report Median PFS for entire sample of 24 patients of 5.1mo; [d]Pellegrini 2016 report global PFS of 39.1% at 29 mo; [e]At end of treatment; [f]Observation made after a median of 4 cycles of treatment

OS: overall survival; PFS: progression-free survival; ORR: objective response rate; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease

Median OS had not yet been reached in two studies.[46, 55] Objective response rates (ORRs) across studies ranged from 60%[75] to 100%,[55] complete remission (CR) rates ranged from 48%[56] to 63% [58] and partial remission (PR) rates from 29%[46] to 50%.[55] The company's submission reported CR of 59% (34/58) and PR of 28% (16/58). In contrast, the Pro et al 2012 publication reports a CR rate of 57% (33/58) and PR of 29% (17/58).[46] The Pro et al 2016 poster of five-year survival data reports that 34 patients achieved CR per independent review and 38 per investigator.[79] The reason for these discrepancies is unclear to the ERG. The results reported by Pro et al 2012 were at the higher end of the range across studies for ORR and CR but at the low end of the range for PR, albeit only three studies reported those data. Median progression-free survival ranged from 5.2 months (after first salvage therapy)[54] to 15.6 months,[55] with Pro et al 2016 reporting 13.3 months.[79]

Rate of stem cell transplantation was reported by three studies: Pro et al 2016[79] reported that 8 of the 38 patients who achieved CR per investigator (21%) underwent consolidative allogeneic SCT and 8 (21%) underwent consolidative autologous SCT. Chihara et al 2015[54] reported that 30 patients underwent autologous SCT and 15 patients underwent allogeneic SCT after salvage chemotherapy. In the study by Gibb et al 2013,[75] two of the five patients (40%) with ALCL underwent allogeneic transplant. The remaining three studies did not report this information.[55, 56, 58]

While it was not all reported in the company submission, several exploratory subgroups were considered in the SG-35-0004 trial. A subgroup analysis on age did not identify any clear differences in ORR and CR between age groups. There was 100% complete response for all individuals in the 12-17 age group while in the 18-64 and 65 and above age groups 56% had a complete response. However, there were only 4 patients in the 12-17 category, and the ORRs vary less between the groups. A second age subgroup analysis was also undertaken and showed similar ORR between those aged 12-40 and those older than 40. The CR rate was however lower in the older than 40 group (54% compared to 71%). Overall, the ERG do not believe there is sufficient data to inform differences in outcomes between children (12-18 years) and adults, and so feel it is appropriate to base the economic modelling on the whole trial sample.

The gender subgroup shows a difference between males (n=33) and females (n=25) with the ORR and CR both higher for females (96% compared to 79%, and 68% in compared to 52%). The median duration of response and progression free survival also favoured females.

The subgroup analysis by baseline weight (≤100kg; >100k) has an uneven number of participants in the two subgroups; 51 ≤ 100kg and only 7 > 100kg. The ORR is the same in both subgroups but there is greater duration of PFS, EFS and CR in the group weighing 100kg or less. With such a small number in the 100kg and above group it is difficult to interpret these results.

Prior radiotherapy (n=26) had the effect of slightly increasing objective response rate (92% versus 82%) and duration of objective response (17.1 months versus 12.6 months). The subgroup analysis using baseline ECOG status (0; 1 and 2) again has the issue with small sample sizes, though it is the case that those in better health (lower ECOG status) have higher ORR (95% versus 82%).

The presence of baseline B symptoms only showed a subgroup difference for PFS. In the subgroup without baseline B symptoms (n=17) the median PFS was 15.6 months compared to 9.4 months.

There were no notable differences between participants who had an autologous stem cell transplant prior to entering the study in comparison to those who did not. The subgroup analysis for relapsed (n=29) and refractory (n=29) disease showed the biggest difference in ORR, with an equal number of participants in the relapsed and refractory subgroups. The ORR was 97% for relapsed disease while it was 76% for refractory disease. Similarly complete response was higher in the relapsed subgroup (69% compared to 48%) and the duration of OR and PFS were longer in the relapsed subgroup. A further subgroup formed on primary refractory disease showed a higher ORR (100%) for those who did not have primary refractory disease (n=22) compared to those who did (78%). However, complete response rates and the duration of CR and PFS were similar in the two subgroups.

There were 16 patients with ALK- disease and 42 patients with ALK+ disease. The ORR was slightly higher in the ALK- group. There was a larger difference in CR (69% for ALK+ compared to 55% for ALK-) which was expected as patients with ALK- disease have a poorer prognosis. The durations of OR and PFS were similar in the two subgroups.

The subgroups on prior therapies were 1 prior therapy (n=8) compared to more than 1 prior therapy (n=50). Whilst the categories were uneven, both ORR (90% in comparison to 63%) and CR (64% compared to 25%) were higher in the group which had received more than 1 prior therapy.

Subgroups were also formed for patients who had not achieved an objective response to any prior therapy and patients who had responded to at least one prior therapy. The ORR (89% v 77%) and CR (64% v 38%) were both slightly higher in the subgroup who had responded to a prior therapy. Amongst patients who received an SCT as their first therapy after stopping treatment with brentuximab vedotin the ORR and CR were 94% and 88%. These are higher than in the group who did not receive SCT post treatment (83% and 48% respectively).

Overall, whilst these exploratory subgroup-analyses suggest there may be differences in outcomes driven by certain patient characteristics and treatment history (particularly refractory versus relapsed disease), the small overall numbers and in many cases unequal distribution between subgroup categories, make it difficult to draw any firm conclusions. The ERG believe that given the limited data, it is appropriate to consider the cohort as a whole for the purposes of economic modeling.

### *4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison*

The ERG considers Pro et al 2012 to be an appropriate source of evidence for the clinical effectiveness of Brentuximab vedotin.[46] As detailed in the scope, the objective was to consider the effect on adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL) and, as Pro et al 2012 has 58 participants all with R/R sALCL, it certainly fulfils the second of these requirements.[46] The company's clarification that only 4 out of the 58 patients were

aged between 12 and 17 and their statement that the trial results are generalisable to the specified population and clinical practice and including these 4 participants will not significantly influence the results satisfies the ERG that an appropriate population has been used. The ERG does not have any concerns with the population in the SG035-0004 trial. It is noted by the ERG that the trial was sufficiently powered.

The ERG agree with the company's statement that the rarity of the disease and the lack of a standard comparator make a randomised controlled trial unfeasible and are therefore open to considering the outcomes from the single-arm trial. The reported outcomes of an 86% objective response rate (CR + PR), 59% complete remission (CR) and 28% partial remission (PR) all support the efficacy of the treatment. The ERG note that these outcomes were assessed by independent review. The overall survival, progression free survival, duration of response and observation times for patients still on the study and in remission again suggest long-term efficacy from the treatment.

While the Gopal and Gibb studies only involve a small number of ALCL patients,[55, 75] the results support those of Pro et al 2012.[46]

The company reports the list of adverse events experienced by patients in the SG035-0004 trial. The list is extensive with every patient experiencing at least one adverse event. The adverse event rates are similar to those presented in the Gopal and Gibb studies and appear consistent with expectation based on the ERGs clinical expert advice.

### *4.4 Critique of the indirect comparison and/ or multiple treatment comparison*

The company did not present an indirect comparison in the clinical effectiveness chapter of their submission. However, the economic modelling relied on a number of sources to make unadjusted comparisons between brentuximab vedotin and chemotherapy. These are discussed further in chapter 5

Briefly, the clinical response rates and progression free survival estimates for chemotherapy were derived from the past history of a subgroup of patients enrolled in SG035-0004 whose most recent treatment (prior to brentuximab) had been for R/R

disease (n=39). The company's justification for this is that it will minimise bias which would be associated with an unanchored indirect comparison. The ERG are concerned that this data comes from a sample of patients who did not respond to chemotherapy and hence were enrolled in the trial of brentuximab vedotin. The selection excludes any long-term responders to salvage chemotherapy who do not require a subsequent line of therapy, and also excludes any patients who die prior to progression or are otherwise deemed to be unfit for subsequent therapy. Therefore, the ERG are of the opinion that this choice of data may bias the results against chemotherapy, and that it may not be appropriate for chemotherapy response rates and PFS in the economic model.

In terms of overall survival, unadjusted indirect comparisons in the economic model are made between the results of the SG035-0004 trial and results reported be Mak et al 2013.[72] While the Mak et al 2013 study was described in the cost effectiveness section of the CS, the ERG were surprised that it was not summarised in the clinical effectiveness section given its pivotal role in determining the incremental effects of brentuximab.[72]

Mak et al. present data on progression free survival and overall survival for a historical cohort of patients on the British Colombia Cancer Agency Lymphoid Cancer database (diagnosed between December 1976 and October 2010) who had relapsed or experienced progressive disease after primary therapy. For purposes of making comparisons with SG035-0004, the company focusses on a subset of the Mak et al 2013 data.[72] This subset includes 89 patients who received chemotherapy for R/R disease. The company provided a table comparing baseline characteristics for this subgroup [72] with those of patients in SG035-0004 in their original submission. The company identifies heterogeneity in age, stage III-IV disease and performance status. However, in the economic model, the comparison with Mak et al [72] is restricted to the subset of SG035-0004 patients who do not go on to receive a SCT. At clarification, the company provided an additional table comparing baseline characteristics for this subgroup of SG035-0004 participants with the n=89 patients from Mak et al (Table 9). [72] While the age heterogeneity is slightly reduced, there is still considerable difference in stage III-IV disease and in performance status. The company explored the possibility of conducting a matching adjusted indirect

comparison (MAIC) at clarification stage, but noted that following adjustment for available variables, the effective sample size for the MAIC would be 4.8. Given the limited availability of data, the ERG agree that the unanchored indirect comparison offers the appropriate choice of comparison. The company do also note that their base case analysis of overall survival (for economic modelling) uses a smaller subgroup of patients from Mak et al 2013[72] with performance status <2 (n=47). This will account for differences in performance status between Mak et al.[72] and SG035-0004. Mak et al[72] do not present the baseline characteristics for the smaller subgroup of patients with PS<2. This subgroup may also be more comparable on disease stage and age (if correlated with performance status), but this cannot be verified without access to the data.

**Table 9 Characteristics for patients in SG035-0004 (no SCT) and Mak et al (2013) (reproduced from Table 3 of the company response to clarification)**

| **Characteristic** | **Mak et al. (2013)** [72] **(N=89)** | **SG035-0004 (no SCT) (before matching) (N=41)** |
|---|---|---|
| Age (median, range) | 65 (29-86) | 55 (14-76) |
| Sex (% male) | 56% | 61% |
| Elevated lactate dehydrogenase (%) | 48% | 46% |
| Stage III-IV disease (%) | 89%* | 54% |
| Performance status ≥2 (%) | 43% | 2% |
| Response to primary therapy<br>• CR<br>• PR/SD<br>• PD<br>• Unknown/other | <br>51%<br>26%<br>24%<br>0% | <br>37%<br>22%<br>29%<br>12% |

*As reported in the Mak et al. (2013) publication; however N=76 which reflects 85% of the cohort. In the matching analysis, 85% was used.

### *4.5 Additional work on clinical effectiveness undertaken by the ERG*

No additional work was undertaken.

### *4.6 Conclusions of the clinical effectiveness section*

The ERG is of the opinion that, given the rarity of the disease and the available data, the company approach is appropriate and correctly applied. The evidence from the SG035-0004 trial and other supporting studies support the efficacy of treatment using brentuximab vedotin. Assessment of the outcomes by independent review strengthens the evidence in the opinion of the ERG.

In the absence of any comparative evidence, the key challenge lies in estimating the magnitude of the incremental benefits of brentuximab vedotin compared to salvage chemotherapy regimens used in practice. The ERG has major concerns about estimating response rates and progression free survival for chemotherapy using a selected subgroup who did not respond to or progressed following chemotherapy. With respect to overall survival, the ERG accepts that it was difficult for the company to make comparisons with chemotherapy and agrees that an unanchored indirect comparison represented the only feasible option. The ERG does not question the outcomes achieved with brentuximab vedotin, but it does have reservations regarding probable heterogeneity between the cohorts used to make comparisons of overall survival between brentuximab vedotin and chemotherapy. These concerns are further discussed in chapter 5.

# 5 Cost effectiveness

This section provides an overview, description and critique of the company's submitted cost-effectiveness systematic literature review and *de novo* partitioned survival model developed in Microsoft Excel®. The model assessed the cost-effectiveness of brentuximab vedotin compared with chemotherapy for patients with relapsed and / or refractory (R/R) systemic Anaplastic Large Cell Lymphoma (sALCL). A budget impact analysis was also conducted.

## *5.1 ERG comment on company's review of cost-effectiveness evidence*

### 5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company conducted a systematic literature review. The objective of the review was to identify and summarise evidence on cost-effectiveness, costs and resource use for adult patients with R/R sALCL. This section discusses the review of cost-effectiveness evidence. The review of resource use and costs studies is critiqued in Section 5.2.8.

An adequate range of databases were searched for cost effectiveness. These were MEDLINE, EMBASE and Econlit (all Ovid), and the NHS Economics Evaluation Database (Cochrane Library). The search strategies are reproduced in full in Appendix 11. Relevant studies were also identified from reference lists of identified relevant economic evaluations and cost and resource use analyses.

The MEDLINE and EMBASE strategies appropriately combined two facets: anaplastic large cell lymphoma and cost or economic terms while for NHSEED and Econlit, the searches were designed retrieved all studies on anaplastic large cell lymphoma. While the thesaurus terms and text terms applied in the lymphoma facet were appropriate, the range of terms used in the economic facet in MEDLINE and EMBASE could have been broader to include thesaurus and text terms relating to decision theory, monte carlo methods, markov chains and technology assessment. In

addition the EMBASE search does not EMTREE terms, but rather maps the appropriate MeSH. In some cases, this has applied inappropriate EMTREE terms e.g. *Models, Economic* maps to *Statistical Models*; *Health Resources* maps to *Health Care Planning.* The MEDLINE and EMBASE strategies therefore may not have achieved ideal sensitivity.

### 5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate.

The systematic literature search included publications (economic evaluations) comparing costs and outcomes in any intervention for R/R sALCL in adults. The inclusion and exclusion criteria were explicitly reported in Appendix 11 of the CS. Table 10 below reproduces the inclusion and exclusion criteria.

**Table 10 Inclusion and exclusion criteria for the economic and cost and resource use SLR (Source: Appendix 11 of the CS)**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | Adults ≥18 receiving treatment for RR sALCL | Newly diagnosed sALCL patients<br>Primary cutaneous ALCL<br>Healthy volunteers |
| Interventions | No restrictions were imposed on intervention | |
| Outcomes | Studies that include a comparison of costs, QALYs or another measure of health outcome/clinical effectiveness between the intervention and comparator arms. | |
| Publication type | Health technology appraisals<br>Journal articles<br>Letters<br>Comment articles<br>Abstracts or conference proceedings | Systematic literature reviews (SLRs) |
| Study design | Cost effectiveness evaluations (including: cost-benefit analysis, cost minimisation analysis, cost-utility analysis, cost-effectiveness analysis and cost-consequence analysis) | |
| Other | English papers only | |

RR: Relapsed and / or refractory; sALCL: systemic Anaplastic Large Cell Lymphoma; QALY: Quality Adjusted Life Year; SLR: Systematic Literature Review

The ERG consider the broad inclusion criteria to be appropriate given the rarity of sALCL.

### 5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies

The PRISMA diagram for the systematic literature review is presented in Figure 5.1 (pg 78) of the CS. In summary, 445 records were screened for eligibility (after de-duplication). However, only two conference abstracts were identified that matched the inclusion criteria.[81, 82] These studies are listed in Table 5.1 of the CS and reproduced below.

**Table 11 Economic evaluations identified in economic SLR (Source: Table 5.1 of the CS; Pg: 80)**

| Study ID | Country | Study design | Patient population | Comparators | Model type | Health states | Model characteristics | Source of treatment effects | Source of HRQL | QALYs | Costs | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hux ASCO 2016 [81] | UK | Cost-utility analysis | R/R sALCL | Brentuximab vedotin vs. conventional chemotherapy | Partitioned survival | Progression-free, post-progression and death | Time horizon: unclear; Cycle length: unclear | Brentuximab vedotin: PFS and OS were obtained from the Phase II, single-arm trial of 58 R/R sALCL patients<br><br>Chemotherapy: PFS and OS obtained from a Canadian cancer registry which had data on 40 sALCL patients | Unclear | Unclear | Unclear | £35,390 |

| Study ID | Country | Study design | Patient population | Comparators | Model type | Health states | Model characteristics | Source of treatment effects | Source of HRQL | QALYs | Costs | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | |
| Zou ISPOR 2016[82] | Taiwan | Cost-utility analysis | R/R sALCL | Brentuximab vedotin vs. conventional chemotherapy | Partitioned survival | Progression-free, post-progression and death | Time horizon: unclear; Cycle length: unclear | Brentuximab vedotin: PFS and OS were obtained from the phase II, single-arm trial of 58 R/R sALCL patients<br><br>Chemotherapy: PFS and OS obtained from a Canadian cancer registry which had data on 40 sALCL patients | Unclear | Unclear | Unclear | $781,300 |

| Study ID | Country | Study design | Patient population | Comparators | Model type | Health states | Model characteristics | Source of treatment effects | Source of HRQL | QALYs | Costs | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Key: ASCO, American Society of Clinical Oncology; HRQL, health related quality of life; ICER, incremental cost effectiveness ratio; ID, identification; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; R/R, relapsed and/or refractory; sALCL, systemic anaplastic large cell lymphoma; UK, United Kingdom | | | | | | | | | | | | |

The company's original submission stated that as these studies were only available as conference abstracts. Zou et al.[82] was further excluded as it did not incorporate a UK perspective. The ERG noted, however, that irrespective of the costing and outcome perspective, the methods for extrapolating survival and simulating comparisons with chemotherapy may still have provided useful insights. As such, given the paucity of available evidence, any studies which compare brentuximab vedotin and chemotherapy in the target population for R/R sALCL are potentially relevant.

Furthermore, the ERG was able to retrieve a full text paper (published in November 2016) associated with Hux et al[83] which meets the inclusion criteria.
The searches undertaken by the company would not have identified this paper as the publication in question is not indexed in the databases that were searched. The journal article had, however, been published at the time the company searching was undertaken. Furthermore, both the studies by Hux et al. and Zou et al. were co-authored by Takeda employees or affiliates, so it would seem reasonable to expect that these data were available to the company for consideration when developing their economic model. The ERG considers Hux et al.[83] to be the most relevant published study informing the cost-effectiveness of brentuximab vedotin vs chemotherapy in a UK adult population with R/R sALCL.

The ERG asked the company clarify the reasons for the difference in the reported incremental cost effectiveness ratios (ICERs) in the company submission and the study reported by Hux et al.,[81] (that is £8,829 per QALY gained in the company submission compared with £35,390 per QALY gained reported in the study by Hux et al.). In response the company provided a table that outlined several key differences (Table 12).

**Table 12 Comparison of cost-effectiveness analyses – CS vs. Hux et al (2016) (Source: Company response to clarification, Table 2)**

| Component | Company submission | Hux et al. (2016)*[81] |
|---|---|---|
| Modelling approach | • The model estimates costs and health effects for the following six cohorts and weights these according to the proportion of patients in each for each treatment arm in order to estimate total costs and QALYs for the respective comparators:<br>1. Patients who only receive brentuximab vedotin<br>2. Patients who receive brentuximab vedotin followed by ASCT<br>3. Patients who receive brentuximab vedotin followed by allo-SCT<br>4. Patients who only receive chemotherapy<br>5. Patients who receive chemotherapy followed by ASCT<br>6. Patients who receive chemotherapy followed by allo-SCT | • The model estimates costs and health effects for brentuximab vedotin and chemotherapy overall (i.e. patients who receive allo-SCT, ASCT and no SCT are modelled as a single cohort for each comparator)<br>• Outcomes associated with ASCT and allo-SCT are assumed to be captured in the overall survival curves for the respective treatment arms (see below) |
| SCT modelling | • PFS and OS for ASCT and allo-SCT were modelled explicitly based on data from Smith et al. (2013)[84].<br>• The associated lifetime costs and QALYs were assigned to 30% of brentuximab patients (ASCT = 14%; allo-SCT = 16%) and 14% of chemotherapy patients (ASCT = 7%; allo-SCT = 7%) | • Costs of allo-SCT are assigned based on the assumption that 50% of brentuximab patients and 20% of chemotherapy patients receive allo-SCT.<br>• Outcomes associated with ASCT and allo-SCT are assumed to be captured in the overall survival curves for the respective treatment arms |

| | | |
|---|---|---|
| Data-cut from SG035-0004 used to parameterise brentuximab vedotin PFS and OS | • PFS and OS data for brentuximab vedotin (no SCT) were based on 5-year follow-up data from SG035-0004 which were presented at the 58th American Society of Haematology (ASH) Annual Meeting in December 2016[79].<br>o The median follow-up was 71.4 months (range, 0.8 to 82.4). | • PFS and OS data for brentuximab were based an earlier data cut from SGN35-0004 which has shorter follow-up than the data cut used in the company submission.<br>o The median follow-up ** |
| Survival analysis for brentuximab PFS and OS | • Long-term PFS and OS for brentuximab vedotin (no SCT) were estimated by fitting parametric cure models to the SG035-0004 data.<br>• These were extrapolated using general population mortality with an excess hazard of 5% for the no SCT cohort. | • Long-term PFS and OS for brentuximab vedotin were estimated by fitting standard parametric models to the SG035-0004 data.<br>• These were only used for the within-trial period, following which the hazard was assumed equivalent to chemotherapy. |
| Data source for chemotherapy PFS and OS | • PFS for chemotherapy (no SCT) was based on PFS achieved with the most recent cancer-related therapy prior to brentuximab vedotin for the subgroup of 39 patients in SG035-0004 whose most recent therapy was for R/R disease.<br>• OS for chemotherapy (no SCT) was based on the subset of PTCL patients from Mak et al.[85] with PS<2 (n=47).<br>o This study reports outcomes for 89 patients with nodal PTCL who received systemic chemotherapy in the British Columbia Cancer Agency (BCCA) Lymphoid Cancer database. | • PFS and OS for chemotherapy were based on a subset of 40 patients with sALCL from the BCCA registry. |

| | | |
|---|---|---|
| List price of brentuximab | • The results presented in the company submission are based on [redacted] | • The results presented are based on the BNF list price (£2,500 per 50mg vial) |
| Date | • The model has been adapted to align with the NICE scope for the appraisal based on the scoping meeting held in October 2016 | • The model built by Hux et al. (2016) was based analyses conducted in 2014 |
| *Based on manuscript; SCT, stem cell transplant; PFS, progression-free survival; OS, overall survival | | |

*** The ERG noted an omission in the company provided table. Correct median observation time from Hux et al. is 33.4 months (range 0.8-45.6)*

### 5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The company's review of cost-effectiveness studies concluded that there was insufficient evidence to make a judgement on cost-effectiveness in the UK setting. Given longer-term follow-up data for SG035-004 has become available since the publication of Hux et al.[83]and Hux, 2016[82] the ERG generally agrees with this conclusion. However, the study by Hux et al[83] does provide a useful reference point to understand the key drivers behind the improved cost-effectiveness estimate in the current submission. In particular, the ERG note the key differences in the approaches to modelling progression free survival and overall survival in both the intervention and comparator arms, which are commented on more fully in Section 5.2.6.

## *5.2 Summary and critique of company's submitted economic evaluation by the ERG*

This section summarises the company submitted evidence on cost-effectiveness and the ERG critique of the company's analyses. The company developed a *de novo* partitioned survival model to assess the cost-effectiveness of brentuximab vedotin compared to chemotherapy.

### 5.2.1 NICE reference case checklist

Table 13 presents the ERG's review of the company submission against the NICE reference case checklist. Major issues are highlighted in the table and discussed in more detail throughout the report.

**Table 13 NICE reference case checklist (Table only)**

| Attribute | Reference case and TA Methods guidance | Does the *de novo* economic evaluation match the reference case |
|---|---|---|
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice | Yes, however the original CS assumed post progression therapy using brentuximab vedotin in the comparator arm of the model. This was not consistent with the NICE scope which states that the comparator is *"established clinical management without brentuximab vedotin"*. A revised model was submitted following clarification which is in line with the NICE scope. |
| **Patient group** | As per NICE scope. "*people with relapsed or refractory systemic anaplastic large cell lymphoma*" " | Yes |
| **Perspective costs** | NHS & Personal Social Services | Partly, the submission clearly takes an NHS perspective. The CS states that a PSS perspective was not considered. |
| **Perspective benefits** | All health effects on individuals | Yes, health effects associated with progression, survival, and adverse events are incorporated using QALYs. |
| **Form of economic evaluation** | Cost-effectiveness analysis | Yes, Cost-Utility Analysis |
| **Time horizon** | Sufficient to capture differences in costs and outcomes | Yes, a life-time (60 year) horizon is modelled for a cohort with a mean starting age of 48. The ERG notes that the model runs to a maximum age of 108 years (though 99% of patients of modelled brentuximab vedotin patients have died by 50 years (age 98) and 99% of modelled chemotherapy patients have died by 43 years (age 91). |

| | | |
|---|---|---|
| **Synthesis of evidence on outcomes** | Systematic review | Yes, a systematic review of HRQoL studies was undertaken, and one study retrieved. |
| **Outcome measure** | Quality adjusted life years | Yes |
| **Health states for QALY** | Described using a standardised and validated instrument | No, health state vignettes were used, based on a published study identified from the SLR. These were valued using TTO methodology to assign utility values by clinical response to treatment. Vignettes were not directly reflective of EQ-5D health states. Additional clinical expert assumption was used to assign utility decrements (from general population norms) to long term survivors. This deviates from the reference case. |
| **Benefit valuation** | Time-trade off or standard gamble | Partly, the single included utility study was based on vignettes valued using TTO methodology. Other utility decrements were based on expert opinion (decrements for long-term survivors) or other published studies (adverse events). |
| **Source of preference data for valuation of changes in HRQL** | Representative sample of the public | Yes, partly. For the Swinburn et al study, a sample of the UK general population was used. |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes. |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes. |

| | | |
|---|---|---|
| **Probabilistic modelling** | Probabilistic modelling | Yes – a wide range of parameters were included, but only reported for the base case analysis. Probabilistic ICERs were not reported. |
| **Sensitivity analysis** | | Yes, but the company mainly explored univariate scenario analyses. Three multiway analyses were conducted on parameters that were not particularly sensitive in the model. Tornado diagrams and multivariate sensitivity analyses (of the most sensitive parameters) would have better illustrated uncertainty. The ERG found that deterministic analyses were in general applied to parameters to which the model was not particularly sensitive, hence underplaying the uncertainty. |

Key: CS: Company submission; HRQoL: health related quality of life; PSS: personal social services; QALY: quality adjusted life year; SLR: systematic literature review; TTO: time trade off

### 5.2.2 Models structure

The company presented a partitioned-survival model to "*assess the cost-effectiveness of brentuximab vedotin compared to established clinical management without brentuximab vedotin for the treatment of patients with R/R s ALCL".*

Three health states were included, namely: progression free survival (PFS), post-progression survival (PPS) and death. The model schematic from the CS is reproduced in Figure 2 below.

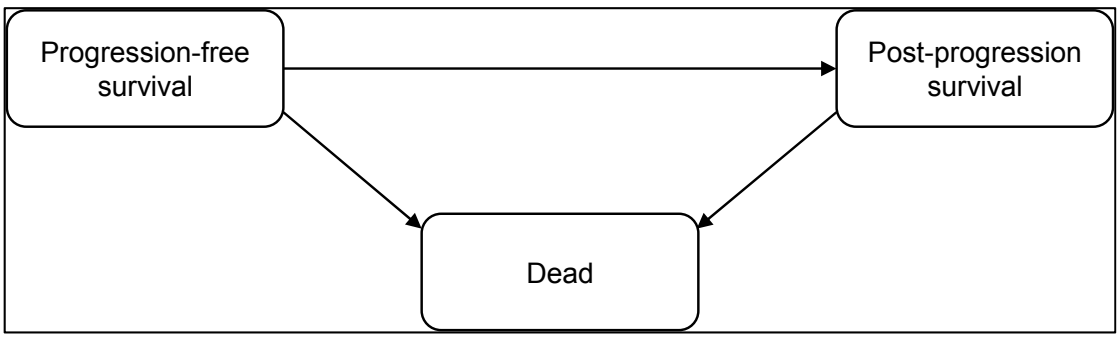



**Figure 2 Model schematic (Re-produced from Figure 5.2; Page 81 of the CS)**

Health state occupancy in a partitioned survival model is reflective of the modelled PFS and OS curves for the respective treatment cohorts, using an area under the survival curve approach. The proportion in the PFS state (at any point in time) is estimated directly from the PFS curve. Similarly, the area under the OS curve determines the proportion of the cohort surviving, and the difference between OS and PFS curves determines the proportion in the post-progression health state at any time. Given the curves were modelled independently, potential existed, particularly in the probabilistic analyses, for estimated progression free survival to exceed OS. This was corrected for in the model by forcing the proportions to be equal in such scenarios.

Costs, life years and QALYs were accrued on a weekly basis according to the proportion of the modelled cohorts in each state. Half cycle corrections were performed. The model time horizon was 60 years and an NHS perspective on costs was adopted. Costs, life years and QALYs gained were discounted at a rate of 3.5% per annum, continuously over each weekly cycle of the model.

The ERG agrees that the use of a partitioned survival model is appropriate in the context of the current decision problem. In general, barring a few minor bugs, the ERG found the model structure to be sound and correctly implemented.

### 5.2.3 Population

The characteristics of the modelled cohorts are sourced primarily from the SG035-0004 trial, intention to treat population (Table 14). As such, the model considers patients with relapsed or refractory systemic Anaplastic Large Cell Lymphoma (R/R sALCL).

**Table 14 Characteristics of the modelled cohorts (Source: CS Table 5.8; Page 88)**

| Parameter | Mean | SD |
|---|---|---|
| **Body weight (kg)** | 76.35 | 20.385 |
| **BSA ($m^2$)** | 1.88 | 0.28 |
| **Starting age (years)** | 47.70 | 16.85 |
| **Male** | 57% | Std. Error: 7%* |
| Key: BSA: Body Surface Area | | |

*Average body weight and average BSA were based on data from patients from SG035-0004, ITT population

In total, 6 different cohorts of patients were modelled, depending on their treatment pathway (brentuximab vedotin or comparator), and whether or not they went on to receive an autologous stem cell transplantation (ASCT) or allogeneic stem cell transplant (allo-SCT). The expected costs and effects in the model for brentuximab vedotin and chemotherapy interventions are weighted according to the assumed proportion in each cohort. Therefore, the model results are determined by the weighted aggregation of the costs and benefits accruing to each sub-cohort in each arm of the model (Table 15).

**Table 15 Modelled cohorts and proportions assumed to be in each for the overall analysis (Source: CS Table 5.7; Page 88)**

| Technology | Model cohort | Name | Description | Base case proportion |
|---|---|---|---|---|
| Brentuximab vedotin | 1 | Brentuximab vedotin, no SCT | Patients who only receive brentuximab vedoti | 71% |
| | 2 | Brentuximab vedotin + ASCT | Patients who receive brentuximab vedotin followed by ASCT | 14% |
| | 3 | Brentuximab vedotin + allo-SCT | Patients who receive brentuximab vedotin followed by allo-SCT | 16% |
| Chemotherapy | 4 | Chemotherapy, no SCT | Patients who only receive chemotherapy | 86% |
| | 5 | Chemotherapy + ASCT | Patients who receive chemotherapy followed by ASCT | 7% |
| | 6 | Chemotherapy + allo-SCT | Patients who receive chemotherapy followed by allo-SCT | 7% |
| SCT, stem cell transplant; ASCT, autologous stem cell transplant; allo-SCT, allogeneic stem cell transplant | | | | |

*Stem cell transplant and transplant rates*

The company's economic model assumes that for a proportion of patients, brentuximab vedotin acts as a bridge to SCT, which is intended as a potentially curative therapy. The rates of bridging to ASCT (14%) and allo-SCT (16%) are higher with brentuximab vedotin compared to chemotherapy (7% for both ASCT and allo-SCT). The ERG's clinical expert opinion confirms that this assumption is plausible, noting that an important role for brentuximab vedotin is its potential to bridge additional patients to SCT. The transplant rates in each intervention were calculated

according to the estimated proportions achieving a complete response (CR) or partial response (PR). Further details are provided in Section 5.2.6.

### 5.2.4 Interventions and comparators

The intervention is brentuximab vedotin, available as a 50 mg vial. The summary of Product Characteristics (SPC) states that the recommended dosage for R/R sALCL is 1.8 mg/kg intravenous infusion over 30 minutes every 3 weeks[51] For patients weighing over 100kg, the dose calculation should use 100kg. The marketing licence for brentuximab vedotin was granted on the basis of the results from the single Phase II (SG035-0004) trial of 58 patients having R/R sALCL. The SmPC states that patients who achieve stable disease or better should receive a minimum of eight cycles and up to a maximum of 16 cycles (almost one year) (SmPC). The mean number of cycles received by patients in the SG035-0004 was eight, ranging from one to 16; treatment was recommended to continue until disease progression or unacceptable toxicity. The intervention was costed on this basis in the economic model, though the ERGs clinical advice suggests that in practice, patients may receive fewer cycles of treatment with brentuximab vedotin than in the SG035-0004 trial. Patients may proceed to transplant after best response which is often seen by 4-6 cycles. Others will stop early because of toxicity and / or progression. Brentuximab vedotin has been designated as an orphan drug by the European Medicines Agency ,[41] prescribed for patients with no other salvage therapy available to them; i.e. following ASCT or for patients who had already undergone a minimum of two other therapies (in which ASCT or multi-agent chemotherapy failed). Brentuximab vedotin was approved for use on the national Cancer Drugs Fund (CDF) in 2013 for *"R/R ALCL when no other salvage treatment is available"*. In the context of the current model, the ERG notes that brentuximab vedotin is modelled according to the inclusions and exclusion criteria from SG035-0004 for a mixed cohort of patients who have progressed following either primary treatment (first line CHOP (Cyclophosphamide, Hydroxydaunomycin, Oncovin®, Prednisolone) chemotherapy), prior salvage therapy, or a previous ASCT. Prior allo-SCT were excluded.

The modelled comparator consisted of multi-agent chemotherapy treatments given as salvage therapy. The multi-agent therapies were ICE (ifosfamide, carboplatin, etoposide), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), DHAP (dexamethasone, high-dose cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin) and Gem-P (gemcitabine, methylprednisolone, cisplatin). The ERG's clinical expert agrees that these treatment regimens are an appropriate comparator for

the assessment. The company's submission specified that the comparator is "*established clinical management without brentuximab vedotin"*. This statement is in line with the NICE scope. However, the economic model originally received with the CS included costs of subsequent brentuximab vedotin treatment for patients progressing following comparator chemotherapy regimens. Whilst the ERG notes that the licence for brentuximab vedotin is broad, and in practice the drug may be used after 1, 2 or even 3 lines of initial and salvage chemotherapy (depending on length of initial remission and fitness of the patient), it is nonetheless in breach of the NICE scope. The ERG further noted at the clarification stage that all patients are assumed to receive further active treatment upon progression. The ERGs clinical advice suggested that best supportive care should have been included as a treatment option for a proportion of patients in whom active treatment may not be considered appropriate following progression.

The economic model considered both ASCT and allo-SCT as subsequent, potentially curative treatments for both the intervention and comparator groups. According to the ERG's clinical expert advice, a key advantage of brentuximab vedotin is the possibility for the treatment to provide a more effective bridge to SCT, and this is how the treatment is most commonly used within the treatment pathway in clinical practice. However, it should be noted that brentuximab vedotin is assumed to be curative without SCT treatment in the economic model, and this is a key driver of QALY gains over standard practice in the base case analysis.

### 5.2.5 Perspective, time horizon and discounting

The analysis perspective adopted in the model was primarily that of the NHS. The CS stated that a personal and social services (PSS) perspective was not considered explicitly in the model. This deviates from the NICE reference case [53]. However, the ERG has no reason to believe that excluding related PSS costs will have unfairly advantaged brentuximab vedotin. The ERG considers the costing perspective chosen for the company submission to be generally appropriate.

A lifetime horizon was chosen, and stated by the company to be 60 years. Based on a mean starting age of 47.7 years (mean age of patients in the SG035-0004 study), this

means that patients are modelled to a maximum age of 108 years. It is not clear how realistic this is for a population with aggressive disease receiving brentuximab vedotin (or comparator therapies). The ERG notes that 99% of the brentuximab vedotin modelled patients have died by 50 years (age 98) whereas 99% of modelled chemotherapy patients have died by 43 years (age 91). Furthermore, residual differences in PFS and OS are maintained between treatment arms over the entire time horizon of the model. The adopted time horizon may therefore introduce a small overestimation of the QALY gains associated with brentuximab relative to chemotherapy. However, the ERG also acknowledges that the impact on the ICER is negligible since the majority of QALY gains for brentuximab are realised in the first 20 years of the model time horizon. A more important determinant of the QALY gain is the adopted approach to modelling PFS and OS in the intervention and comparator arms, particularly in those who do not receive a SCT (see section 5.2.6).

Discounting was applied in the model at a constant rate of 3.5% per annum to costs life years and QALYs in the base case analysis. This is appropriate and in line with the NICE reference case.[53] A minor error was noted by the ERG with respect to the apparent double discounting of post progression treatment costs. That is, the post progression treatment costs are sourced from the discounted values of the original treatment course and recycled into the model at a later date and re-discounted. Given that the discount factor references time since the model commencement, this effectively over-discounts post-progression treatment costs in both arms of the model. The ERG queried the approach at clarification stage and the company responded that:

> *"PPS therapy costs have been double-discounted intentionally". The discounting which is calculated in cells BB5:BE5 in the TraceBV and TraceChemo tabs reflects time elapsing from initiation to discontinuation of treatment. These are then discounted back to t = 0 in the model to reflect the time at which patients enter the PPS state (which differs across treatment arms) and therefore begin to accrue the associated costs."*

The ERG disagrees with this justification. All costs and outcomes should be discounted back to the starting point in the model, not the time point when post progression therapy is initiated. The ERG has corrected this error and finds that the

impact of removing the second discounting of post-progression therapy costs is minimal.

### 5.2.6 Treatment effectiveness and ***extrapolation***

Treatment effectiveness in the company's economic model is based on a combination of clinical response rates (complete response, partial response, stable and progressed disease), stem cell transplant rates by response categories, and PFS and OS by transplant status (no SCT, ASCT and allo-SCT). It should be noted that for those who receive a transplant, PFS and OS is modelled to be equivalent irrespective of treatment arm. However, for those who receive no transplant, there are substantial differences in PFS and OS between the brentiximab vedotin and chemotherapy which are based on a naïve indirect comparison. Thus the key drivers of life-year and QALY gains with brentuximab vedotin are: 1) the increased proportion of patients who received a SCT; and 2) improved progression free and overall survival over salvage chemotherapy in those who do not receive a SCT.

*5.2.6.1. Clinical outcomes – data sources used in the model*

**Response rates & proportions receiving SCT**

Clinical response rates have three important functions within the model. They are used to 1) determine the proportion of patients who enter the PFS state post treatment *(See the following section)*; 2) to calculate response based utilities *(See Section 5.2.7)*; and 3) to determine the proportion of patients receiving a SCT.

The company noted that only a proportion of complete and partial responders intended for SCT will actually receive a SCT. Data for clinical response rates and subsequent SCT rates (by response rates) for brentuximab vedotin were sourced from SG035-0004 in the base case analysis, including the ratio of ASCT to allo-SCT (47%: 53%). This results in 29% of brentuximab vedotin treated patients receiving SCT (14% ASCT; 16% allo-SCT). In addition, the company also provided 2 scenario analyses, 1) where SCT rates (by clinical response rate) were based on expert opinion about the percentage of CRs and PRs that would be intended for treatment (100% and 50% respectively) and 2) where data from Mak et al.[72] about the percentages of those intended for SCT actually receiving SCT were assumed.

For the salvage chemotherapy arm, the company considered several possible data sources for clinical response rates (SG035-0004; Crump et al. and Dong et al.[86, 87]). Base case response rates were based on a subset of patients in SG035-0004 on their most recent chemotherapy prior to brentuximab vedotin. These self-controls were restricted to 39 patients whose prior therapy was for remitting or relapsed disease. However, no details were provided in the original submission regarding the previous chemotherapies received by these 39 self-controls, and whether they are consistent with the comparators for the current assessment. The ERG queried this at clarification stage, and the company noted that 7.7% had received CHOP, 23.1% had received ICE, 2.6% had received R-CHOP and 66.7% had received another unknown treatment. It is therefore not possible to determine if the prior treatments used to estimate response rates are representative of the chemotherapy comparators applied in the model. However, the company did note that, based on feedback from their survey of clinical experts, clinical efficacy of the chemotherapy regimens used in practice is not expected to differ.

A potentially greater problem with the use of self-controls to estimate comparator response rates is the possible underestimation of complete response due to exclusion of those who achieve long-term remission on chemotherapy or die prior to progression. The alternative sources considered by the company, however, were also of limited value as they reported on patients with predominantly newly diagnosed PTLC (Dong et al) or patients with recurrent/refractory B-Cell non-Hodgkin's lymphoma (Crump et al).

The base case analysis calculated SCT rates for both brentuximab vedotin and chemotherapy by multiplying response data (CR / PR) by the respective proportions observed to receive SCT in SG035-0004. Sensitivity analysis explored the use of equal rates in both arms (as observed in Mak et al.),[72] where 29% were intended for transplant and 69% of those actually received it (calculated SCT rate = 20%). A second sensitivity analysis applied clinical expert opinion that all patients achieving CR and half of those achieving PR would be intended for transplant and 69% of those intended for transplant would actually receive one.[72] The alternative possible response rates and proportions receiving SCT (by response rate) are summarised in Table 16. The ERG notes that there is substantial uncertainty surrounding the estimated

response rates and SCT rates, particularly in the comparator arm due to the use of the self-controls.

**Table 16 Response rates and proportions receiving SCT in the model**

| | BV response rates (ITT) | | Chemotherapy response rates (ITT) | | | Proportion receiving SCT by response category | | |
|---|---|---|---|---|---|---|---|---|
| | **BV (Per INV)*** | **BV (Per IRF)** | **Chemo (self-control)*** | **Chemo (Dong et al)** [87] | **Chemo (Crump et al)** [86] | **% receiving SCT (data observed in SG035-0004)*** | **% receiving SCT (expert opinion)** | **% receiving SCT (equal in both arms)** |
| **Complete Response** | 38/58 (66%) | 34/58 (59%) | 12/39 (31%) | 12 /26 (46%) | 8/51 (16%) | 16/38 (42%) | 69% | 20% |
| **Partial Response** | 12/58 (21%) | 16/58 (28%) | 5/39 (13%) | 11 /26 (42%) | 17/51 (33%) | 1/12 (8%) | 35% | 20% |
| **Stable Disease** | 4/58 (7%) | 2 / 58 (3%) | 4/39 (10%) | 1 /26 (4%) | 9/51 (17%) | 0% | 0% | 0% |
| **Progressive Disease** | 2/58 (3%) | 3/58 (5%) | 14/39 (36%) | 2 /26 (8%) | 9/51 (17%) | 0% | 0% | 0% |
| **Unknown** | 2/58 (3%) | 3/58 (5%) | 4/39 (10%) | 0 /26 (0%) | 9/51 (17%) | 0% | 0% | 0% |

Key: INV: investigator; IRF: independent review facility; ITT: intention to treat; SCT: stem cell transplantation

** Company Submission Base case analysis*

***Calculated proportion (rounded to nearest percentage) receiving SCT following brentuximab vedotin: 29% (14% ASCT; 16% AlloSCT)*

***Calculated proportion (rounded to nearest percentage) receiving SCT following chemotherapy: 14% (7% ASCT; 7% AlloSCT)*

**Progression free survival and overall survival**

A summary and critique of the clinical-effectiveness data from SG035-004 and potential comparators has been provided in Sections 4.3 and 4.4 respectively. Table 17 reports a summary of the clinical-effectiveness data sources for PFS and OS that are used in the company's base case model.

**Table 17 Summary of clinical effectiveness data sources used in the CS (Source: CS, Table 5.10; pg93)**

| Treatment | Endpoint data source | | Model cohort(s) * |
|---|---|---|---|
| | PFS | OS | |
| Brentuximab vedotin, no SCT | SG035-0004 patients who didn't receive subsequent SCT (*n*=41) | SG035-0004 patients who didn't receive subsequent SCT (*n*=41) | 1 |
| Chemotherapy, no SCT | SG035-0004 self-control patients (*n*=39) | Mak et al., 2013[72] PTCL patients with PS<2 (*n*=47) | 4 |
| ASCT | Smith et al., 2013[73] ASCT patients (*n*=115) | Smith et al., 2013[73] ASCT patients (*n*=115) | 2,3,5,6 |
| Allo-SCT | Smith et al., 2013[73]allo-SCT patients (*n*=126) | Smith et al., 2013[73] allo-SCT patients (*n*=126) | 2,3,5,6 |
| PS, performance status; ASCT, autologous stem cell transplant; allo-SCT, allogeneic stem cell transplant; * | | | |

As mentioned, PFS and OS following SCT are equal irrespective of the initial treatment received. Therefore, the following critique focusses on assumptions surrounding PFS and OS for those who do not receive SCT.

*5.2.6.2. Progression free survival*

**Brentuximab vedotin (No SCT)**

*Trial based data*

PFS data for brentuximab vedotin (with no SCT) were sourced from the sub-group of patients in SG035-0004 (n=41 / 58 (71%)) who did not receive SCT.

Disease progression in the SG035-0004 trial was assessed by two alternative methods: as per investigator (INV) decision and as per independent review facility (IRF) decision. The primary endpoint for the trial was per IRF, with per INV as a secondary analysis. However, per INV was used for the base case model analysis as longer term follow up data (71.4 months (range 0.8 to 82.4)) have recently become available.[79] Specifically, for the 'no SCT' subgroup, maximum INV follow-up was 76 months compared to 40 months for IRF data. Figure 3 shows the KM curves illustrating important differences between the INV and IRF assessments for the N=41 patients in SG035-0004 who did not receive SCT.

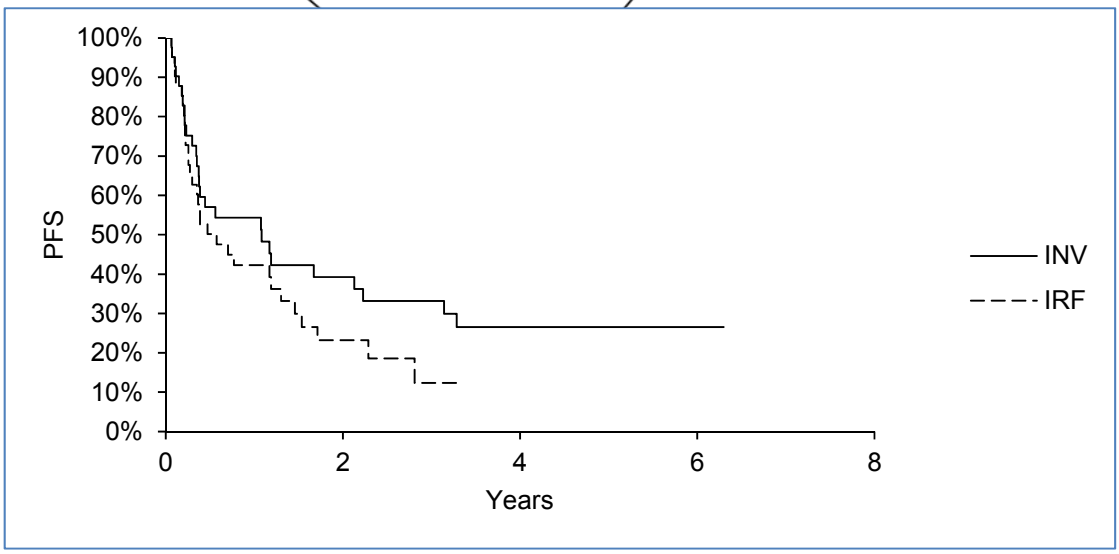



**Figure 3 Kaplan Meier curves for Brentuximab Vedotin (no SCT) PFS (Source: CS Figure 5.3, page 94).**

The ERG notes advantages and disadvantages with each approach. The IRF assessment is likely to be more objective and have a lower risk of bias. However, the ERG also acknowledges that the INV assessment provides the best available long term data.[79]The company state in response to clarification that per INV assessment is also more consistent with the approach taken for the self-controls. The ERG further note that both assessments are subject to a high rate of censoring at later follow-up time points. Therefore, the tails of the Kaplan Meier curves are subject to a high degree of uncertainty and need to be interpreted with caution.

*Extrapolation*

Figure 3 above shows a long plateau in the KM curve for INV data, which the company assumes is indicative of cure. The company therefore estimate a mixture-cure model, where a proportion of patients (the cure fraction) are assumed to no longer be at risk of progression and have a progression free survival function tending towards general population mortality. The remainder (uncured fraction) have a survival function tending towards zero. In all cases (cured or uncured) an additional 5% excess mortality risk is applied in the model. The mixture cure model applied is as follows:

$$S(t) = S^*(t)\left[\pi\left(S(t|u)\right) + 1 - \pi\right]$$

Where:

$t$ = Time

$S^*(t)$ = Expected general population survival

$S(t|u)$ = Survival function for uncured patients

π = The probability of not being cured.

The ERG queries the appropriateness of a mixture cure model for two reasons. First, the IRF data do not show evidence of cure, though the company explain that this is likely due to insufficient follow up. Secondly, the IRF KM curve shows lower PFS at the end of follow up than the INV curve. This is indicative that the cure fraction may be over-estimated in the per INV data.

The company assessed the suitability of exponential, weibull, lognormal and log-logistic models for extrapolating trial data *(Table 5.12 and 5.13 of the CS)*. Survival models were selected using a combination of AIC / BIC statistics, visual inspection of the models against the KM data, and the plausibility of the cure fraction. The approach appears to be appropriate and in line with NICE DSU TSD 14.[88] recommendations. A log logistic model, with a cure fraction of 24% (per INV data) or 9% (per IRF data) was selected. Figures 4 and 5 illustrate the survival models applied to INV and IRF assessed data respectively.

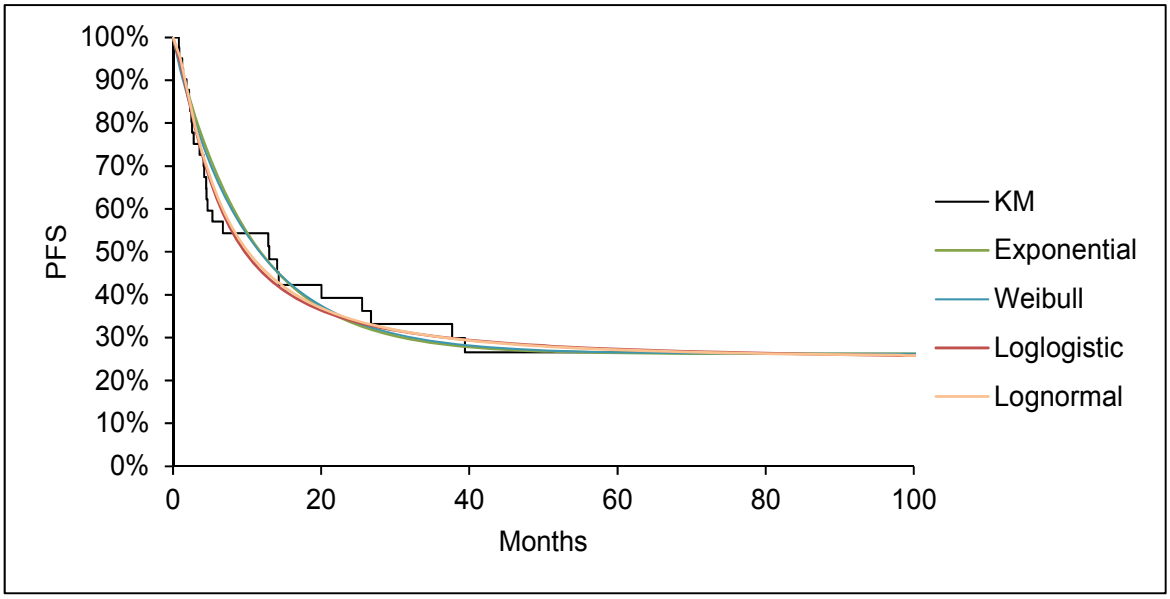



**Figure 4 Parametric models explored in the CS for brentuximab vedotin (no SCT), per INV assessment (Source: Figure 5.4; pg 96 of the CS)**

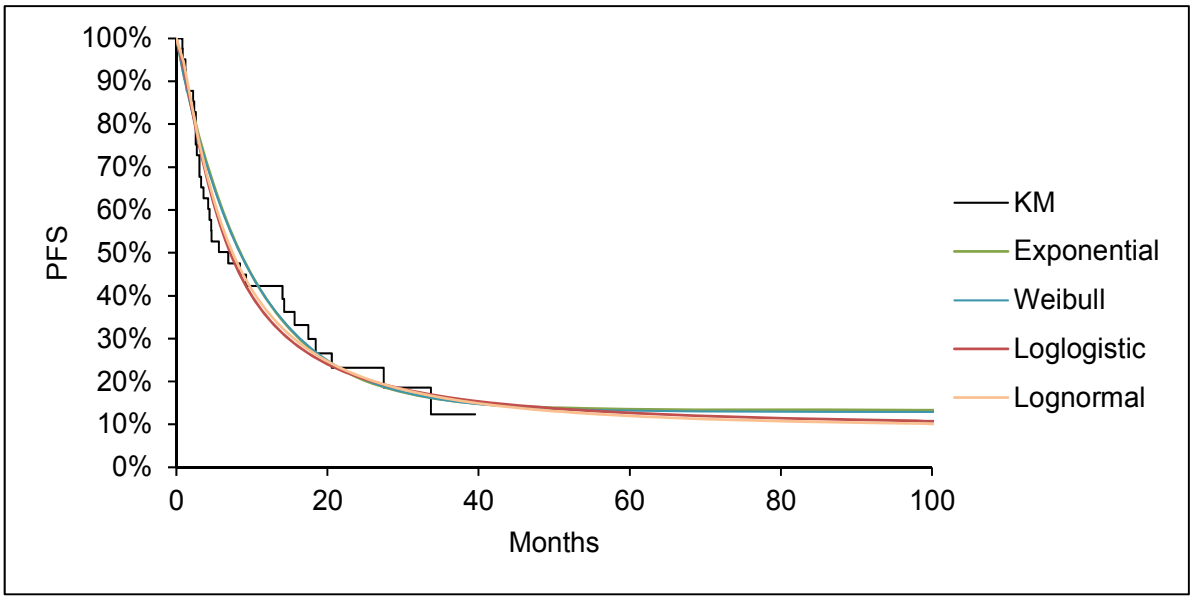



**Figure 5 Parametric models explored in the CS for brentuximab vedotin (no SCT), per IRF assessment (Source: Figure 5.8; pg. 98 of the CS)**

Due to insufficient model functionality, the ERG were unable to assess the impact on cost-effectiveness of all the survival curves explored in the CS. The company stated that as all survival curves had similar fit to the trial data, only the preferred base case (i.e. minimising AIC / BIC) and selected sensitivity analyses were programmed into the model. Figure 6 below compares the company's chosen extrapolation approach

for PFS for brentuximab vedotin (No SCT) per INV and per IRF over the full model time horizon. The ERG note that there is a substantial additional PFS gain using per INV data compared to per IRF.

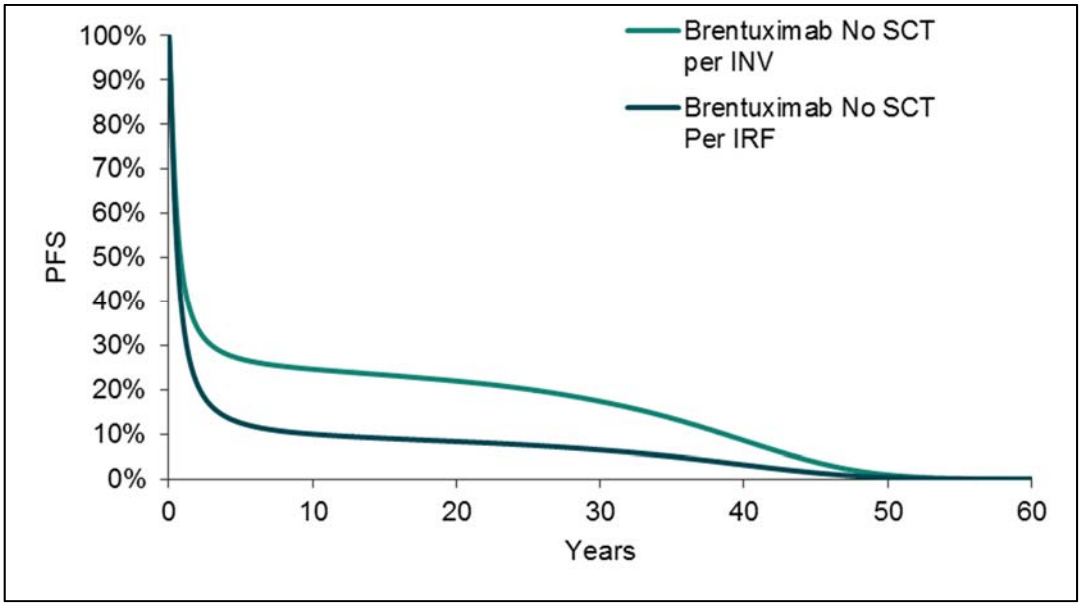



*Figure reproduced from data available within the company submitted economic model.*
**Note the values for PFS underpinning the curves presented are for the extrapolations before any adjustments, e.g. to ensure OS>PFS; Data sourced from Brentuximab tab of the company model.*

**Extrapolations are based on log-logistic for both INV and IRF data as per the company submission.*

**Figure 6 Comparison of companies preferred extrapolation method for Brentuximab PFS per INV and per IRF**

**Chemotherapy (No SCT)**

*Trial based data*

The SG035-0004 study was a single arm, open label, non-randomised study. There were no comparative data available between brentuximab vedotin and chemotherapy and an adjusted indirect comparison was not possible. Therefore, alternative sources of data were used for chemotherapy.

Internal self-controls from the SG035-0004 study

The company's base case analysis of PFS for chemotherapy, no SCT was based on internal self-controls from the SG035-0004 study. As discussed above, this consisted of a subgroup of n=39/58 (67%) patients who had previously had a salvage

chemotherapy for R/R disease. To reflect the NICE scope, patients whose last therapy was frontline chemotherapy were excluded.

The ERG disagrees with this choice of data and the analytical approach used for PFS for chemotherapy. As the company point out in their submission, patients achieving a long term remission on chemotherapy will not have been captured in the analysis. This is likely to create a bias in favour of brentuximab vedotin. Furthermore, by the nature of the analysis undertaken, there are no deaths in the self-control data, and so it does not equate with PFS or time to progression (which would censor patients at time of death). Therefore, it is not suitable for combining with OS data from an alternative source in a partitioned survival model.

Mak et al.[72]

Given the potential biases associated with the internal self-control cohort, the ERG consider the Canadian registry data reported in Mak et al. (considered in the CS as a sensitivity analysis only) to offer a preferred source of PFS data. Another reason to prefer Mak et al. is to maintain consistency in the source of data used for OS in the chemotherapy arm (e.g. avoiding scenarios where PFS from the self-controls is greater than OS from the Mak et al cohort).

Mak et al.[72] report both PFS and OS for a cohort of 153 patients with PTCL following first relapse or progression. The company considered two subgroups of patients from Mak et al as potentially relevant for informing PFS and OS in the chemotherapy arm. The first was a subgroup of ALCL patients (N=17), which reflects the T-cell lymphoma subtype for this appraisal. The second broader subgroup consisted of N=47 PTCL patients with performance status <2. The ERG notes that whilst the PTCL, with PS<2 subgroup is not vastly different from the ALCL pure group, it may contain a number of histologies with inherently different responses and survivals. Despite the broader inclusion of T-Cell lymphoma subtypes, this larger subgroup is comparable with respect to performance status of patients enrolled in SG035-0004 (where only 2% of patients in SG035-0004 had performance status >2).

The ERG queried the possibility of conducting a matching adjusted indirect comparison (MAIC) between Mak et al[72] and SG035-0004 at clarification stage, using

reported variables that could be compared between studies. The company noted a very small effective sample size (n=4.8) following matching of the patient level data in SG035-0004 to the characteristics of patients in Mak.[72] Due to the high level of uncertainty this would create, and in line with the NICE DSU guidance[88] the decision to abandon the MAIC appears appropriate. Further details can be found in Section 4.4. A further point to note is that the company used subgroups of patients from Mak et al to model PFS and OS, and the baseline characteristics of these subgroups are not reported. The company therefore relied on a naïve unadjusted indirect comparison when using data from Mak et al to model PFS.[72]

As illustrated in Table 9, the ERG acknowledges that there are concerns regarding heterogeneity between the cohorts, particularly relating to age (likely to bias in favour of brentuximab vedotin), stage of disease (likely to bias in favour of brentuximab vedotin) and performance status (likely to bias in favour of brentuximab vedotin). However, by basing PFS on the subgroup from Mak et al.[72] with performance status <2, this should improve comparability with SG035-0004, assuming stage of disease and age are also correlated with performance status.

The company's model provides PFS data for each of the three alternative datasets described above, namely: 1) Self-controls (base case analysis); 2) the ALCL subgroup from Mak et al (n=17); or 3) the PTCL with PS<2 subgroup from Mak et al (n=47).[72] However as will be noted in the following section, there was no flexibility to model alternative survival functions fitted to Mak et al data for PFS. Figure 7 illustrates the respective KM curves for the three alternative sources.

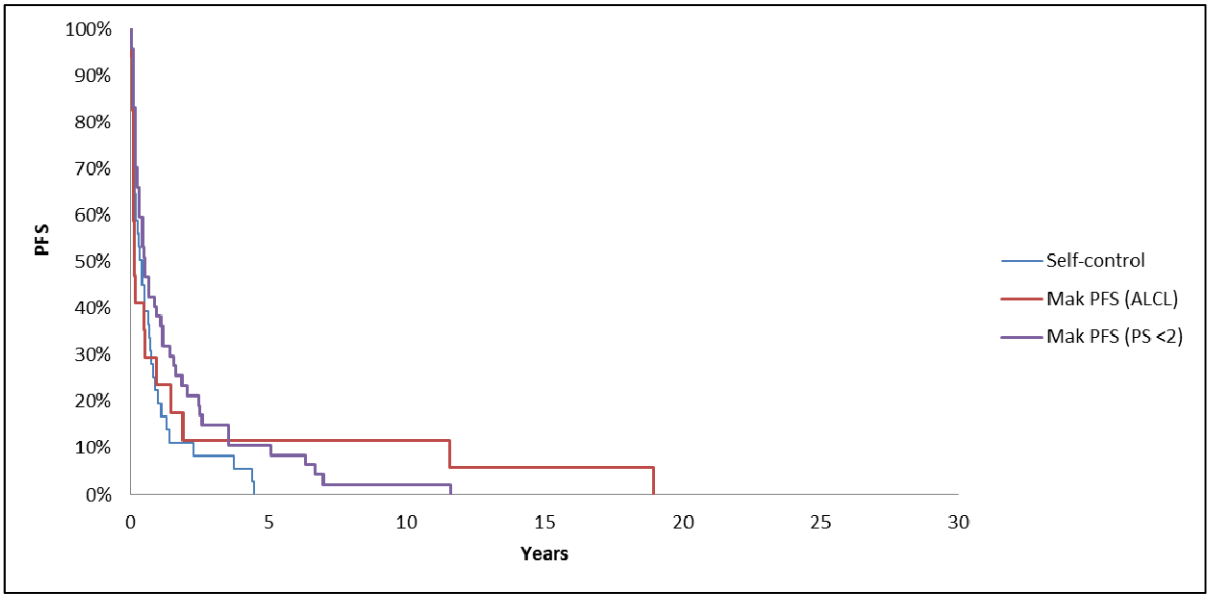



**Figure 7 KM curves for PFS for chemotherapy (Source: Reproduced from the company submitted electronic model)**

*Extrapolation*

The CS uses standard parametric models rather than cure models to extrapolate chemotherapy PFS, using the self-control data from SG035-0004. However, the ERG's clinical advice suggests that a small proportion of patients could be expected to achieve a long term remission (and thus be considered cured) using salvage chemotherapies. The Kaplan Maier curve from ALCL patients in Mak et al.[72] (*See Figure 7 above*) illustrates this possibility. The ERG therefore believe that the use of mixture-cure models for brentuximab vedotin (no SCT), and standard survival models for chemotherapy (no SCT), may generate a bias in favour of brentuximab vedotin; i.e. a proportion of patients (the cure fraction) will never experience progression with brentuximab vedotin, whilst the cohort receiving chemotherapy remain at risk of progression for the duration of the model. This may over-estimate the incremental benefit (life years and QALYs) of brentuximab vedotin relative to chemotherapy in the base case analysis. The ERG asked the company to explore the use of mixture cure models for the PFS data reported by Mak et al. The company responded that this was not possible as:

> "*None of the distributions converged using any of the available link functions*" and that "*this was likely due to proximity of the proportion who are event-free beyond 10 to 15 years to the numerical limit of the cure fraction (i.e. [0, 1]).*"

With respect to selection of the available standard survival models, the company again based their choice on a combination of visual inspection and AIC / BIC. The ERG consider the selection process to be appropriate. For the base case analysis (based on the self-control data), a log-normal standard parametric model was selected. 99% of the cohort experienced progression by 6.6 years using this model *(See Table 5.14 of the CS).* The resultant survival curves for the range of parametric survival models (based on SG035-0004 self-control data) are presented in Figure 8.

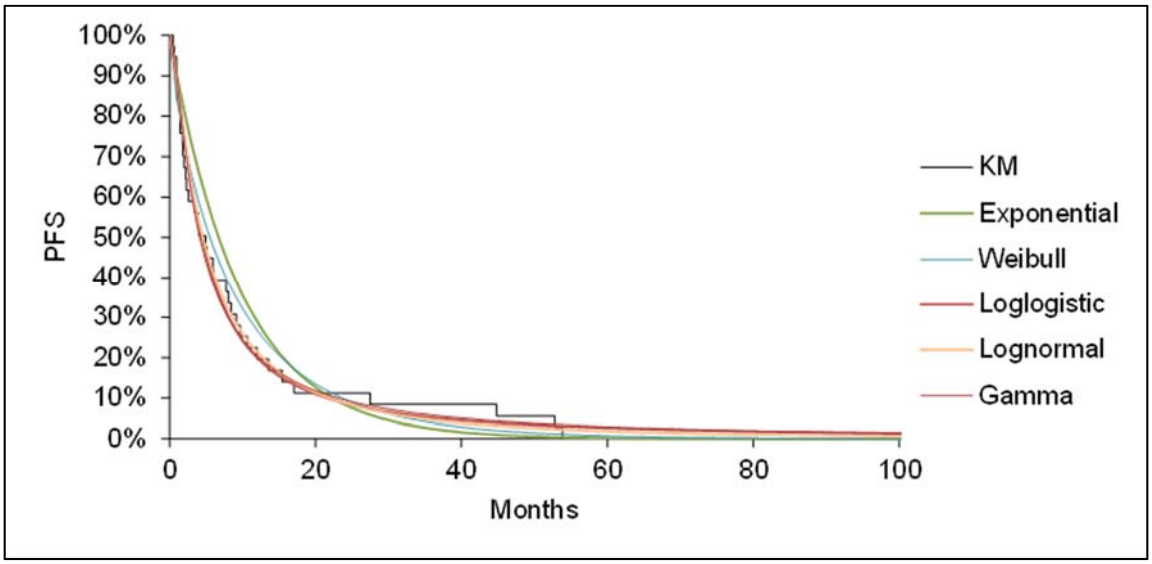



**Figure 8 Parametric models for chemotherapy (No SCT) PFS based on self-controls (Source: Figure 5.10; pg 100 of the CS)**

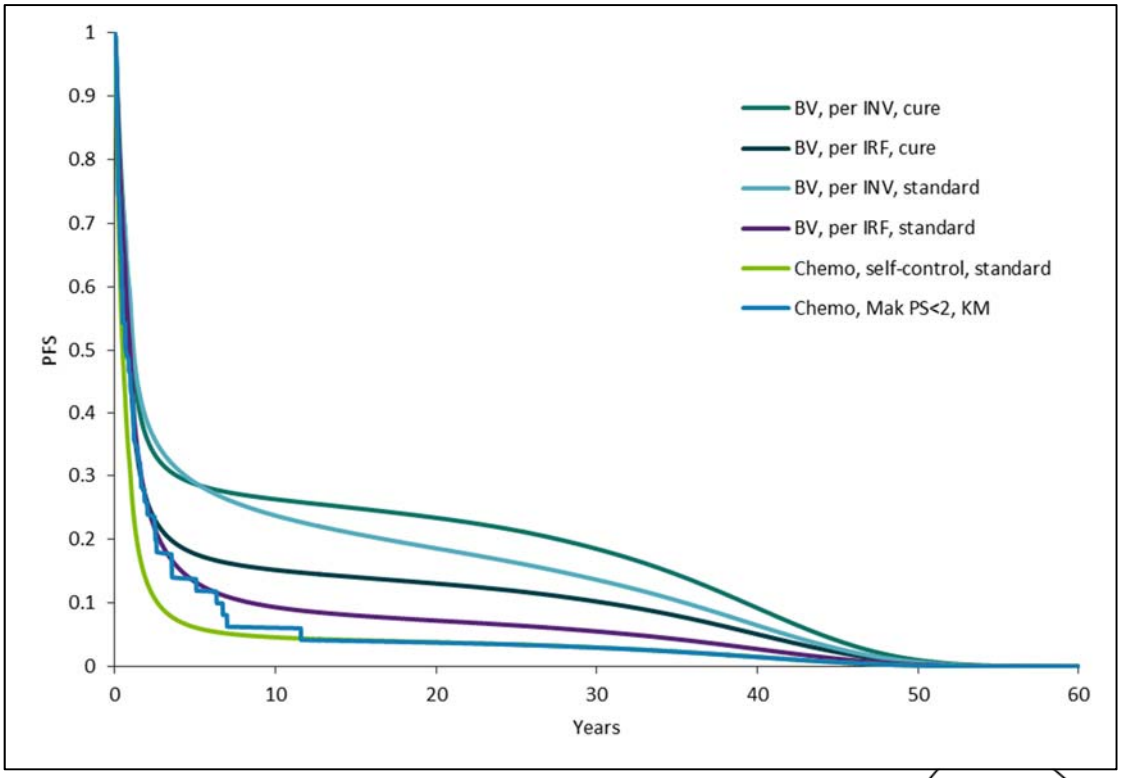
The respective survival curves show little difference between the different models. The ERG however re-iterates the concerns associated with extrapolation of data based on the internal self-controls from SG035-0004 which apply regardless of the extrapolation model chosen. Furthermore, the ERG notes that similar data to those in Figure 8 were not presented by the company for either of the possible cohorts from Mak et al..[72] The company's model only allows PFS based on Mak et al[72] to be modelled using the raw Kaplan Maier data. As such, the company has neglected to explore all the potential options available for modelling PFS using the data from Mak et al.[72]

**Comparison of PFS for brentuximab vedotin and chemotherapy (No SCT cohorts)**

Whilst the ERG accepts that cure models may be plausible for the per INV assessed brentuximab vedotin data, concerns remain (as outlined above) relating to the potential bias created in favour of brentuximab vedotin by adopting a cure model in comparison to a standard model for chemotherapy (particularly when using the data from Mak et al.).[72]

Given the great uncertainty arising the lack of a randomised or appropriately adjusted comparator group, the ERG considers that a more conservative analysis where both brentuximab vedotin and chemotherapy are modelled using a standard parametric survival models as an appropriate sensitivity analysis. The ERG notes that the ICER for brentiximab vedotin is relatively sensitive to the choice of data for PFS in the model, and substantial uncertainties exist regarding the most appropriate choice of data. Figure 9 presents six different survival curves for PFS that could be implemented in the model to illustrate the range of uncertainty underpinning the choice of data:

1. Brentuximab vedotin, no SCT (per INV assessment) using a log-logistic cure model (CS base case model)
2. Brentuximab vedotin, no SCT (per IRF assessment) using a log logistic cure model
3. Brentuximab vedotin, no SCT (per INV assessment) using a standard, non-cure gamma model;
4. Brentuximab vedotin, no SCT (per IRF assessment) using a standard non-cure Log normal model
5. Chemotherapy, no SCT (self-control data) using a standard log normal
6. Chemotherapy, no SCT (Mak et al cohort, PS<2) using KM curve[72]




Key: BV: Brentuximab vedotin; INV: Investigator; IRF: Independent review facility; KM: Kaplan Meier; PS: Performance Status

**Figure 9 Exploration of the impact of alternative data choices on PFS curves**

The company's preferred base case assumptions (per INV assessment, using a log-logistic mixture cure model) was the most optimistic scenario for modelling brentuximab vedotin PFS. By contrast, PFS modelled on the basis of IRF assessment with a standard non-cure parametric model represents a worst case for brentuximab vedotin. Conversely, in the chemotherapy arm, the base case uses a standard parametric log-normal model fitted to the self-control data, which represents the most pessimistic approach for chemotherapy PFS. Overall, the ERG notes that there is a substantial difference in the excess PFS benefit of brentuximab vedotin, depending on the sources of data and extrapolation approach used. The impact of this uncertainty on the ICER is explored further in Section 5.3.2.

*5.2.6.3. Overall survival (OS)*

**Brentuximab vedotin (No SCT)**

*Trial based data*

As with PFS, OS data were reported according to the SG035-0004 study for the subset of n=41 patients who did not receive SCT. The estimated 5 year OS rate for

brentuximab vedotin, full ITT sample (N=58) was 60%, 95% CI (47% to 73%). Median OS duration was not estimable. Whilst the company have not reported 5-year OS (95% CI) for the No SCT subgroup (N=41), the model trace shows that 49% remained alive at 5 years. As with PFS, heavy censoring is observed at the tails of the KM curves.

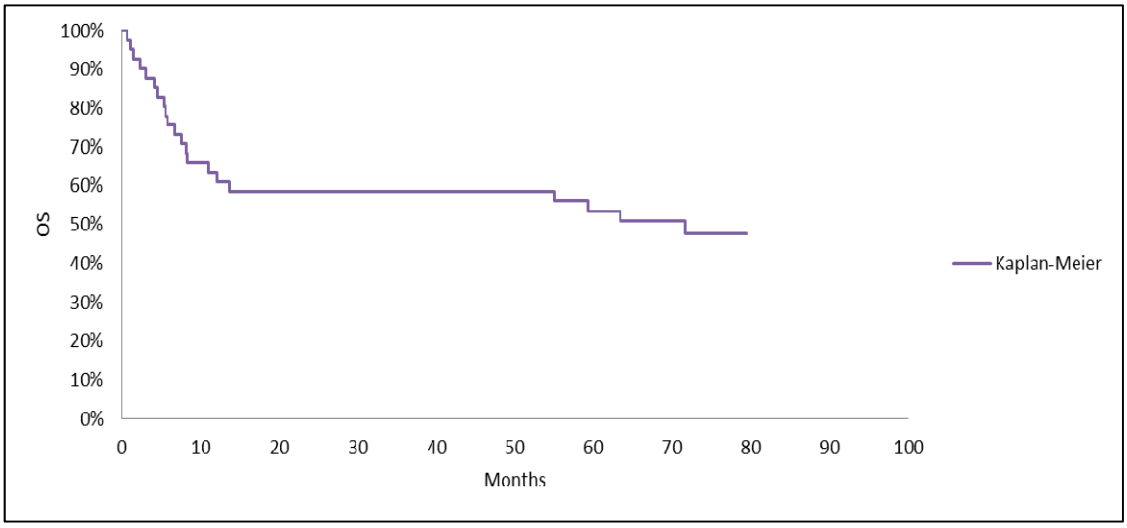



**Figure 10 Kaplan Meier curve for OS on brentuximab vedotin (No SCT) (Source: Figure 5.15, pg. 104 of the CS)**

*Extrapolation*

As with PFS, a similar plateau in the OS KM curve is observed in Figure 10, leading the company to apply a similar mixture-cure model for the longer term extrapolations. This has the implication of assuming that longer term mortality for brentuximab vedotin approaches that of the expected rate of general population mortality. In order to reflect that there may be an additional residual mortality risk, the company applied an additional 5% excess mortality, based on clinical expert opinion, to all parametric OS extrapolations. All models explored had similar predicted cure fractions ranging between 44% (log logistic and log normal) to 47% (exponential) *(See Table 5.17 of the CS)*. The company have chosen a log-logistic model as it had the lowest AIC and BIC statistics. The ERG deem the selection criteria for the extrapolation model to be appropriate. Figure 11 presents the alternative models explored by the company.

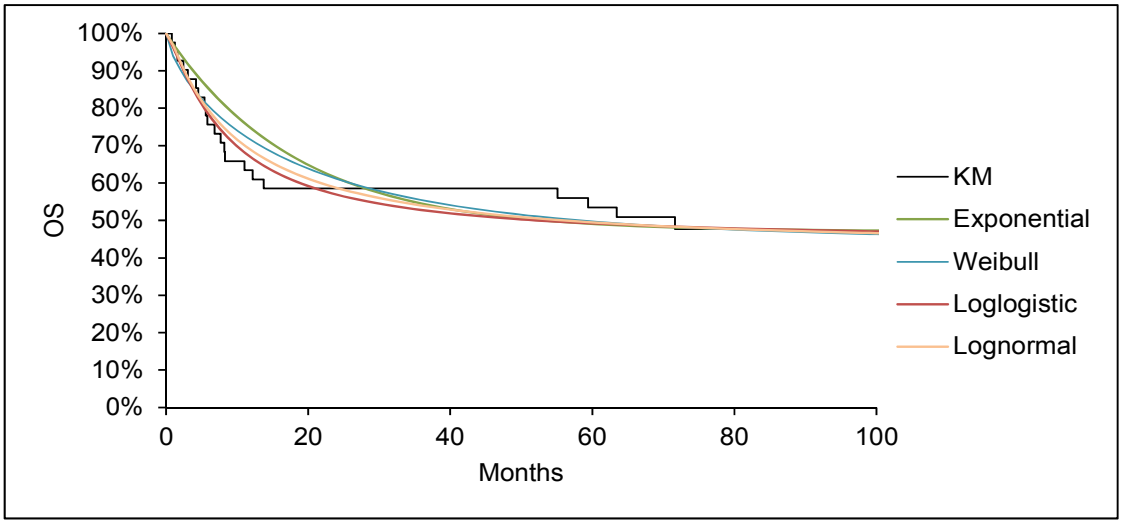



**Figure 11 Parametric models explored for brentuximab vedotin, no SCT, OS (Source: Figure 5.16, pg 105 of the CS)**

As the CS outlined, a visual inspection of the data in Figure 11 indicates that all the models over-estimate OS for the early part of the curve (up to ~30 months), but underestimate between months 30-80, illustrating that all of the explored models struggle to incorporate the high number of early events and long tail on the KM curve. Figure 12 illustrates the impact on OS of adopting log logistic cure (orange curve) vs. standard gamma (blue curve) parametric survival model for extrapolation.

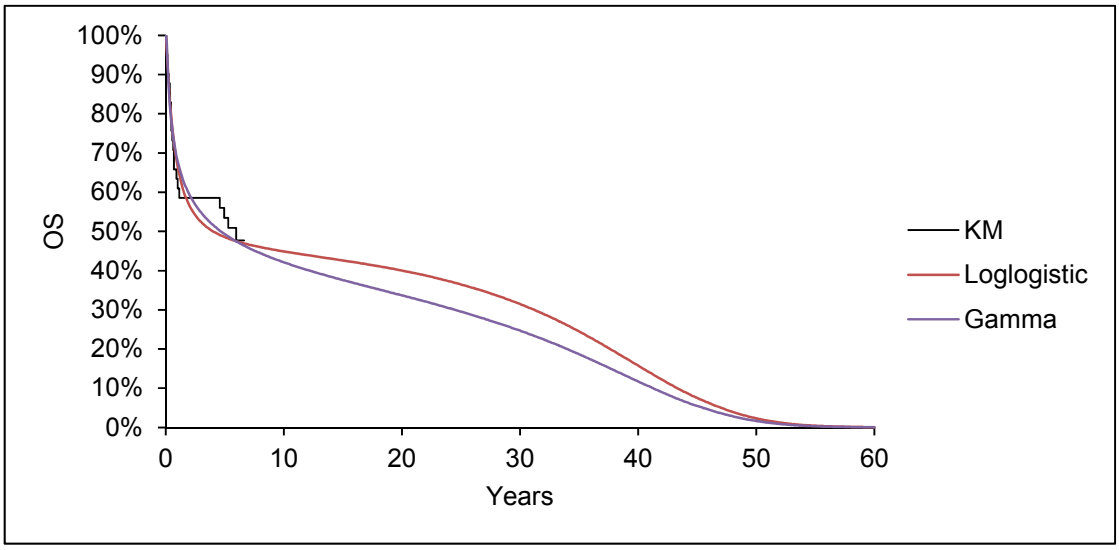



**Figure 12 Comparison of cure (log-logistic) and standard (gamma) models for brentuximab vedotin (No SCT) OS (Source: Figure 5.19, pg 107 of the CS).**

**Chemotherapy (No SCT)**

*Trial based data*

Due to the study design, self-control data from SG035-0004 could not be used to estimate OS in the chemotherapy arm. Therefore, Kaplan Meier curves from Mak et al. were digitised to estimate the overall survival probability at each time point for the chemotherapy comparator. Both subgroups (i.e. ALCL, N=17 and PTCL, PS<2, N=47) were considered. A published algorithm was used to estimate individual patient data, generating a time to event for each patient based on the number at risk at time =0. The ERG are satisfied that the approach to obtain data from Mak et al is appropriate.[72]

The company chose not to use the ALCL subgroup as they generated implausible results when used alongside the self-controls used to model PFS (i.e. OS<PFS to 5.5 months). Therefore, for the base case analysis, the company used data from the subgroup of patients from Mak et al. with PTCL and performance status <2 (N=47). This approach also attempts to account for potential bias introduced through differences in performance status between patients in SG035-0004 and those reported by Mak et al.[72]

Whilst the approach seems reasonable, the mis-match between OS for the ALCL subgroup from Mak et al[72] and the self-control progression data from SG035-0004, further re-enforces the ERGs concern that using two alternative data sources for PFS and OS was inappropriate. The ERG would have preferred the Mak et al data to be used for both PFS and OS to avoid such issues. Ideally, given that clinical expert opinion is that ALCL data are preferable, the company could have considered modelling both PFS and OS on the ALCL cohort from Mak et al.[72] This would have addressed the issues of inconsistency that the company correctly acknowledges in their submission. The ERG further noted at clarification stage that the previous model of brentuximab vedotin versus chemotherapy reported by Hux et al., used individual data on 40 patients with sALCL from the Canadian BC Cancer registry who had received salvage therapy between 1980 and 2012.[81, 83] Given the company's involvement in this prior study, the ERG questioned why this source of data was not considered for modelling of PFS and OS in the current submission. The company noted that the Mak et al.[72] data was used because this decision was in line with NICE

guidance which states that "…*estimates of treatment effect should be based on the results of systematic review*". It should also be noted that the cohort used by Hux et al. comes from the same source as the data reported by Mak et al.,[72] and the company were asked to comment on the overlap between these cohorts. However, they noted that they had insufficient time to ascertain this. Whilst the data used by Hux et al[81, 83]. may provide a larger group of comparable ALCL patients, the Kaplan Maier curves for this cohort are strikingly similar to those considered in the current analysis based Mak et al.[72] (suggesting there is likely a high degree of overlap between the cohorts).

Figure 13 presents KM curves for chemotherapy OS by the two subgroups from Mak el al for comparison.[72]

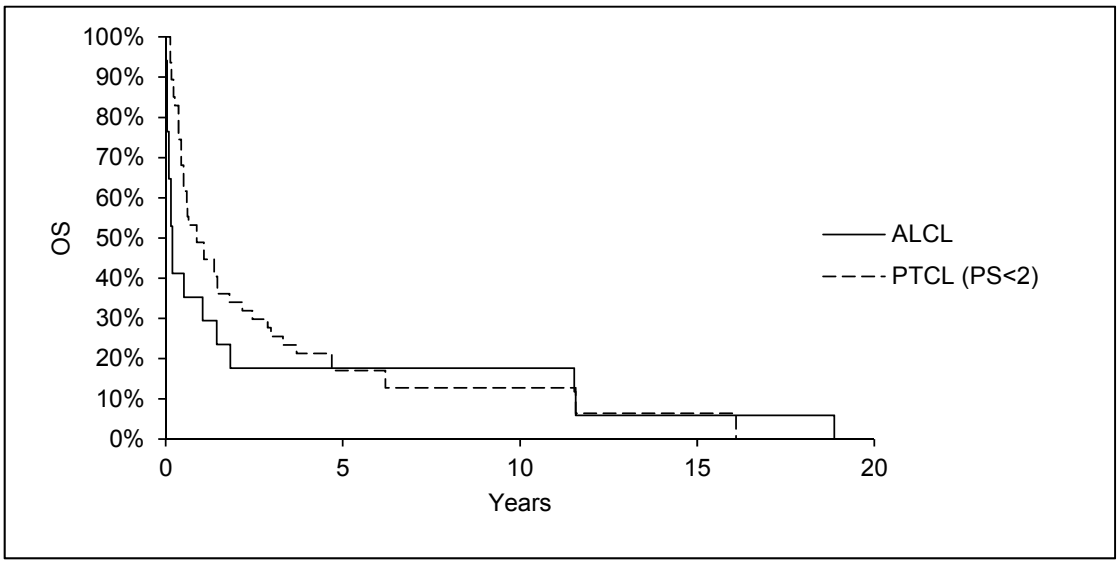



**Figure 13 KM curves for ALCL and PTCL < 2 for Chemotherapy OS, (Source; company submission Fig 5.20; Pg. 107)**

*Extrapolation*

Extrapolation models were reported in the CS for the preferred PTCL, PS< 2 subgroup from Mak et al.[72] The ERG deemed the process adopted to choosing a parametric distribution for OS followed best practice, in terms of selecting the lowest AIC / BIC, resulting in log normal and gamma distributions being preferred (*See Table 5.18 in the CS*). However, the ERG notes substantial differences in the number of years at which 99% of the modelled cohort have died, ranging from 13.8 years for an exponential model, to 49.3 years in a log logistic model. For gamma and gompertz

models, 99% had not reached this endpoint by 60 years. Despite a gamma model providing the preferred AIC score, the base case analysis applies the next preferred log-normal model as it had the preferred BIC score, and the company felt it provided better face validity. Due to a lack of functionality in the model, it was not possible for the ERG to replicate all the OS models considered in the CS. There are substantial uncertainties driven by the long tail on the KM curve for OS. The OS models explored by the company are illustrated in Figure 14.

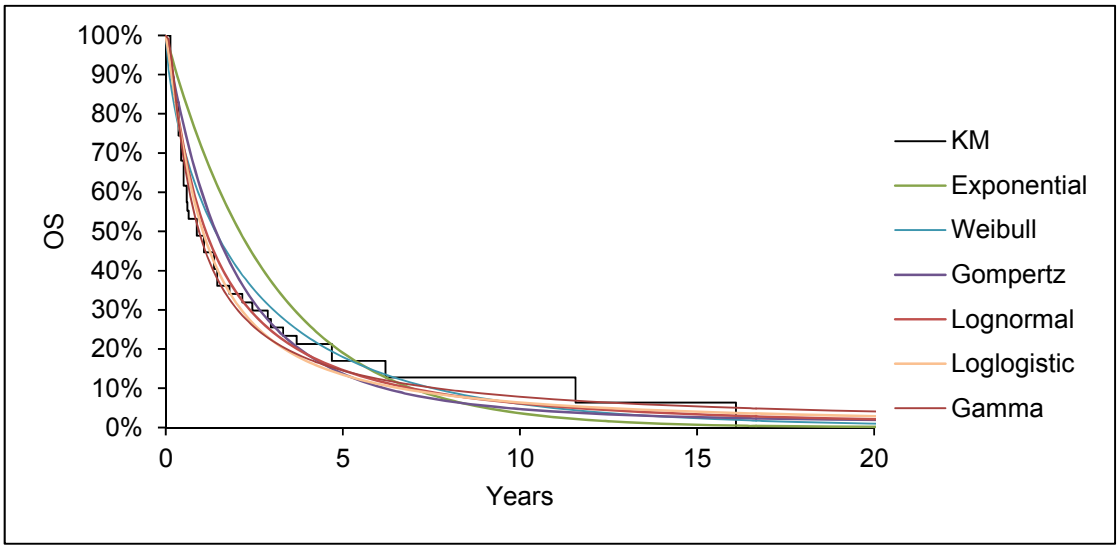



**Figure 14 Parametric models for chemotherapy, OS (No SCT) (Source: Figure 5.21, pg 109 of the CS)**

*Comparison of OS for brentuximab vedotin and chemotherapy (No SCT cohorts)*

As with the analysis of PFS, the ERG consider that the use of standard parametric models for chemotherapy, compared with cure models for brentuximab vedotin, may generate a bias in favour of brentuximab vedotin for OS. The company explored the use of cure models for OS in response to clarification queries and stated that the models based on data from Mak et al would not converge, and hence could not be explored.[72] The ERG therefore consider a scenario analysis where OS for both brentuximab vedotin and chemotherapy are modelled according to standard models to offer a plausible (though more conservative) estimate of the difference in overall survival between the arms. Figure 15 below illustrates the survival curves and the impact on the ICER is reported in Section 5.3.

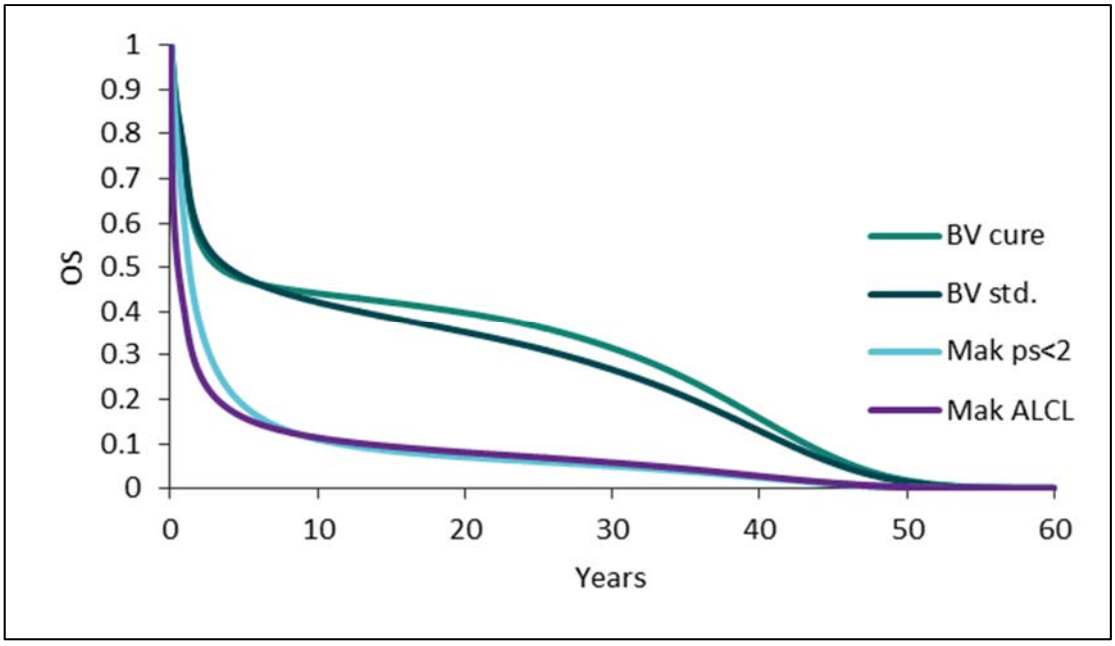



**Figure 15 OS models for brentuximab vedotin (cure and standard models) and alternative Mak cohorts. (Source: Adapted from CS electronic model, response to clarification version)**

*5.2.6.4. Stem cell transplants:*

**PFS and OS**

PFS and OS were modelled in a similar manner for both ASCT and Allo SCT. Sources of survival data were identified from the systematic literature review (*See Section 4.1*). Briefly, 4 studies were retrieved for ASCT and 2 retrieved for allo-SCT. For both cases, Smith et al (2013) was chosen as the preferred study as it had the greatest sample size and the KM curves excluded those who were transplanted in the frontline setting[73]. The ERG agrees with the choice of data used and notes that KM data were reconstructed using accepted methods.

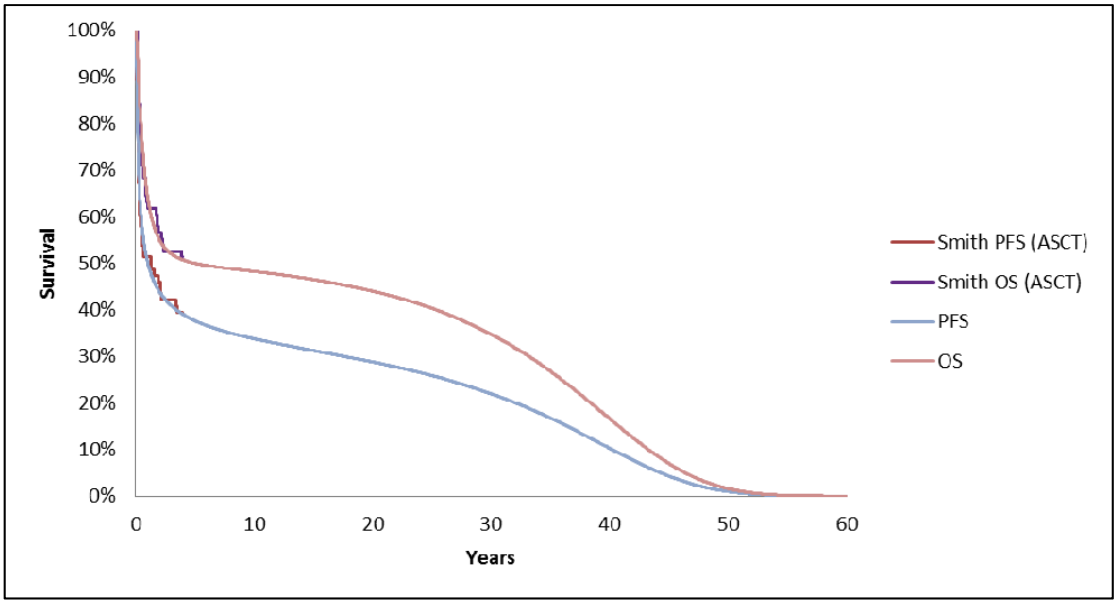
Mixture cure models were fitted in a similar manner to that adopted for the brentuximab vedotin, no SCT cohort. Selection of parametric survival distributions used the same approach based primarily on an assessment of AIC / BIC criteria and visual inspection of the parametric and KM curves.

*ASCT*

PFS and OS data for ASCT were both modelled using the subgroup of N=115 patients who received ASCT in Smith et al.[73]

- The ASCT cure fraction ranged from 26% (Gamma) to 39% (Weibull and log-normal). The base case analysis for PFS used a gamma parametric survival model as it had the lowest AIC (Table. 5.15 and Figure 5.12 of the CS). The ERG considers the choice of model to be appropriate, but notes the variation in the cure fraction depending on the model selected. A log-normal model was considered in sensitivity analysis.
- The base case analysis for OS used a log normal parametric survival model on the basis of it having the lowest BIC. The ERG notes however, that a gamma model had the preferred AIC score and a substantially lower cure fraction (50% for Log-Normal vs. 38% for Gamma) and could also have been a suitable model (see Table 5.19 of the CS). The company explored a gamma model in sensitivity analysis.

The ERG considers the approach taken by the company to be appropriate, however cautions that it was not possible to assess the cost-effectiveness impact of all explored analyses due to a lack of model functionality. The ERG draws attention to the substantially different cure fractions depending on the selected model. The company's base case KM and survival models are presented in Figure 16 for OS and PFS.




Key: ASCT: ASCT, autologous stem cell transplant; KM: Kaplan Meier; OS: Overall survival; PFS: Progression free survival.

**Data reproduced from KM curves in the company's electronic model, response to clarification version*

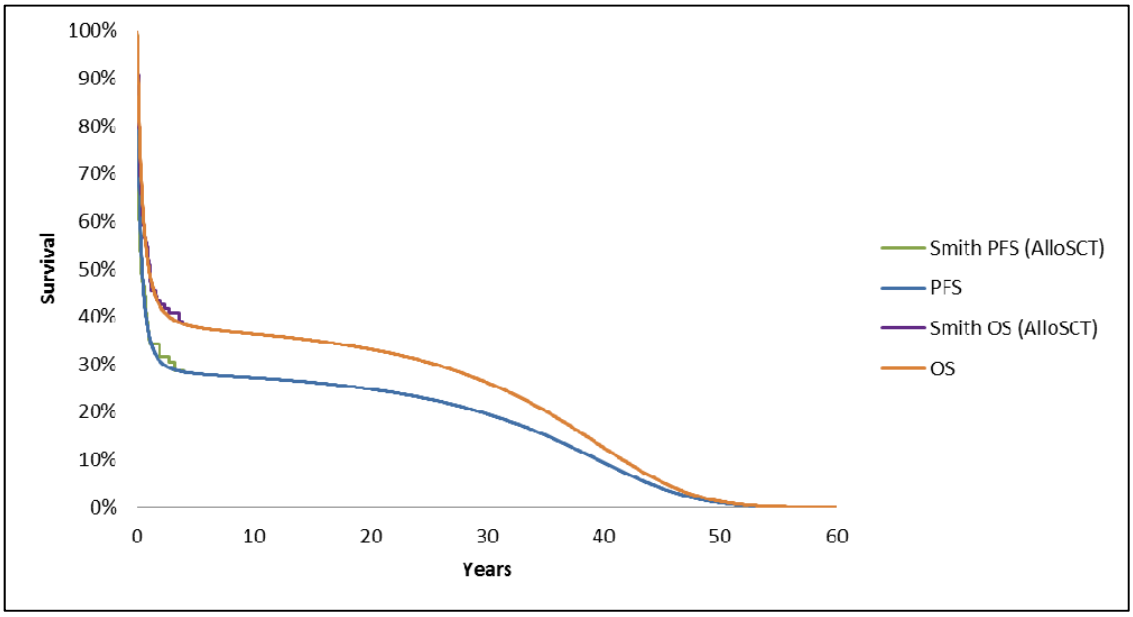
**Figure 16 KM curves and extrapolation of OS and PFS data for ASCT**

*Allo-SCT*

The approach taken for allo-SCT also used data from Smith et al (Subgroup receiving AlloSCT, N=126 patients), for both PFS and OS, and used similar methods to ASCT.[73]

- For PFS, estimated cure fractions were lower compared to ASCT (as expected), but similar across the three different parametric models explored – Weibull, Log Normal and Gamma (See Table 5.16 of the CS). The company have not justified why other models (e.g. log logistic) were not explored. Only gamma and log normal parametric cure models were incorporated within the company's model. The base case used a log-normal model (lowest AIC / BIC), which the ERG considers appropriate. Sensitivity analysis considered a gamma model.
- For OS, three functions were considered - Weibull, Log Normal and Gamma, (see Table 5.20 in the CS) - though only the latter two were incorporated in the company model. Log normal was preferred on the basis of having the lowest AIC / BIC score, though the ERG note that the AICs were similar for all models as were the associated cure fractions (36% - 39%). The ERG considers this approach

to be appropriate. The ERG noted an error in the company's submission whereby Figure 5.23 (OS for ASCT) and Figure 5.25 (OS for allo-SCT) were identical. By tracing back to the company model, it appears as if Figure 5.25 in the CS is incorrect. In the interests of clarity and to avoid confusion, the ERG presents the KM curves and modelled survival curves for both OS and PFS applied to allo-SCT using the correct data from within the company's model in Figure 17 below.




Key: AlloSCT: allogeneic stem cell transplant; KM: Kaplan Meier; OS: Overall survival; PFS: Progression free survival.

**Note that this figure corrects an error in the CS (Figure 5.25).*

***Data reproduced from KM curves in the company's electronic model, response to clarification version*

**Figure 17 KM curves and extrapolation of OS and PFS data for allo-SCT**

In general, the ERG is less concerned with the approach taken to model PFS for SCT treatments, given that the models were applied similarly across the brentuximab vedotin and chemotherapy arms, varying only in terms of the proportion entering each cohort. Equally, the assumption of cure appears justified in SCT therapy, given that the ultimate aim of treatment is to progress patients to a curative SCT, a key hypothesised advantage of brentuximab vedotin treatment.

*5.2.6.5. General population mortality & Excess mortality risk*

The company stated that, for all analyses, general population mortality, based on UK life tables was applied as a competing risk for both PFS and OS, incorporated directly (rather than parametrically) in the model. The excess applied mortality did not depend on the estimated cure fraction in the model or the type of extrapolation model used (i.e. cure or standard). Excess mortality was applied to all data with the exception of those sourced directly from KM curves. The excess mortality risks were applied to ensure clinical plausibility (keeping mortality higher than the general population) for the full duration of the model.

The company added excess mortality risks (5% brentuximab vedotin, 7% chemotherapy, 10% SCT) to reflect the remaining risk of secondary malignancies due to residual effects of therapy, even among those who have long term remission. Risks were based on the expert opinion of one single clinical expert in the base case model. Whilst the ERG's clinical advice confirms that applying an excess mortality risk is appropriate, the ERG are concerned about the values chosen. In particularl, there appears little evidence to support the assumption that long term excess mortality for brentuximab vedotin should be less than for chemotherapy. The company have not provided alternative estimates, or variation in opinion sought from their clinical experts. In light of the uncertainty the ERG has undertaken a number of additional sensitivity analyses, exploring alternative assumptions, including equating the mortality risks, and assuming a higher mortality risk applied to all patients *(See Section 5.3).*

Furthermore, the ERG notes that excess mortality risks are applied to both OS and PFS in the brentuximab vedotin arm. However, the company does not appear to have applied the excess mortality to chemotherapy PFS in the model. This omission only has a minor impact on the ICER and creates a minor bias against brentuximab vedotin in terms of modelling PFS.

### 5.2.7 Health related quality of life

This section discusses the approach taken by the company to incorporate health related quality of life into the economic model. We summarise the company's systematic review and provide a critique. It should be noted that no health related

QoL data were collected within SG035-0004, hence a systematic literature review was used to obtain utilities for the model.

*Systematic literature review of health related quality of life*

Separate searches were undertaken for the measurement and valuation of health effects and are replicated in full in Appendix 11. MEDLINE and EMBASE were searched in November 2016 for English language publications without date restrictions. The MEDLINE and EMBASE strategies appropriately combined two facets: anaplastic large cell lymphoma and quality of life or utilities terms. For both databases, the search strategies for the quality of life/utilities facet comprised only a limited list of text word terms which may have limit the sensitivity of the searches. The searches may have benefited by the addition of text terms such as *quality adjusted life, standard gamble* and *time trade off* and thesaurus terms *Quality adjusted life years/* (for both databases) and *Value of life/* (MEDLINE).

The systematic review of literature pertaining to HRQoL, including a PRISMA flowchart, is outlined in Section 5.4.3.1 (Figure 5.26, page 117) of the company submission. Two articles were retrieved and one study was identified meeting all the inclusion criteria.[89] The reason for exclusion of the second study was *"an irrelevant study design"*. No further details were provided. Therefore, without detailed information on reasons for exclusions, or references for excluded studies, the ERG were not able to formally critique the appropriateness of the company's exclusion process. However, given the known lack of available data in this disease area, it is likely that the company have included the only appropriate and relevant study for sALCL health states.

*Modelled utilities for the "No SCT" cohorts*

**Base case data**

The single included study [89] reported utility values for both relapsing / remitting Hodgkins Lymphoma (R/R HL) and systemic Analplastic Large Cell Lymphoma (sALCL). The study captured health state utility values for Complete Response, Partial Response, Progressive Disease and Stable Disease, together with selected adverse events. The study was designed and conducted by ICON patient reported outcomes on behalf of Takeda Pharmaceuticals International Co. Therefore, the

utilities collected match directly with the responses included in the economic modelling. Utilities were obtained by using health state vignettes valued using the TTO approach among the general population for N=601 respondents in 7 countries (Mexico, Brazil, South Korea, Taiwan, Thailand, Australia and the UK). UK data (N=100) were used in the base case model, which the ERG considers appropriate.

The ERG has reviewed the Swinburn et al study, [89]which suggests that the vignettes were developed in a manner consistent with the EQ-5D descriptive system. The ERG disagrees with this assumption and feels that the health state vignettes are not directly reflective of the EQ-5D dimensions and levels. Furthermore, it is unclear how accurately the vignettes reflect the health state of the average patient by clinical response status. The ERG also note NICE DSU's recommendations[90] on the use of vignette studies that:

> "*Vignettes not based on standardized and validated measures of HRQL and patient own health state valuations do not meet the NICE Methods Guidance and have a limited role. These methods should only be used where there are no other data based on validated HRQL measures*" [90]

The ERG notes that the language presented in the vignettes is condition specific (for example: *"You have a number of lumps in your body that are increasing in size…")* and emotionally charged (e.g……*"You have a life threatening illness"*). For example, the descriptors provided for the progressive disease vignette include things like fever, night sweats, appetite and "severe" weight loss. The ERG considers that such condition-specific and emotionally charged language would not generally be present in EQ-5D descriptors.

Despite these concerns, due to the paucity of available evidence, the choice of Swinburn et al may be justifiable.[89] However, the ERG notes that the company could have considered alternative, but similar disease areas in which EQ-5D data may exist. Furthermore, the data as applied in the economic model are based on pooled values for both R/R HL and R/R sALCL. The ERG questions the clinical plausibility of combining HL with NHL data.

**Alternative sources of utility data**

The ERGs clinical expert has indicated that quality of life among patients with all relapsing or remitting aggressive forms of NHL could be broadly reflective of the QoL experienced among patients with R/R sALCL. The ERG thus conducted a further structured, but targeted and rapid search of MEDLINE and EMBASE, broadening the inclusion criteria to NHL. The search was undertaken on March 14th 2017 and is reproduced in Appendix 1. Four potentially relevant studies were identified which included utilities for aggressive NHL. Studies measuring utilities in indolent forms (such as follicular lymphoma) were excluded. Three of the four studies were excluded as they were either in the form of a conference abstract ,[91] or had insufficient information to derive generic (EQ-5D or SF-6D based) utility weights for the model.[92, 93] One study was included. Doorduijn et al[94] reported EQ-5D data in a Dutch / Belgian population, aged 65 and over, with a newly diagnosed aggressive NHL with stages II, III or IV disease and a left ventricular ejection fraction ≥45%. Data from this study have also been applied in the NICE appraisal of Bortezomib for previously untreated mantle cell lymphoma[95] and include data on utility of progression free and progressed disease after both a first and second line of therapy. Data following a second line of therapy are used for the ERG's exploratory analysis. NICE guideline NG52 for Non-Hodgkin's lymphoma: diagnosis and management was considered as a source by the ERG,[96] but excluded as the relevant data referred to follicular lymphoma, and as such is not representative of aggressive NHL.

The company's base case model and the alternatively explored utility values from TA370 are presented in Table 18.

**Table 18 Utility values for model states**

| | Company submission<br><br>Utilities based on Swinburn et al[89] UK subgroup (N=100) | | ERG exploratory analysis<br><br>Utilities based on Doorduijn et al., as used in TA370[94] | |
|---|---|---|---|---|
| **State** | **Mean** | **Decrement **** | **Mean** | **Decrement **** |
| **Base** | 0.95* | N/A | 0.802* | N/A |
| **CR** | 0.91 | 0.05 | 0.764 | 0.04 |
| **PR** | 0.79 | 0.16 | 0.764 | 0.04 |
| **SD** | 0.71 | 0.24 | 0.764 | 0.04 |
| **PD** | 0.38 | 0.57 | 0.450*** | 0.35 |

Key: N/A: Not Applicable.

Notes:

*The base value in the CS was inflated to account for an additional 5% utility decrement for CR over the general population. All decrements were applied to the base value. The ERG's use of Doorduijn follows a similar approach to maintain consistency with the company approach.

**Decrement as per implementation within the CS model, changing only mean values in the model; Decrements calculated relative to a complete response + 5%.

***Progressed from 2nd line treatment. Derived from Doorduijn et al as: {[aaPI 0-1 Baseline (0.74) + progression (-0.24)] + [aaPI 2-3 Baseline (0.44) + progression (-0.04)]} / 2 = 0.45.

The ERG notes that there are a number of limitations associated with both Swinburn et al[89] (CS base case) and Doorduijn et al. (ERG exploration).[94] The limitations in the CS include: 1) Using disease specific vignettes that are not directly reflective of EQ-5D; and 2) Combining data on R/R HL and sALCL. The limitations of the ERG identified EQ-5D data are: 1) the data are based on an older age group; 2) the use of Dutch / Belgian as opposed to UK data; and 3) the assumption that utility depends only on progression status, rather than on clinical response. The impact of the alternative data sources on the ICER is reported in Section 5.3.

**Incorporation of utilities in the economic model**

As Swinburn et al[89] reported utility according to clinical response (CR, PR, SD) for PFS, the modelled PFS utility is treatment cohort specific. Response rates sourced from the SG035-0004 study (for brentuximab vedotin, and self-control data for

chemotherapy) were rescaled (removing progressive disease) to weight utility in the PFS state.

Patients achieving a CR were assigned the utility of 0.91, based on the general population norm for mean age 38 from Swinburn et al. [89] To reflect a decrement of utility for CR vs. general population, a further 5% decrement was applied. The base utility was therefore 0.95. The ERG are concerned that a 5% decrement may not be sufficient to capture the health state of patients obtaining a CR, as they recover from cancer, in the short term in particular.

Patients who do not progress by an assumed cure time point (5 years in the base case analysis) are assumed to follow age adjusted population norm utilities, with the same additional 5% decrement applied based on clinical expert opinion. Patients experiencing progressive disease were assumed to receive the appropriate decrement from Swinburn et al.[89] The ERG are concerned that by assuming a cured time point of 5 years in the brentuximab vedotin arm but not the chemotherapy arm, the model assigns different utility decrements to longer term survivors across the different cohorts. This creates a scenario which biases against chemotherapy survivors. The impact of removing the cured time point (setting this parameter to 100 years in the model, allowing long term utility to follow a similar trajectory for all long term progression-free survivors) and varying the general population decrement on the ICER is explored in Section 5.3.

In general, the ERG found that the CS lacked clarity on assumptions, calculations or methods of implementing utility data within the model. The ERG's understanding of the modelling approach is that the decrements from Table 18 are subtracted from the age and gender specific population EQ-5D norms,[97] which change over time in the economic model. The ERG notes that it may be inappropriate to apply decrements from a vignette study to EQ-5D based norms, noting the different methodologies may add uncertainty. The ERG considers using an indexed multiplicative approach, rather than an additive utility model would have been preferable, but note also that there is limited empirical evidence to validate either approach. The ERG have explored the impact of using a multiplicative approach based on multiplying the respective utilities by an age adjustment index based on population norms (rather than applying a constant utility decrement to age adjusted population norms) in the model. Whilst not

fully in line with DSU recommendations, this approach serves to illustrate the uncertainty associated with using a multiplicative rather than an additive utility model.

*Modelled utilities for the SCT cohorts*

Utilities applied in the SCT cohorts depended on: 1) the type of SCT, with greater decrements applied to allo-SCT than ASCT; and 2) the time elapsed since commencement of treatment.

**Time from brentuximab vedotin or chemotherapy to SCT**

Time from commencement of salvage treatment to SCT was based on data from SG035-0004, assuming 29.7 weeks and 49.7 weeks for ASCT and allo-SCT respectively. The approach to modelling utilities in this time period was equivalent to that taken for the 'no SCT' cohorts. Response specific utilities[89] were multiplied by the appropriate response rates (weighted to remove progressive disease) for each salvage therapy prior to SCT *(See* Table 19).

**Table 19 Weighted response rates and utilities for salvage therapy prior to SCT for PFS state**

| **Response** | **Brentuximab Rates** *Source: SG035-0004* | | **Chemotherapy Rates** *Source: Smith et al.* | | **Utility applied** *Source: Swinburn et al.* | |
|---|---|---|---|---|---|---|
| | **ASCT** | **allo-SCT** | **ASCT** | **allo-SCT** | **Mean** | **Decrement** |
| **Base** | | | | | **0.95** | **N/A** |
| CR | 100% | 89% | 52% | 40% | 0.91 | -0.05 |
| PR | 0% | 11% | 37% | 42% | 0.79 | -0.16 |
| SD | 0% | 0% | 11% | 18% | 0.71 | -0.24 |

ASCT, autologous stem cell transplant; allo-SCT, allogeneic stem cell transplant CR, complete response; N/A: Not Applicable; PR, partial response; SD, stable disease

**Time from SCT to progression or cure**

Utility decrements from the general population norms in the PFS state post-SCT were assumed to be greater than in the 'No SCT' cohorts. The decrements were applied as the average of 4 clinical expert's opinions, as follows:

- 0-6 months post SCT**:** Decrements for CR vs. general population were 32% (ASCT) and 50% (allo-SCT)

- 6 months to cure point: Decrements for CR vs. general population were 10% (ASCT) and 28% (allo-SCT).

For complete response these decrements were applied multiplicatively to the base value of 0.95 (i.e. Swinburn et al CR,[89] adjusted to reflect 5% decrement from general population). For progressive disease, the additional decrements were applied to the Swinburn et al reported value for progressive disease (0.38). [89] As utility decrements in the model were subtracted from age adjusted general population norms, the approach lead to negative utility for progressive disease, particularly in allo-SCT among older patients. The company therefore applied a correction in the model to ensure that utility was bounded at 0. However, the ERG note that if the company implemented a multiplicative model, this would reduce the absolute reduction in health state utility associated with progressive disease, particularly over the longer-term as the cohort ages.

Utilities for PR and SD were derived as follows: [calculated CR utility for SCT]-[the difference between PR or SD and CR observed in Swinburn et al]. This approach maintained the difference between response categories observed in Swinburn et al.[89] The utilities for SCT and their associated decrements as applied in the model are outlined in Table 20.

**Table 20 Utilities post-SCT (Source: Table 5.32, pg127 of the CS)**

| SCT type | Response | 0-6 months post SCT | | 6 months post SCT to cure point | |
|---|---|---|---|---|---|
| | | **Mean** | **Decrement** | **Mean** | **Decrement** |
| Base | | **0.95** | **N/A** | **0.95** | **N/A** |
| ASCT | CR | 0.65 | 0.30 | 0.86 | 0.10 |
| | PR | 0.54 | 0.41 | 0.74 | 0.21 |
| | SD | 0.45 | 0.50 | 0.66 | 0.29 |
| | PD | 0.26 | 0.69 | 0.34 | 0.61 |
| Allo-SCT | CR | 0.48 | 0.48 | 0.68 | 0.27 |
| | PR | 0.36 | 0.59 | 0.57 | 0.38 |
| | SD | 0.28 | 0.67 | 0.49 | 0.47 |
| | PD | 0.19 | 0.76 | 0.27 | 0.68 |

Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; CR: complete response; N/A: not applicable; PR: partial response; PD: progressive disease; SD: stable disease.

**Time from cure to death**

Utility in the PFS state after the cured time point reverts to the general population norms with a 5% excess utility decrement applied, as in the No SCT cohorts. The cure-time point was adjusted to reflect the time from salvage therapy to SCT. Beyond 60 months post-SCT, the utility for PD was calculated as the PD decrement from Swinburn et al, subtracted from age adjusted population norms.[89] Table 21 and Figure 18 help to illustrate the approach taken to modelling utility in the SCT cohort for a hypothetical patient achieving PR following salvage and then ultimately achieving CR following allo SCT.

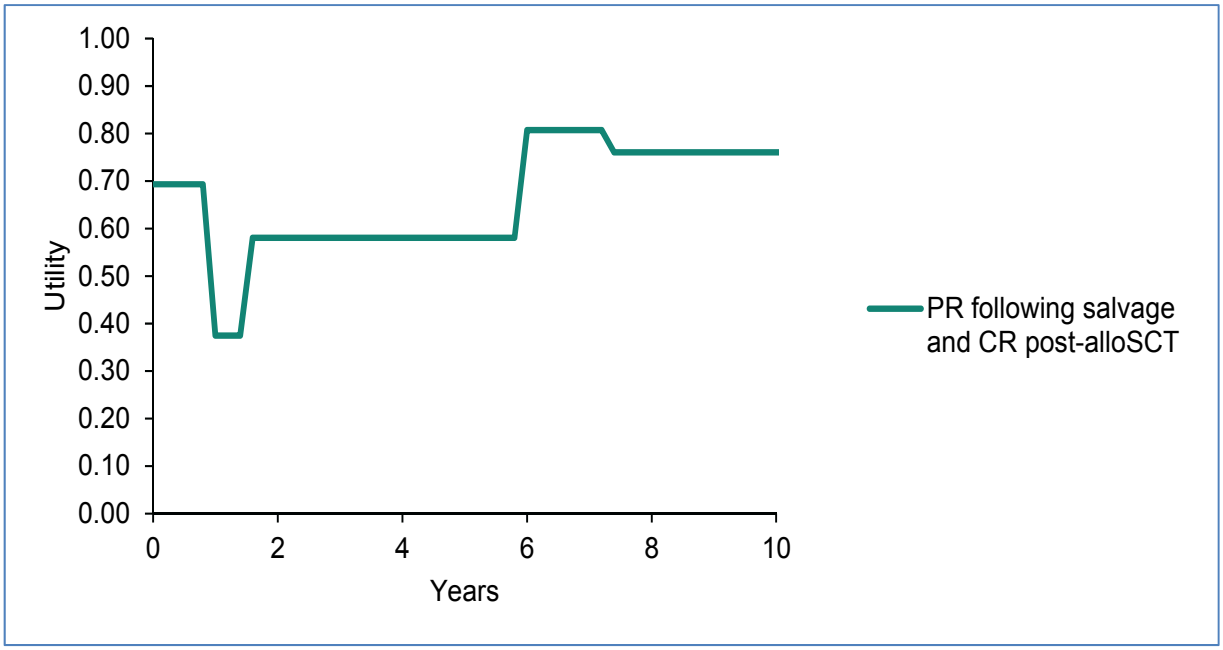
**Table 21 Description of utility profile for a hypothetical patient (Adapted by ERG from CS Table 5.34; pg129)**

| Interval (years) | Description of interval | Description of utility | Utility value | Calculation by ERG:** |
|---|---|---|---|---|
| 0.00-0.92 | Partial response to salvage therapy until allo-SCT | Age-adjusted population norm incorporating the decrement for PR | 0.70 | =0.85 (gen pop norm) – 0.16 (Swinburn decrement PR) = 0.69 |
| 0.92-1.42 | First 6 months post-allo-SCT | The decrease at the start of this interval reflects the impact of the patient undergoing allo-SCT | 0.37 | =0.85 (gen pop norm) – 0.48 (Swinburn pop norm: 0.95*50% decrement for CR to allo sct in months 0-6) = 0.37 |
| 1.42-5.92 | 6-60 months post-allo-SCT | The increase at the start of this interval reflects clinical expert opinion that the decrement associated with allo-SCT for a patient in CR compared to age-adjusted population norm will reduce from 50% to 28% | 0.58 | =0.85 (gen pop norm) – 0.27 (Swinburn pop norm: 0.95*28% decrement for CR to allo sct in months 6-60) = 0.58 |
| 5.92-death | Cure until death | The increase at the start of this interval reflects the patient being considered cured after remaining progression-free for 5 years post-allo-SCT. Utility will follow the trajectory of the population norm with a 5% decrement thereafter | 0.80, 0.75 | =0.85 (gen pop age adj norm)– 0.05 (decrement for CR over general popupation in Swinburn et al) = 0.80<br><br>0.80 (gen pop age adj norm, reflecting ageing) – 0.05 (decrement over gen pop) = 0.75 |

Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; CR: complete response; N/A: not applicable; PR: partial response; PD: progressive disease; SD: stable disease.

**Assumes that the CS example is based on start age of 48 in the model.*

***Differences of less than 0.1 are due to rounding.*




Key: allo-SCT: allogeneic stem cell transplant; CR: complete response; PR: partial response

**Figure 18 Utility plot for hypothetical patient described in Table 12 (Source: CS Figure 5.27; pg129)**

Whilst the approach to incorporating utility in the SCT cohorts is difficult to follow from the CS, the ERG are satisfied that the described approach has been appropriately incorporated within the economic model. However, as noted, the application of a multiplicative model would likely have addressed some of the issues the company faced with utilities.

*Adverse event dis-utilities*

QALY decrements for AE (grade 1-2 [≥10%] and 3-4 [≥5%]) were based on estimated durations of events, proportion of patients experiencing the event in each cohort and the associated utility decrement for each event. Utility decrements were based on the Swinburn et al[89] for peripheral sensory neuropathy and other published literature on solid tumors and previous NICE STAs for the remaining adverse events. The approach conducted by the company seems reasonable, though many of the adverse event durations seem short. Table 22 outlines the assumed event durations and utility decrements applied for each AE in the economic model.

**Table 22 Adverse event duration and utility decrement by treatment**

| Grade | Event | BV (No SCT) | BV (SCT) | ICE | ESHAP | DHAP | GDP | Gem-P | Gem. | Allo SCT | Duration (Days) | Utility dec. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | |
| 1-2 | Alopecia | 10% | 12% | 0% | 0% | 0% | 45% | 0% | 0% | 0% | 183 | 0.114 |
| | Constipation | 12% | 12% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 6 | 0.103 |
| | Diarrhoea | 12% | 29% | 11% | 0% | 0% | 0% | 0% | 0% | 0% | 6 | 0.103 |
| | Fatigue | 22% | 24% | 0% | 0% | 0% | 50% | 0% | 0% | 0% | 31.5 | 0.115 |
| | Myalgia | 12% | 24% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 31.5 | 0.069 |
| | Nausea | 32% | 12% | 29% | 49% | 0% | 90% | 0% | 0% | 0% | 6 | 0.103 |
| | Neutropenia | 0% | 0% | 25% | 0% | 0% | 55% | 0% | 38% | 0% | 15.1 | 0.09 |
| | Peripheral sensory neuropathy | 32% | 59% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 3 | 0.1 |
| | Pyrexia | 12% | 6% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 12.3 | 0.03 |
| | Rash | 12% | 6% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 6 | 0.03 |
| | Thrombocytopenia | 7% | 24% | 32% | 0% | 0% | 10% | 0% | 46% | 0% | 23.2 | 0.273 |
| | Upper respiratory tract infection | 15% | 12% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 15.1 | 0.2 |
| | Vomiting | 15% | 12% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 6 | 0.103 |
| | Anaemia | 0% | 0% | 64% | 0% | 0% | 50% | 0% | 0% | 0% | 16.1 | 0.09 |
| | Petechiae | 0% | 0% | 0% | 0% | 0% | 10% | 0% | 0% | 0% | 0 | 0 |
| | Liver transferase elevation | 0% | 0% | 0% | 0% | 0% | 15% | 0% | 36% | 0% | 0 | 0 |
| | Leukocytopenia | 0% | 0% | 14% | 0% | 0% | 0% | 0% | 0% | 0% | 15.1 | 0.09 |
| 3-4 | Diarrhoea | 0% | 0% | 0% | 0% | 20% | 0% | 0% | 0% | 0% | 6 | 0.103 |
| | Neutropenia | 15% | 24% | 0% | 30% | 53% | 35% | 63% | 0% | 0% | 15.1 | 0.09 |
| | Peripheral sensory neuropathy | 10% | 18% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 3 | 0.331 |
| | Thrombocytopenia | 7% | 24% | 54% | 0% | 39% | 15% | 0% | 0% | 0% | 23.2 | 0.273 |
| | Tumour lysis syndrome | 0% | 0% | 0% | 0% | 6% | 0% | 0% | 0% | 0% | 31.5 | 0.115 |
| | Nausea | 0% | 0% | 0% | 6% | 0% | 5% | 0% | 0% | 0% | 6 | 0.103 |
| | Increased creatinine levels | 0% | 0% | 0% | 22% | 20% | 0% | 0% | 0% | 0% | 0 | 0 |
| | Respiratory failure | 0% | 0% | 0% | 0% | 7% | 0% | 0% | 0% | 0% | 15.1 | 0.09 |
| | Sepsis | 0% | 0% | 0% | 0% | 31% | 0% | 0% | 0% | 0% | 23.2 | 0.2 |
| | aGVHD | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 19% | 14 | 0.51 |
| | Pulmonary infection | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 11% | 15.1 | 0.2 |
| | Anaemia | 0% | 0% | 21% | 0% | 0% | 0% | 13% | 0% | 0% | 16.1 | 0.09 |
| | Leukopenia | 0% | 0% | 75% | 0% | 0% | 0% | 63% | 0% | 0% | 15.1 | 0.09 |
| **Total QALY decrement by treatment** | | **0.015** | **0.023** | **0.023** | **0.002** | **0.014** | **0.042** | **0.005** | **NR** | **0.005** | | |

Key: aGVHD: acute graft vs. host disease; Dec.: Decrement; NR: not reported; QALY: quality adjusted life year

The ERG makes a number of observations on how adverse event disutility has been incorporated into the economic model, as follows:

- In the original CS, adverse event QALY decrements were incorrectly incorporated as increments in the deterministic analyses. The company provided an erratum

after clarification stage, with a revised set of clarification stage results together with a revised and corrected economic model. The ERG reviewed the revised model and AE disutility is now correctly incorporated. The ERG notes that given the small magnitude of QALY implications modelled for AEs and the fact that the error applied across all arms of the model, there were no substantial changes to the ICERs.

Additional adverse event disutilities were incorporated for ASCT following brentuximab vedotin. However, no additional adverse event disutility was applied to ASCT following chemotherapy. Furthermore, the adverse event disutility for ASCT following brentuximab vedotin is all front loaded in the first weekly cycle. Given that the AEs of ASCT would not be realized until later in the model trace, this is a potentially inappropriate assumption. The ERG notes that AE disutilities associated with allo SCT following both brentuximab vedotin and chemotherapy have been correctly implemented. Given the small magnitude of AE disutilities applied in the model, the net impact of this assumption is likely to be negligible and has not been considered further. The ERG notes that any minor biases created are likely to act against brentuximab vedotin.

### 5.2.8 Resources and costs

The company carried out a systematic literature review (SLR) in November 2016 to identify relevant costs and resource use studies. The review was combined with the cost-effectiveness review outlined in Section 5.1 (See also appendix 11 of the CS). Inclusion and exclusion criteria were similar and no relevant studies were identified. The ERG is confident that no appropriate costing studies were omitted.

*Drug acquisition costs*

**Brentuximab vedotin**

The drug acquisition cost of brentuximab vedotin is calculated in accordance with its product licence, at a rate of 1.8mg per kg of body weight as a 30-minute infusion every three weeks, until disease progression or unacceptable toxicity. It should be noted that, for patients weighing over 100KG, the maximum allowable dosage per cycle is 180mg. The NHS list price is £2,500 per 50 mg vial. The discount price

offered by the [redacted] (a [redacted] discount). The discounted price was used for all analyses in the original CS.

Per cycle drug costs were based on the average patient from the SG035-0004 study. Average weight (76.35 KG) was multiplied by dosage rate (1.8mg / KG) generating a total drug requirement (137.43mg). Based on a vial size of 50mg, 2.75 vials (3 accounting for the appropriate assumption of drug wastage) are required per patient per treatment cycle. Patients in the no SCT cohort received an average of 8 treatment cycles (range 1 to 16). This translates to a total mean drug cost of [redacted] (range [redacted]). Patients receiving SCT after brentuximab vedotin had on average 8.8 cycles of treatment (total cost: £[redacted]). The ERGs clinical expert noted that, in practice, the average number of cycles of treatment with brentuximab vedotin may be lower (4-6 cycles) than that seen in the trial. After a request for clarification, the company provided additional information on stopping rules, stating that patients typically receive 3-4 cycles of treatment. If CR or PR is not observed after a PET scan, treatment would likely be stopped. The company's expert opinion suggests that if patients respond, they usually do so by cycle 4. The ERG notes that the company provided alternative cost scenarios with stopping rules (by cycle 4) per INV and per IRF response categories (Table 23).

**Table 23 Brentuximab vedotin exposure (Source: Table 31, company response to clarification letter)**

| **Parameter** | **No SCT cohort (*N* = 41)** | | **SCT cohort (*N* = 17)** | |
|---|---|---|---|---|
| | **IRF** | **Investigator** | **IRF** | **Investigator** |
| Number of patients that did not have CR or PR by cycle 4 | 8 | 10 | 1 | 0 |
| Number of patients that did not have CR or PR by cycle 4 and that received more than 4 cycles of brentuximab | 0 | 1 | 1 | 0 |
| Number of cycles administered beyond cycle 4 to patients that did not have CR or PR by cycle 4 | 0 | 3 | 3 | 0 |
| IRF, independent review facility; CR, complete response; PR, partial response; SCT, stem cell transplant | | | | |

Mean number of cycles and relative dose intensity were recalculated to reflect the stopping rule (*Table 24)*.

**Table 24 Mean cycles and RDI based on cycle 4 stopping rule (Source: Table 32 of the company response to clarification queries)**

| Parameter | No SCT cohort (*N* = 41) | | | | SCT cohort (*N* = 17) | | | |
|---|---|---|---|---|---|---|---|---|
| | IRF | | Investigator | | IRF | | Investigator | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Number of cycles | 7.98 | 5.26 | 7.90 | 5.29 | 8.59 | 3.74 | 8.76 | 3.58 |
| RDI | 94.49 % | 11.18 % | 94.49 % | 11.18 % | 94.59 % | 12.23 % | 94.59 % | 12.23 % |
| SCT, stem cell transplant; SD, standard deviation; RDI, relative dose intensity; IRF, independent review facility | | | | | | | | |

The ERG notes that the mean number of cycles is quite similar to those used in the base case analysis with only a minor reduction in the ICER.

**Chemotherapy**

The mixed chemotherapy regimens and their usage frequency were obtained from UK clinical experts (identifying ICE [25%], ESHAP [25%], DHAP [25%], GDP [12.5%] and Gem-P [12.5%]). The dose, duration of treatment, time on treatment and cost per treatment per week vary between the regimens. The company used a weighted average cost based on the proportion of patients assumed to receive each treatment. The required dosing and time on treatment were based on sources identified in the National Comprehensive Cancer Network (NCCN) guidelines on non-Hodgkin' s lymphomas which are no longer current. Full details can be found in Table 5.40 (pg 134) of the CS. The total undiscounted drug acquisition cost of chemotherapy was [redacted] (no SCT cohort) and [redacted] (SCT cohorts). The ERG notes that chemotherapy drug acquisition costs are substantially lower than for brentuximab vedotin. The ERG's clinical advisor agreed that the costed regimens are reflective of current UK clinical practice, but also noted that treatment with GDP is increasing year on year, and that it is likely to be used more often in the future. It is therefore appropriate that the company have used sensitivity analyses to explore the impact of applying the most (Gem-P) and least (ESHAP) expensive regimen (in terms of drug acquisition costs) to all chemotherapy patients.

In addition, palliative radiotherapy was administered as a one-off outpatient treatment cost to between 5% (base case) and 40% (sensitivity analysis) of chemotherapy patients based on clinical expert opinion. 5% was used for the base case with 40% tested in sensitivity analysis. The model was not sensitive to this parameter.

**ERG observations on drug acquisition costs**

The ERG note that despite brentuximab vedotin being administered in clinical practice once every 3 weeks, modelled costs are applied weekly (1/3 of per cycle cost). The ERG note that this is not consistent with clinical practice. Given that discounting is applied weekly, drug acquisition costs are slightly underestimated. However, given that a similar approach is applied to both brentuximab vedotin and chemotherapy, and in the first year of the model, alternative discounting would only have a very a small impact on the ICER. As it is the more expensive treatment, any biases could be considered to favour brentuximab vedotin.

*Drug administration costs*

Drug administration costs were obtained from the NHS reference costs 2015-2016, determined according to infusion times found within the NCCN and reference costs guidelines. Brentuximab vedotin was costed as an outpatient treatment [redacted] per 3-week treatment cycle). The total administration cost for 8 treatment cycles is [redacted] over 24 weeks, or [redacted] per week. The administration cost was higher for chemotherapy [redacted] over the 24 week period, or [redacted] per week). This is because, for chemotherapy, only GDP and Gem-P were costed as outpatient treatments, with all other chemotherapies assumed to require a day case admission. The ERGs clinical expert considers the administration resource use and setting adopted by the company for the different treatments to be consistent with clinical practice.

*Concomitant medications*

Brentuximab vedotin was considered a low anti-emesis risk treatment, and as such only dexamethasone (12mg daily dose) was applied as concomitant therapy. The total cost per treatment cycle was £4.68 (£1.56 per week, £37 over 24 weeks).

The relevant concomitant medications commonly given to chemotherapy patients were identified by clinical experts using regimens based on NCCN and NHS

guidelines. Concomitant medications were dependent on anti-emesis risk. Table 5.43 to 5.46 of the CS provide further details of costing methods. The average weekly cost of concomitant medication (weighted according to the assumed proportions receiving each chemotherapy treatment) was £41 (£984 over 24 weeks).

*SCT treatment costs*

The cost of SCT includes cost of donation, BEAM conditioning, transplant and follow-up care for both ASCT and allo-SCT.

The base case analysis assumes a total cost of £53,790 and £108,241 (stated in CS as £108,052) for ASCT and allo-SCT respectively. These costs were sourced from the BMT Unit at the Beatson West of Scotland Cancer Centre (WoSCC). No further details were provided regarding the resource use assumed to generate these costs. For example, it was not clear if the costs of treating associated adverse events were included. As such, it was not possible for the ERG to determine the appropriateness of these costs for ASCT or allo-SCT.

In both cases, the company provided an alternative sensitivity analysis, based on national unit costs for key components of the transplant process. The resultant costs were £10,573 (stated in CS as £10,884) and £57,550 for ASCT and allo-SCT respectively, substantially lower than the costs sourced from the Beatson WoSCC. The company justified their rejection of this NHS reference costing approach as the base case because it was felt to substantially under-estimate the true costs of SCT.

The ERG note that the base case analysis uses an approach that is inconsistent with the costing of other cost parameters in the model. Whilst in general, it would be preferable to use NHS reference costs where possible, the base case chosen by the company may be justified on the grounds that the NHS reference costs appear to substantially underestimate costs of SCT. The details provided in the submission with regards to the elicited base case costs are insufficient for the ERG to determine the most appropriate approach. Given the uncertainty, the ERG accepts that the approach used by the company can be considered conservative (in favour of chemotherapy) in the base case analysis.

In addition, it was assumed that 100% of patients would receive BEAM conditioning for ASCT. For Allo SCT, data from Smith et al were used to populate this parameter, assuming 59% and 36% of patients receive myeloablative and non-myeloablative conditioning respectively. The costings seem broadly appropriate from a UK clinical perspective.

*Adverse events*

Grade 1-2 adverse events occurring in ≥10% of patients and grade 3-4 occurring in ≥5% of patients were included in the model. Brentuximab vedotin treatment related adverse event rates were based on the ITT population in the SG035-0004 trial. The ITT population was chosen (as opposed to SCT / No SCT subgroups) due to small numbers in the study.

Adverse event rates for the chemotherapy regimens were based, where possible, on the same studies that reported dosing schedules (Table 5.3 of the CS). Where data from these studies were not available, alternative studies were obtained through targeted literature searches. The company have not detailed the search methods used, nor provided a justification for the choice of studies used to populate the model. Table 5.55 of the CS presents the adverse event rates used in the model, and were considered plausible by the ERG's clinical expert. Adverse events were costed using NHS reference costs where possible, assuming a day case admission would be required for the majority of events. It is not clear if some of these events may require overnight stay (more severe events), or could be treated in an outpatient setting (less severe events). The net effect of these assumptions on adverse event costs is unclear, but is unlikely to materially impact on the ICER.

A component based costing approach was used for grade 3-4 neutropaenia, peripheral sensory neuropathy, anaemia and thrombocytopenia. In general, the ERGs clinical expert considers the resources used (a combination of BNF, NHS reference costs and PSSRU data) for the component-costing exercise to be appropriate. The ERG note one concern with the applied cost of treating acute graft vs host disease (GvHD). The cost is based on a US study by Lee 2000, bibliographic details of which were not provided by the company. It was published 17 years ago, with USD ($28,100) converted and inflated to a present day GBP cost. Whilst acknowledging the

complexity of costing acute GvHD, the ERG note that it is not clear whether the cost applied in the model (£31, 480) is appropriate in the UK setting. Furthermore, the CS did not provide sufficient information to replicate this calculation (e.g. inflation / exchange rates and sources used to make the calculation). The ERG notes that applying substantially lower and higher costs to this model parameter has a minimal impact on the ICER. Other than the single exception outlined, the ERG is satisfied with the company's approach to costing grade 3-4 adverse events. Full details of adverse event costs are provided in Tables 5.56 and 5.57 (pages 148 and 150) of the CS.

In relation to adverse events following ASCT, the ERG notes that additional costs were included in the brentuximab vedotin arm, but not following chemotherapy treatment. The ERG considers this to underestimate the adverse event costs associated with ASCT in the chemo arm. The company have not provided a reason for this omission. The ERG notes that any biases are small in magnitude and would act against brentuximab vedotin.

*Post progression therapies*

In the company's original submission, 100% of patients were assumed to receive a further line of active treatment following progression. Furthermore, 80% of patients with progressive disease following chemotherapy were modelled to receive brentuximab vedotin. The ERG considers it inappropriate to include brentuximab vedotin as a subsequent line of therapy in the chemotherapy arm as this breaches the NICE scope which states that the comparator for the submission should be "*Established clinical management without brentuximab vedotin"*. However, the ERG also realises that in clinical practice, a patient could feasibly receive CHOP, then brentuximab vedotin or CHOP, DEHAP and then brentuximab vedotin, both of which would be within the drug's licence.

The ERG's clinical advice also suggests that upon progression following chemotherapy or brentuximab vedotin treatment, a substantial proportion of patients would likely receive best supportive care rather than further active treatment. However, Table 5.54 of the original CS lists the post-progression therapy distribution, with 100% of patients receiving either brentuximab vedotin or chemotherapy.

After a clarification query from the ERG, the company provided a revised economic model incorporating two alternative distributions of post-progression therapy that were within the NICE scope. The first (trial based distribution) included the distribution of treatments according to the studies used to obtain OS data, the second (clinical expert based distribution) was developed after further contact with clinical expert advisors. The company suggested that the 'clinical expert distribution' should form the base case analysis given that non-licenced treatments were used in the SG035-0004 trial following progression. However, the ERG notes that these unlicensed treatments were replaced with multi-agent chemotherapy in the company's 'trial based distribution' *(See Table 11 of the response to clarification queries).* Whilst the ERG prefers the use of the trial based distribution (to be in keeping with modelled effects), it is noted that these data allow more than one subsequent therapy following progression after brentuximab vedotin, but not after chemotherapy. This may present a bias against brentuximab vedotin. Alternatively, it may reflect the impact of adding an extra treatment option to the care pathway. The ERG rescales the company's trial based distribution to 100% as an exploratory analysis. Table 25 summarises the company's revised distributions of post-progression therapy.

**Table 25 Post-progression therapy distribution by cohort (original and revised company submissions) (Source: Table 5.54 of the CS and Tables 11 and 12 of the company's response to clarification queries)**

| | PPS therapy Company's original submission | | **PPS therapy** Company's revised submission following clarification queries – (trial based data). ***ERGs preferred analysis.*** | | | | | | | **PPS therapy** Company's revised submission following clarification queries. (Clinical expert opinion). ***Company's preferred Analysis*** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cohort | **BV** | **Chemo** | **BV** | **Single-agent Chemo** | **Multi-agent Chemo** | **Inhibitors** | **Allo SCT** | **ASCT** | **BSC** | **BV** | **Single-agent Chemo** | **Multi-agent Chemo** | **Inhibitors** | **Allo SCT** | **ASCT** | **BSC** |
| BV (no SCT) | 33% | 67% | 65% | 35% | 17% | 30% | 13% | 4% | 0% | 0% | 30% | 30% | 0% | 0% | 0% | 40% |
| BV + ASCT | 50% | 50% | 0% | 57% | 0% | 0% | 0% | 0% | 43% | 0% | 22% | 38% | 0% | 0% | 0% | 40% |
| BV + allo-SCT | 50% | 50% | 0% | 57% | 0% | 0% | 0% | 0% | 43% | 0% | 24% | 36% | 0% | 0% | 0% | 40% |
| Chemo (no SCT) | 80% | 20% | 0% | 57% | 0% | 0% | 0% | 0% | 43% | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| Chemo + ASCT | 80% | 20% | 0% | 57% | 0% | 0% | 0% | 0% | 43% | 0% | 60% | 0% | 0% | 0% | 0% | 40% |
| Chemo + allo-SCT | 80% | 20% | 0% | 57% | 0% | 0% | 0% | 0% | 43% | 0% | 60% | 0% | 0% | 0% | 0% | 40% |

Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BSC: best supportive care; PPS: post-progression survival

The cost of multi-agent therapy was based on the cost of GDP (presenting the second highest total cost of all chemotherapy treatments). The cost of single-agent chemotherapy was based on the cost of Gemcitabine. The cost of inhibitors was based on the cost of multi-agent chemotherapy as none of the inhibitors used in the SG035-0004 trial were licensed in the UK. These decisions were based on clinical expert opinion. The post-progression therapy treatment costs used in the original and revised submissions are compared in Table 26.

**Table 26 Post-progression therapy costs (Source: Table 13 of the company's response to clarification queries.)**

| Therapy | Company Original Submission | Company response to clarification |
|---|---|---|
| Allo-SCT | Not included | £111,551 |
| ASCT | Not included | £52,737 |
| Brentuximab vedotin | [redacted] | [redacted] |
| Single-agent chemotherapy | [redacted] | [redacted] |
| Multi-agent chemotherapy | | [redacted] |
| Inhibitor treatments | Not included | £12,310 |
| BSC | Not included | £0 |

Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BSC: best supportive care.



*Follow-up care*

Patients in all cohorts require follow up care (both pre and post progression).

For both brentuximab vedotin and chemotherapy, patients in the model incur costs associated with follow-up both on and off treatment. The CS costed follow-up care (on treatment) as follows: CT scan (3), PET scan (2), consultation (1 per treatment cycle), blood count (1 per treatment cycle) and biochemistry (1 per treatment cycle). Follow-up care for the first three years off-treatment was costed as one CT and one PET scan over the three year period. Blood counts, biochemistry and consultations were converted to weekly frequencies (0.07 per week). From year three (post treatment) onwards, no follow up was assumed for the pre-progression state in the base case analysis. Frequencies were based on one clinical expert's opinion. Costs of pre-progression follow-up were slightly higher in the chemotherapy group. This is

driven by slightly higher weekly costs for CT and PET scans for chemotherapy, due to differing time on treatment in the model.

Post progression follow up costs were based on discounted pre-progression follow up care costs, weighted according to the proportion of patients receiving each treatment post-progression. The ERG makes two observations on this approach. First, it is inappropriate to include discounted costs, and re-discount them again. The double-discounting error is noted in Section 5.2.5. Secondly, the ERG noted a minor formula error in the chemotherapy trace providing this weighting. As the formula referenced brentuximab vedotin following progression on chemotherapy (i.e. 0% in the revised model), the error didn't impact on cost-effectiveness in the revised model. Therefore, the ERG do not consider this issue further.

Follow-up care post receiving ASCT was also based on clinical expert opinion. Patients were followed-up with two CT scans and one PET scan post-transplant and 0.07 blood counts, biochemistry and consultations per week (until year 5).

Follow-up treatment post allo-SCT was assumed over a longer duration, *(see Table 5.50 and 5.51 of the CS).* Resource use was dependent on time from transplant. One CT scan, one PET scan and bi-weekly blood count, biochemistry and consultations were assumed in the first 3 months follow up. Frequency was reduced in a stepped manner between 3 months and 2 years, and again between 2-3 years. Beyond 3 years, patients were assumed to be followed up with a consultation, blood count and biochemistry every 6 months until progression or death.

The ERG notes some uncertainty in follow up treatment resource use, driven by variation in opinion between clinical experts. However, the resources applied in the model appear reasonable and are considered plausible by the ERG's clinical expert.

### 5.2.9 Cost effectiveness results

Section 5.2.9.1 outlines the results (base case, deterministic and probabilistic sensitivity analyses) of the company's original submission. Section 5.2.9.2 reports the revised results and scenario analyses presented by the company in response to clarification queries (erratum to clarification response dated 22/03/2017, accounting for a bug in the model). Section 5.2.9.2 is split to report results according to both the 'trial based' and 'clinical expert based' post-progression therapy distributions.

#### *5.2.9.1 Company's original submission*

Compared to chemotherapy, brentuximab vedotin was associated with 6.18 additional discounted life years and 3.56 additional discounted QALYs. Brentuximab vedotin was also more costly, at an additional cost of £31,426 per patient, giving an incremental cost per QALY gained of £8,829 for the original base case analysis.

**Table 27 Base-case results (with PAS) (Source: Table 5.69, p. 189 of the CS)**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £8,829 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

**Treatment effectiveness**

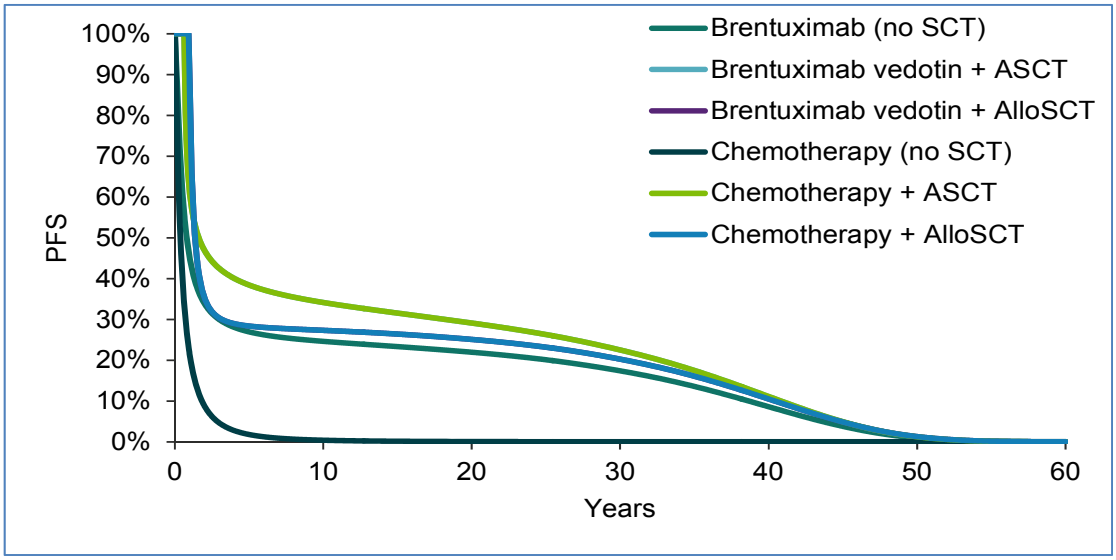
PFS and OS for ASCT and allo-SCT did not differ according to prior line salvage therapy (brentuximab vedotin or chemotherapy) – although more receive SCT with brentuximab vedotin. Overall, ASCT had the longest mean PFS and OS, indicating its superiority to allo-SCT when comparing mortality risks. Both SCT treatments have longer PFS and OS than the no SCT cohorts, indicating their preferable disease control and curative nature. In the 'no SCT' cohorts, brentuximab vedotin was associated with an additional 8.5 years PFS and 13.64 years OS over chemotherapy. Table 28 outlines the treatment effectiveness results by cohort and combined for each treatment (brentuximab vedotin and chemotherapy).

**Table 28 Clinical outcomes, by cohort (Source: Table 5.70 (pg190) & Table 5.71 (pg 191) of the CS)**

| Cohort | | Mean years | |
|---|---|---|---|
| | Proportional weighting | PFS | OS |
| Brentuximab vedotin (no SCT) | 71% | 9.29 | 16.43 |
| Brentuximab vedotin + ASCT | 14% | 12.52 | 18.06 |
| Brentuximab vedotin + allo-SCT | 16% | 10.84 | 14.18 |
| **Brentuximab vedotin (combined)** | | **9.97** | **16.31** |
| Chemotherapy (no SCT) | 86% | 0.80 | 2.79 |
| Chemotherapy + ASCT | 7% | 12.52 | 18.06 |
| Chemotherapy + allo-SCT | 7% | 10.84 | 14.18 |
| **Chemotherapy (combined)** | | **2.31** | **4.64** |

Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; OS: overall survival; PFS: progression free survival.

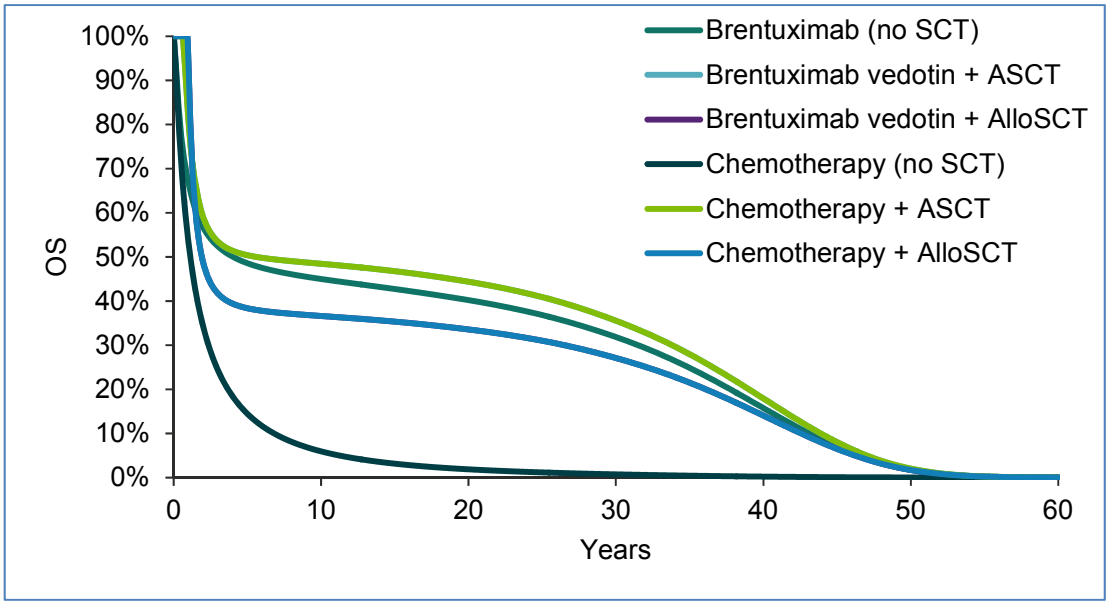
The respective survival curves are outlined in Figure 19 and Figure 20 for PFS and OS respectively.




Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; OS: overall survival; PFS: progression free survival.

**Note the appearance of only 4 (rather than 6) curves as BV+ASCT = Chemo+ ASCT and BV + allo-SCT = Chemo+ allo-SCT*

**Figure 19 PFS, by cohort (Source: Figure 5.28; pg 190 of the CS)**




**The ERG note that given the Company's assumptions, curves for BV+ASCT = Chemo+ ASCT and BV + AlloSCT = Chemo+ AlloSCT, hence the appearance of 4, rather than 6 curves.*

**Figure 20 OS, by cohort (Source Figure 5.29; pg 191 of the CS)**

**Life years and QALYs gained**

ASCT was associated with the highest QALY gain, followed by allo-SCT. As per the company's assumptions regarding PFS and OS, life years gained were equivalent in the brentuximab vedotin (SCT) and chemotherapy (SCT) cohorts. Patients in the SCT cohorts with previous brentuximab vedotin as salvage therapy had slightly higher QALYs compared to chemotherapy, driven by the superior response profile for brentuximab vedotin and the response specific utility applied in the base case model. The benefits of SCT were primarily driven by the accrued life years (and QALYS) in the PFS state.

Overall, patients in the brentuximab vedotin intervention fared considerably better in terms of LY and QALYs, driven primarily by differences in the 'No SCT' cohorts. Overall, brentuximab vedotin treated patients had longer life expectancy (6.18 years additional life years gained), better response rates and slower disease progression, were less likely to end up in the PPS state and spent more time in the PFS state than chemotherapy treated patients, thereby leading to improved HRQoL.

As a result, brentuximab vedotin treated patients experienced an additional 3.56 QALYs accrued over a 60 year time horizon under the company's base case assumptions. Results for LY and QALYs according to health state, cohort and for the overall interventions are summarised in Table 29.

**Table 29 Summary of mean and incremental Life years and QALYs, by health state for each cohort.**

| | LYs | | | QALYs | | | |
|---|---|---|---|---|---|---|---|
| **Cohort** | **PFS** | **PPS** | **Total** | **PFS** | **PPS** | **AEs** | **Total** |
| Brentuximab vedotin (No SCT) | 5.55 | 4.05 | 9.59 | [redacted] | [redacted] | 0.01 | [redacted] |
| Brentuximab vedotin + ASCT | 7.56 | 2.93 | 10.49 | [redacted] | [redacted] | 0.02 | [redacted] |
| Brentuximab vedotin + allo-SCT | 6.50 | 1.87 | 8.37 | [redacted] | [redacted] | 0.03 | [redacted] |
| **Brentuximab vedotin (combined)*** ** | **5.97** | **3.55** | **9.53** | [redacted] | [redacted] | **0.02** | [redacted] |
| Chemotherapy (No SCT) | 0.76 | 1.60 | 2.36 | [redacted] | [redacted] | 0.02 | [redacted] |
| Chemotherapy + ASCT | 7.56 | 2.93 | 10.49 | [redacted] | [redacted] | 0.02 | [redacted] |
| Chemotherapy + allo-SCT | 6.50 | 1.87 | 8.37 | [redacted] | [redacted] | 0.02 | [redacted] |
| **Chemotherapy (combined)*** ** | **1.64** | **1.71** | **3.35** | [redacted] | [redacted] | **0.02** | [redacted] |
| **Incremental (BV vs chemo)** | **4.34** | **1.84** | **6.18** | [redacted] | [redacted] | **0.00** | [redacted] |

Key: AE: adverse events; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BV: brentuximab vedotin; LY: life year; PFS: progression free survival; PPS: Post-progression survival; QALY: quality adjusted life year.

**Data in this table were re-produced using the Company submitted economic model.*
***Note that AE's were initially incorrectly added in the original CS. This error has been corrected in the erratum to the response to clarification queries. The table above reports the initial, uncorrected values.*
****Weighted for the proportion of patients receiving ASCT and allo-SCT*

**Costs**

The Aggregated total costs by health state are presented in Table 30 for each cohort and overall intervention, mean and incremental costs. Brentuximab vedotin costs were higher in the PFS state, and lower in the PPS state due to patients spending less time in the PPS state, and the superior survival benefit of brentuximab vedotin.

**Table 30 Aggregated costs by health state****

| | PFS | PPS | AEs | Total |
|---|---|---|---|---|
| Brentuximab vedotin | [redacted] | [redacted] | £690 | [redacted] |
| Brentuximab vedotin + ASCT | [redacted] | [redacted] | £1,187 | [redacted] |
| Brentuximab vedotin + AlloSCT | [redacted] | [redacted] | £6,905 | [redacted] |
| **Brentuximab vedotin (combined)*** | [redacted] | [redacted] | **£1,723** | [redacted] |
| Chemotherapy | [redacted] | [redacted] | £1,118 | [redacted] |
| Chemotherapy + ASCT | [redacted] | [redacted] | £1,118 | [redacted] |
| Chemotherapy + Allo-SCT | [redacted] | [redacted] | £6,836 | [redacted] |
| **Chemotherapy (combined)*** | [redacted] | [redacted] | **£1,543** | [redacted] |
| **Increment (BV vs. Chemo)** | [redacted] | [redacted] | **£180** | [redacted] |

**Weighted by proportion of patients assigned to each cohort (company base case assumptions*
***Data reproduced from CS: Table 5.76 and 5.77, p. 196 and economic model.*

Brentuximab vedotin was [redacted] more expensive than chemotherapy, driven primarily by brentuximab vedotin drug acquisition costs [redacted], accounting for [redacted] of total brentuximab vedotin costs) which were [redacted] times higher than chemotherapy drug acquisition costs [redacted], representing only 8% of modelled chemotherapy costs). Brentuximab vedotin was also associated with higher SCT costs, due to the higher proportion of patients receiving these treatments. Additional costs were partly offset by cost savings on administration (outpatient setting for brentuximab vedotin) and concomitant medications. Also, the cost of post-progression therapies was higher in the chemotherapy arm due to the large proportion (80%) assumed to receive brentuximab vedotin post progression under the company's original base case assumptions. The company provided a revised analysis with these costs removed/substituted after response to clarification queries *(See Section 5.2.9.2 for*

*revised results)*. The disaggregated costs from the company's original base case analysis are presented by in Table 31.

**Table 31 Disaggregated and total costs by cohort and resource category**

| | Acquisition | Admin | Concomitant meds | AEs | SCT | Follow-up care (pre-progression) | Follow-up care (post-progression) | Post-progression therapies | Total |
|---|---|---|---|---|---|---|---|---|---|
| Brentuximab vedotin | [redacted] | [redacted] | £37 | £690 | £0 | [redacted] | [redacted] | [redacted] | [redacted] |
| Brentuximab vedotin + ASCT | [redacted] | [redacted] | £41 | £1,187 | £52,737 | [redacted] | [redacted] | [redacted] | [redacted] |
| Brentuximab vedotin + allo-SCT | [redacted] | [redacted] | £41 | £6,905 | £105,833 | [redacted] | [redacted] | [redacted] | [redacted] |
| **Brentuximab vedotin (combined)*** | [redacted] | [redacted] | £38 | £1,723 | £23,696 | [redacted] | [redacted] | [redacted] | [redacted] |
| Chemotherapy | [redacted] | [redacted] | £791 | £1,118 | £0 | [redacted] | [redacted] | [redacted] | [redacted] |
| Chemotherapy + ASCT | [redacted] | [redacted] | £791 | £1,118 | £52,737 | [redacted] | [redacted] | [redacted] | [redacted] |
| Chemotherapy + allo-SCT | [redacted] | [redacted] | £791 | £6,836 | £105,833 | [redacted] | [redacted] | [redacted] | [redacted] |
| **Chemotherapy (combined)*** | [redacted] | [redacted] | £791 | £1,543 | £11,338 | [redacted] | [redacted] | [redacted] | [redacted] |
| **Incremental costs** | [redacted] | [redacted] | **-£753** | **£180** | **£12,359** | [redacted] | [redacted] | [redacted] | [redacted] |

Key: AE: adverse events; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant

**Weighted for the proportion of patients assigned to each cohort under the company's base case assumptions*

***This table have been reproduced by the ERG using a combination of information from the CS report (Table 5.74, p. 194 and Table 5.75, p. 195 (by resource category)) and the company's submitted economic model.*

**Deterministic sensitivity analyses (DSA)**

The company provided a range of deterministic, primarily uni-variate sensitivity analyses. Analyses were implemented in the company model using a macro function to aide swift reproducibility of all analyses. The ERG has checked and reproduced each analysis, manually changing the relevant cells and are satisfied that the deterministic analyses have been correctly implemented and the reported data are an accurate reflection of the impact of the analyses on the ICER. None of the explored analyses resulted in an ICER greater than £20,000 per QALY gained *(Table 32)*.

**Table 32 Scenario analyses results (Source: Table 5.81; pg 204 of the CS)**

| SA | Parameter | Base case | Scenario | ICER | Change vs. base case |
|---|---|---|---|---|---|
| | **Base case** | | | **£8,829** | |
| 1 | Discount rate (costs, benefits) | 3.5% | 1.5% | £6,524 | -26% |
| 2 | Assessment type | Investigator | IRF | £12,415 | +41% |
| 3 | Source of response data for brentuximab patients receiving SCT | SGN35-0004 (self- control) | Equivalent to chemotherapy | £8,864 | 0% |
| 4 | Brentuximab (no SCT) PFS per INV distribution | Log-logistic | Exponential | £8,719 | -1% |
| 5 | Brentuximab (no SCT) PFS per IRF distribution | Log-logistic | Exponential | £11,401 | +29% |
| 6 | Brentuximab (no SCT) OS distribution | Log-logistic | Kaplan-Meier | £8,604 | -3% |
| 7 | Brentuximab (no SCT) PFS and OS distribution | Log-logistic cure model | Gamma standard model | £9,943 | +13% |
| 8 | Source of chemotherapy (no SCT) PFS data | Self-control | ALCL (n=17)[72] | £10,601 | +20% |
| 9 | Source of chemotherapy (no SCT) PFS data | Self-control | PS<2 (n=47)[72] | £10,503 | +19% |
| 10 | Chemotherapy (no SCT) PFS distribution | Lognormal | Log-logistic | £8,937 | +1% |
| 11 | Chemotherapy (no SCT) PFS hazard | Original data | Increased 25% | £8,475 | -4% |
| 12 | Chemotherapy (no SCT) PFS hazard | Original data | Decreased 25% | £9,647 | +9% |

| | | | | | |
|---|---|---|---|---|---|
| 13 | Source of chemotherapy (no SCT) OS data | PS<2 (n=47)[72] | ALCL (n=17)[72] | £8,016 | -9% |
| 14 | Combined scenarios 8 and 13 | | | £9,656 | +9% |
| 15 | Chemotherapy (no SCT) OS distribution | Lognormal | Kaplan-Meier | £8,946 | +1% |
| 16 | Chemotherapy (no SCT) OS hazard | Original data | Increased 25% | £8,494 | -4% |
| 17 | Chemotherapy (no SCT) OS hazard | Original data | Decreased 25% | £9,469 | +7% |
| 18 | Combined scenarios 12 and 17 | | | £10,386 | +18% |
| 19 | ASCT PFS distribution | Gamma | Lognormal | £8,746 | -1% |
| 20 | ASCT OS distribution | Lognormal | Gamma | £8,840 | 0% |
| 21 | ALCL calibration for ASCT | Exclude | Include | £8,289 | -6% |
| 22 | Allo-SCT PFS distribution | Lognormal | Gamma | £8,850 | 0% |
| 23 | Allo-SCT OS distribution | Lognormal | Gamma | £8,829 | 0% |
| 24 | ALCL calibration for allo-SCT | Exclude | Include | £8,644 | -2% |
| 25 | Combined scenarios 20 and 23 | | | £8,125 | -8% |
| 26 | Rate of stem cell transplant | Response-based (SGN35-0004) | Response-based (clinical opinion) | £14,256 | +61% |
| 27 | Rate of stem cell transplant | Response-based (SGN35-0004) | Equal in both arms [72] | £8,692 | -2% |
| 28 | Proportion receiving ASCT vs. alloSCT | Base case (SGN35-0004) | AlloSCT = 75% | £9,561 | +8% |
| 29 | Cured time-point (years) | 5 years | 2 years | £8,955 | +1% |
| 30 | RDI adjustment | On | Off | £8,829 | 0% |
| 31 | Chemotherapy RDI | 100% | Equivalent to BV | £8,843 | 0% |
| 32 | Vial sharing | Off | On | £8,129 | -8% |
| 33 | ASCT cost | Clinical expert | NHS reference costs | £7,973 | -10% |
| 34 | AlloSCT cost | Clinical expert | NHS reference costs | £7,712 | -13% |
| 35 | Adverse event disutilities | Include | Exclude | £8,833 | 0% |
| 36 | Chemotherapy costs; all patients receive cheapest expensive | Mix | ESHAP | £7,838 | -11% |
| 37 | Chemotherapy costs; all patients receive most expensive | Mix | Gem-P | £8,570 | -3% |
| 38 | Radiotherapy | 5% | 40% | £8,707 | -1% |

Key: AE: adverse events; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; ALCL: anaplastic large cell lymphoma; BV: brentuximab vedotin; PFS: progression free survival; RDI: relative dose intensity

Table 32 shows that, under the company's conducted analyses, the ICER was most sensitive to changing the discount rate to 1.5% (26% decrease), using IRF as data for PFS on brentuximab vedotin instead of investigator assessed progression (41% increase), and using an exponential function instead of log-logistic for estimating PFS in the brentuximab vedotin arm (no SCT) (29% increase).

In relation to SCT, basing the SCT rate on clinical expert opinion instead of the SG035-0004 trial increased the ICER by 61%. It is worth noting that the greater the difference in rates of SCT for brentuximab vedotin over chemotherapy, the higher the resultant ICER for brentuximab vedotin. This is due to the favourable OS and PFS modelled for brentuximab vedotin (no SCT) without the substantial costs of SCT. There is a greater benefit to be accrued from progressing chemotherapy patients to SCT than there is for progressing brentuximab vedotin patients to SCT, given the higher cure percentage and superior survival assumptions applied to the brentuximab vedotin (No SCT) cohort under the base case assumptions. Given the assumptions applied in the model, the ERG considers these findings to be plausible, however it is noted that increasing progression to SCT increases the ICER for brentuximab vedotin. Decreasing the rate of SCT on brentuximab vedotin to equate with chemotherapy substantially lowers the base case ICER.

Finally, using data from Mak et. al. 2013[72] (ALCL patients) or (PTCL patients with PS<2) for PFS on chemotherapy (no SCT), rather than the self-controls from SG035-0004, leads to a 20% and 19% increase in the ICER respectively.

Whilst the company presented many deterministic scenario analyses, the ERG are not convinced that the original submission sufficiently tested the aspects of the model which generate the greatest uncertainty in the ICER, namely the distribution of post-progression therapy as well as the comparative effectiveness (PFS and OS) between brentuximab vedotin and chemotherapy. In particular, the scenarios chosen for two-way, combined analyses by the company were based on analyses with minimal impact on the ICER. Sections 5.2.9.2 and 5.3, report a range of further analyses conducted by both the company (in response to clarification) and the ERG respectively.

**Probabilistic Sensitivity Analyses (PSA)**

Parameter uncertainty was addressed by conducting a probabilistic sensitivity analysis (PSA), sampling 5000 Monte Carlo simulations on each parameter. Table 33 presents the groups of parameters that were varied in the probabilistic sensitivity analyses, as reported in the CS.

**Table 33 Groups of parameters considered in the PSA (Source Table 5.78, p. 197 of the CS)**

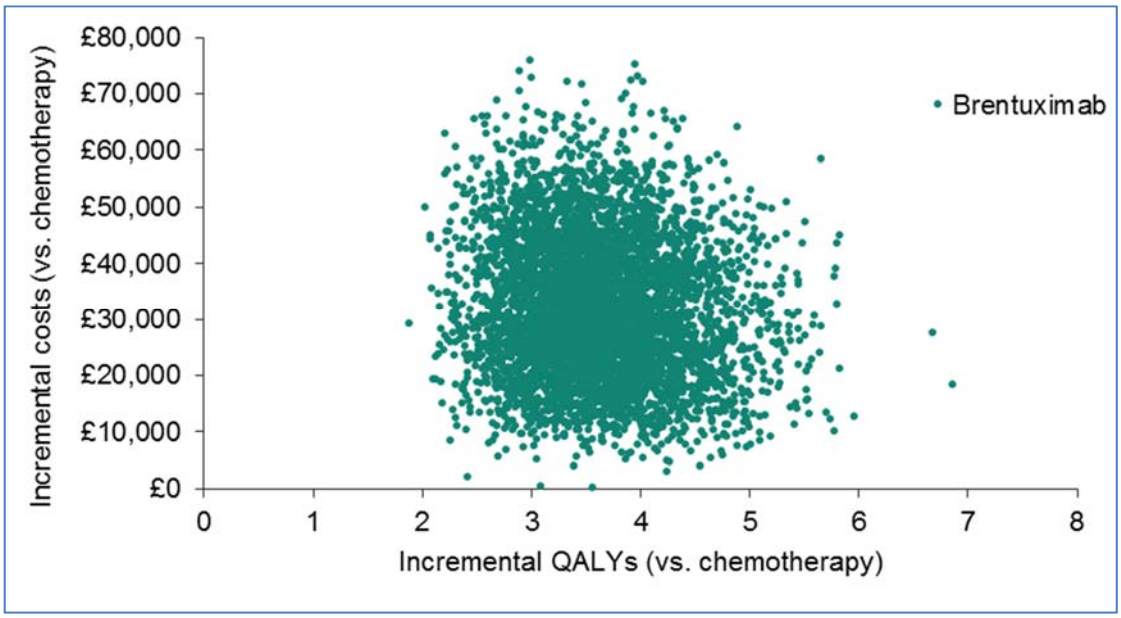
| Parameter | Distribution | Rationale |
|---|---|---|
| Discount rates | N/A | Not subject to sampling uncertainty |
| Response probabilities | Dirichlet | Constrained on an interval of 0 to 1 and reflect multinomial nature of response categories |
| Regression parameters | Multivariate normal | To capture correlation between normally distributed regression parameters |
| Kaplan-Meier | Beta | Constrained on an interval of 0 to 1 |
| Starting age | Normal | Assumption |
| Drug costs | N/A | Not subject to sampling uncertainty |
| Other unit costs | Gamma | Constrained on an interval of 0 to positive infinity |
| Brentuximab time on treatment | N/A | Sampling with replacement used to more accurately reflect the shape of the distribution |
| Chemotherapy time on treatment | Normal | Assumed to be normal in absence of data |
| Resource use rates | Gamma | Constrained on an interval of 0 to positive infinity |
| Resource use probabilities | Beta | Constrained on an interval of 0 to 1 |
| Health state utilities | Beta | Constrained on an interval of 0 to 1 |
| Adverse event disutilities | Gamma | Constrained on an interval of 0 to positive infinity |
| Adverse event durations | Gamma | Constrained on an interval of 0 to positive infinity |
| Adverse event probabilities | Beta | Constrained on an interval of 0 to 1 |

N/A, not applicable as parameter was excluded from the probabilistic sensitivity analysis

In general, the ERG are satisfied that the probabilistic analysis is appropriate and correctly implemented. Table 5.67 of the CS provides a full list of probabilistic

parameters used in the model. However, a justification for chosen distributions was not provided. The distributional parameters (e.g. alpha, beta parameters) were not reported, though measures of uncertainty (e.g. inter-quartile ranges or standard errors) were. The ERG noted an error in how the parameters for chemotherapy treatment distributions were incorporated in the PSA, allowing treatments to sum to a value > or < 1 in the PSA. The ERG has corrected this error to ensure that in the PSA, the distribution of chemotherapy treatment in the model sums to 100%. The ERG has undertaken a number of checks regarding how the PSA has been implemented within the model and, apart from the identified concern, are satisfied that the remaining parameters have been correctly incorporated probabilistically.

The company did not report a probabilistic ICER. The ERG re-ran the PSA and estimated the probabilistic ICER to be £8,868, only slightly higher than the deterministic ICER of £8,829 per QALY gained. The PSA simulations are presented a scatter-plot on the cost-effectiveness plane in Figure 21.

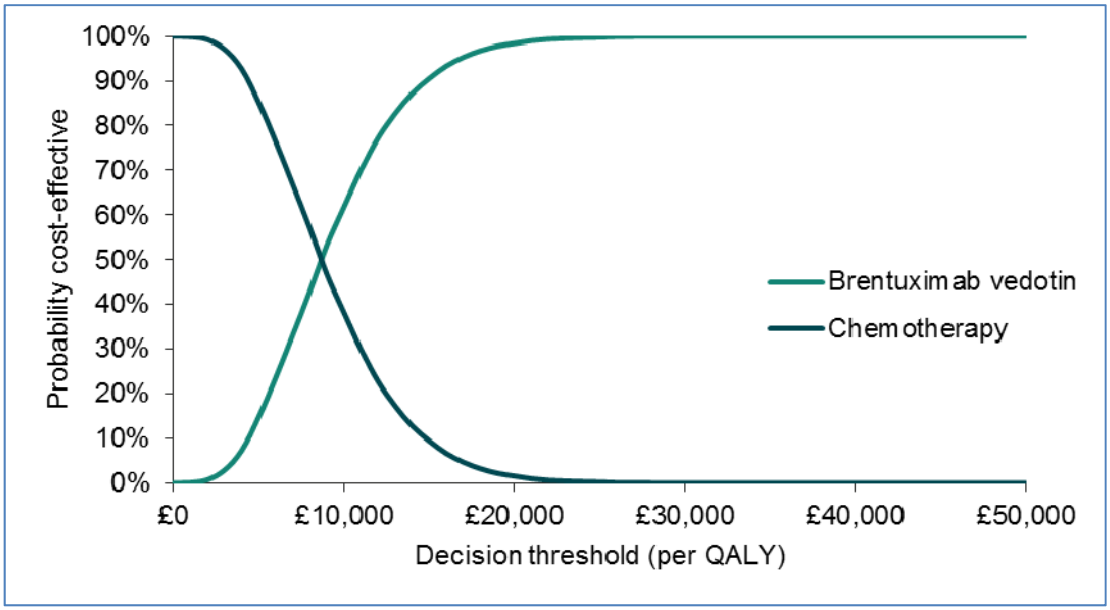



**Reproduced from Company's originally submitted model. Corresponds to version equating to probabilistic ICER = £8,868 per QALY gained.*

**Figure 21 Probabilistic simulations on a cost-effectiveness plane (Source: Company submitted model)**

All simulations lie in the NE quadrant of the cost-effectiveness plane, indicating that brentuximab vedotin is significantly more costly and more effective than

chemotherapy under the base case model inputs and assumptions. The corresponding CEACs, presented in Figure 22 illustrate that the probability of brentuximab vedotin being cost-effective at the thresholds of £20,000, £30,000 and £50,000 per QALY gain is 99%, 100% and 100% respectively.




**Reproduced from Company's originally submitted model. Corresponds to version equating to probabilistic ICER = £8,868 per QALY gained.*

**Figure 22 Cost-effectiveness acceptability curve (Source: Company submitted model)**

Whilst the results are reflective of the sampling uncertainty in the company's original submission, the ERG consider a probability of cost-effectiveness equal to 100% at a threshold of £30,000 per QALY gained is unreasonable, particularly given the uncertainties arising from the lack of randomised or adjusted comparative data. As such, the ERG would have considered it helpful to see some probabilistic analysis undertaken for some of the more pessimistic scenarios analyses that generate smaller point estimates of incremental QALY gains.

*5.2.9.2 Company's revised model following response to clarification queries*

As noted in Section 5.2.8, the company provided two revised distributions of post-progression therapy at clarification stage alongside a revised economic model. The main purpose of the revision was to remove the assumption that 80% of patients

receive brentuximab vedotin following chemotherapy progression (i.e. an assumption that was out with the NICE scope for this appraisal). This section of the ERG report refers to the model received on March 22nd, 2017 (including correction of a minor model error around adverse event disutility). As outlined in Section 5.2.8, the ERG's preferred distribution for post-progression therapy costs is 'SG035-0004 trial based' and the company's preferred distribution is 'expert based'. The following refers to the trial based distribution results, with the expert based distribution results reported in a further table at the end of the section.

**Trial-based post-progression therapy distribution**

*Revised cost-effectiveness base case results*

The deterministic base case results (including PAS) are shown in Table 34 and compared to the original submission. Life years gained did not change between the original and revised submission and QALYs only changed marginally to reflect the correction of a bug in adverse event disutility. The main differences relate to the costs of the respective cohorts, which have increased for brentuximab vedotin and decreased for chemotherapy, giving an incremental cost of [redacted] and a revised base case ICER equal to £19,470 per QALY gained.

**Table 34 Revised base-case results (with PAS); 'trial based' distribution of post-progression therapy**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| **Original Submission** | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £8,829 |
| **Revised Submission *(Trial based post-progression therapy – ERG preferred analysis)*** | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £19,470 |
| ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years | | | | | | | |

*Revised deterministic sensitivity analyses*

The ERG reproduced the company's set of deterministic analyses using the revised post-progression therapy ('trial based') distribution (*Table 35)*. The ICERs ranged from £14,492 to £29,296, and as per the base case were most sensitive to the choice of PFS data used for brentuximab vedotin in the model. The ERG notes that in the revised set of analyses, 12/38 (32%) of analyses push the ICER above £20,000, though none rise above £30, 000 per QALY gained. The ERGs concerns and critique remain as per Section 5.2.9.1 above.

**Table 35 Deterministic sensitivity analyses applied to trial based post-progression therapy distribution**

| Analysis | Parameter | Base case | Scenario | ICER | Change vs. base case |
|---|---|---|---|---|---|
| | **Base case** | | | **£19,470** | |
| 1 | Discount rate (costs, benefits) | 3.5% | 1.5% | £14,492 | -26% |
| 2 | Assessment type | Investigator | IRF | £29,296 | 50% |
| 3 | Source of response data for brentuximab patients receiving SCT | SGN35-0004 (self-control) | Equivalent to chemotherapy | £19,549 | 0% |
| 4 | Brentuximab (no SCT) PFS per INV distribution | Log-logistic | Exponential | £19,222 | -1% |
| 5 | Brentuximab (no SCT) PFS per IRF distribution | Log-logistic | Exponential | £26,912 | 38% |
| 6 | Brentuximab (no SCT) OS distribution | Log-logistic | Kaplan-Meier | £18,974 | -3% |
| 7 | Brentuximab (no SCT) PFS and OS distribution | Log-logistic cure model | Gamma standard model | £21,934 | 13% |
| 8 | Source of chemotherapy (no SCT) PFS data | Self-control | ALCL (n=17)[72] | £21,495 | 10% |
| 9 | Source of chemotherapy (no SCT) PFS data | Self-control | PS<2 (n=47)[72] | £21,267 | 9% |
| 10 | Chemotherapy (no SCT) PFS distribution | Lognormal | Log-logistic | £19,663 | 1% |
| 11 | Chemotherapy (no SCT) PFS hazard | Original data | Increased 25% | £18,989 | -2% |
| 12 | Chemotherapy (no SCT) PFS hazard | Original data | Decreased 25% | £20,550 | 6% |
| 13 | Source of chemotherapy (no SCT) OS data | PS<2 (n=47)[72] | ALCL (n=17)[72] | £18,594 | -4% |
| 14 | Combined scenarios 8 and 13 | | | £20,593 | 6% |

| | | | | | |
|---|---|---|---|---|---|
| 15 | Chemotherapy (no SCT) OS distribution | Lognormal | Kaplan-Meier | £19,728 | 1% |
| 16 | Chemotherapy (no SCT) OS hazard | Original data | Increased 25% | £18,732 | -4% |
| 17 | Chemotherapy (no SCT) OS hazard | Original data | Decreased 25% | £20,883 | 7% |
| 18 | Combined scenarios 12 and 17 | | | £22,127 | 14% |
| 19 | ASCT PFS distribution | Gamma | Lognormal | £19,293 | -1% |
| 20 | ASCT OS distribution | Lognormal | Gamma | £19,494 | 0% |
| 21 | ALCL calibration for ASCT | Exclude | Include | £18,417 | -5% |
| 22 | AlloSCT PFS distribution | Lognormal | Gamma | £19,517 | 0% |
| 23 | AlloSCT OS distribution | Lognormal | Gamma | £19,471 | 0% |
| 24 | ALCL calibration for alloSCT | Exclude | Include | £19,101 | -2% |
| 25 | Combined scenarios 20 and 23 | | | £18,087 | -7% |
| 26 | Rate of stem cell transplant | Response-based (SGN35-0004) | Response-based (clinical opinion) | £23,609 | 21% |
| 27 | Rate of stem cell transplant | Response-based (SGN35-0004) | Equal in both arms[72] | £21,448 | 10% |
| 28 | Proportion receiving ASCT vs. alloSCT | Base case (SGN35-0004) | AlloSCT = 75% | £20,315 | 4% |
| 29 | Cured time-point (years) | 5 years | 2 years | £18,686 | -4% |
| 30 | RDI adjustment | On | Off | £19,470 | 0% |
| 31 | Chemotherapy RDI | 100% | Equivalent to BV | £19,522 | 0% |
| 32 | Vial sharing | Off | On | £17,681 | -9% |
| 33 | ASCT cost | Clinical expert | NHS reference costs | £18,389 | -6% |
| 34 | AlloSCT cost | Clinical expert | NHS reference costs | £17,576 | -10% |
| 35 | Adverse event disutilities | Include | Exclude | £19,460 | 0% |
| 36 | Chemotherapy costs; all patients receive cheapest expensive | Mix | 72.9 | £18,335 | -6% |
| 37 | Chemotherapy costs; all patients receive most expensive | Mix | 5625 | £19,205 | -1% |
| 38 | Radiotherapy | 5% | 40% | £19,308 | -1% |

At clarification stage, the ERG requested and the company provided a further set of 7 exploratory analyses based on the 'trial-based' post progression therapy distribution. Table 36 reports the results of these analyses. The ERG notes that there is wider variation in the ICER, ranging from £19,271 per QALY to £37,915. The ERG considers that these analyses better reflect the range of uncertainties in the model, and notes that further uncertainty would be evident when exploring additional combinations of scenarios (either in favour or against brentuximab vedotin).

**Table 36 Cost-effectiveness results for additional scenario analyses in response to clarification – trial-based post-progression therapy distribution (with PAS)**

| | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Base case scenario | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £19,470 |
| 1. Data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS with chemotherapy | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £21,267 |
| 2. IRF-assessed data for clinical response rates and PFS for brentuximab vedotin | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £29,296 |
| 3. Cost-effectiveness results for combined scenarios (scenarios 1 and 2) | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £33,186 |
| 4. 53.11 year time horizon | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £19,473 |
| 5. Standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £37,915 |
| 6. Standard gamma model for brentuximab vedotin (no SCT) PFS per IRF | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £31,368 |
| 7. Cycle 4 stopping rule | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £19,271 |

*Revised probabilistic sensitivity analyses*

The ERG re-ran the PSA using the revised model. The revised probabilistic ICER for the 'trial based' post-progression therapy distribution was £19, 034 per QALY gained, similar to the deterministic analysis (£19,470). The revised cost-effectiveness scatterplot and CEACs are presented in Figure 23 and 24 respectively. The probability of brentuximab vedotin being cost-effective at the thresholds of £20,000, £30,000 and £50,000 per QALY gain was 59%, 83% and 100% respectively, substantially lower at thresholds of £20k and £30k than in the original company submission.

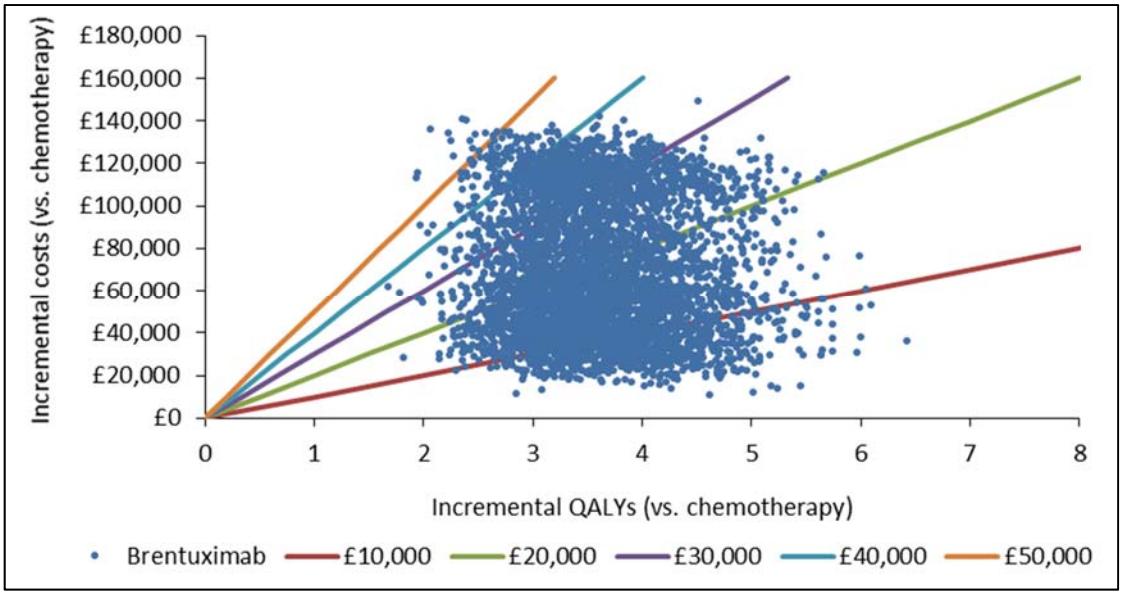



**Figure 23 Probabilistic simulations on the cost-effectiveness plane (Company revised submission: Trial based post progression therapy distribution)**

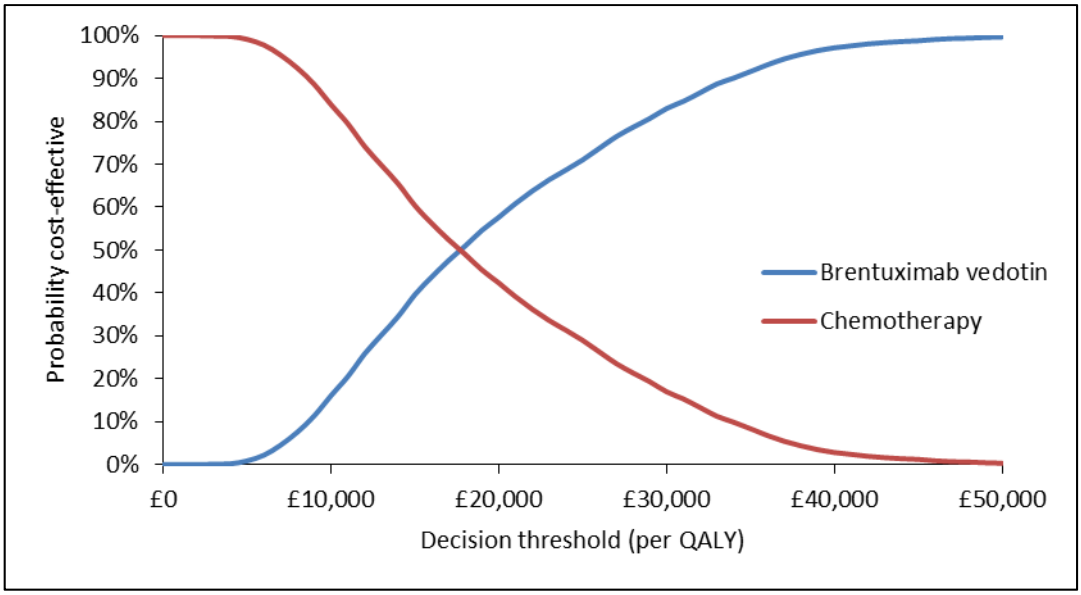



**Figure 24 Cost-effectiveness acceptability curve (Company revised submission: Trial based post progression therapy distribution)**

**Post-progression therapy distribution based on clinical expert opinion**

The company re-produced the same set of additional scenario analyses at clarification stage using an alternative distribution of post-progression therapy costs based on clinical expert opinion. Table 37 reports the exploratory analyses conducted by the company in response to clarification applied to the 'expert opinion' based distribution of post-progression therapies. The revised ICER in the base case for this scenario is £12,873, compared to £8,829 in the original submission and £19,470 using the trial-based post progression therapy distribution. For the set of deterministic sensitivity analyses considered, the resulting ICERs ranged from £12,727 to £22,187.

**Table 37 Cost-effectiveness results based on clinical expert opinion**

| Technologies | Total costs | Total LYs | Total QALYs | Inc. costs | Inc. LYs | Inc. QALYs | ICER (per QALY) |
|---|---|---|---|---|---|---|---|
| Base case scenario | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £12,873 |
| 1. Data from Mak et al. PTCL patients with performance status <2 (n = 47) for PFS[72] | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £14,137 |
| 2. IRF-assessed data for response and PFS for brentuximab vedotin | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £17,496 |
| 3. Cost-effectiveness results for combined scenarios (scenarios 1 and 2) | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £19,951 |
| 4. 53.11 year time horizon | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £12,875 |
| 5. Standard lognormal model for brentuximab vedotin (no SCT) PFS per IRF | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £22,187 |
| 6. Standard gamma model for brentuximab vedotin (no SCT) PFS per IRF | | | | | | | |
| Chemotherapy | [redacted] | 3.29 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.54 | [redacted] | [redacted] | 6.25 | [redacted] | £18,785 |
| 7. Cycle 4 stopping rule | | | | | | | |
| Chemotherapy | [redacted] | 3.35 | [redacted] | - | - | - | - |
| Brentuximab | [redacted] | 9.53 | [redacted] | [redacted] | 6.18 | [redacted] | £12,727 |

The analyses show that ICERs are in general higher compared to the original submission, but lower compared to the ERGs preferred trial based assumption of post-progression therapy distribution. This is driven by the fact that none of the cohorts

receive brentuximab vedotin in post-progression and are therefore not accruing the high acquisition costs of brentuximab vedotin.
The ERG also re-ran the company's PSA using the revised model, according to the company's preferred clinical expert based distribution of post-progression therapies as an alternative base case. The revised probabilistic ICER was £12, 752 per QALY gained. The probability of brentuximab vedotin being cost-effective at the thresholds of £20,000, £30,000 and £50,000 per QALY gain was 81%, 99% and 100% respectively, lower than the base case analysis, but higher than the ERG's preferred trial based distribution of post progression therapy asumption.

*5.2.10 Model validation and face validity check*

The company submission, Section 5.10, states that two independent health economists (who were not involved in model construction) reviewed the model parameters, checking formulae and VB code. Whilst the CS does not explicitly state that identified errors were rectified, the ERG assumes that they were.

In addition to the validation exercises undertaken by the company, the ERG have conducted a number of checks on the company's model to identify any errors (as opposed to unjustified assumptions or critique of methodology). Model error checking was conducted using the check-list developed by Tappenden and Chilcott.[98] The outcomes of this exercise are presented in Table 38. The company model predicted results that were in line with the model check-list verification criteria explored by the ERG.

**Table 38 ERG conducted 'black-box' verification tests applied to the company submitted model**

| Model component | Model test | Unequivocal criterion for verification | Issues identified in company model |
|---|---|---|---|
| Clinical trajectory | Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events) | All treatments produce equal estimates of total LYGs and total QALYs | None |
| | Sum expected health state populations at any model timepoint (state transition models) | Total probability equals 1.0 | None |
| | Sum expected probability of terminal nodes (decision-tree models) | Total probability equals 1.0 | None |
| QALY estimation | Set all health utility for living states parameters to 1.0 | QALY gains equal LYGs | None |
| | Set QALY discount rate to 0 | Discounted QALYs = undiscounted QALYs for all treatments | None |
| | Set QALY discount rate equal to very large number | QALY gain after time 0 tend towards zero | None |
| Cost estimation | Set intervention costs to 0 | ICER is reduced* | None |
| | Increase intervention cost | ICER is increased* | None |
| | Set cost discount rate to 0 | Discounted costs = undiscounted costs for all treatments | None |
| | Costs after time 0 tend towards zero | Set cost discount rate equal to very large number | None |
| Input parameters | Produce n samples of model parameter m | Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.) | One minor issue: distribution of chemotherapy component treatments was not restricted to add to one. Error corrected by the ERG. |
| General | Set all treatment-specific parameters equal for all treatment groups | Costs and QALYs equal for all treatments | Partially checked by the ERG. Setting selected parameters equal moved the ICER in the anticipated direction. No issues identified. |

| | | | |
|---|---|---|---|
| | Amend value of each individual model parameter* | ICER is changed | None |
| | Switch all treatment-specific parameter values* | QALYs and costs for each option should be switched | Partially checked by the ERG. Switching selected parameters moved the ICER in the anticipated direction. No issues identified. |
| ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function | | | |

The ERG also checked the model for accuracy by comparing all data included in the report with the corresponding fields in both the originally submitted and revised economic models. These comparisons led to the detection of a number of differences between the respective models and the company submission report, listed in Table 39. Checks were applied to the company's model submitted at clarification stage.

**Table 39 Comparison of company model and report – updated model**

| | **Model** | | **Report** | |
|---|---|---|---|---|
| | **Sheet, cell** | **Value** | **Page/table number** | **Value** |
| CR (base), s.d. | Utilities, D10 | 0.08 | Table 5.28 | N/A |
| Utility decrement, se | Utilities, F12 | 0.02 | Table 5.35 | 0.01 |
| Utility decrement, se | Utilities, F14 | 0.03 | Table 5.35 | 0.02 |
| Utility decrement, se | Utilities, W11 | 7% | Table 5.35 | 20% |
| Utility decrement, se | Utilities, W12 | 2% | Table 5.35 | 20% |
| Utility decrement, se | Utilities, W15 | 11% | Table 5.35 | 20% |
| Utility decrement, se | Utilities, W16 | 6% | Table 5.35 | 20% |
| Gem-P, dose (mg) | Resource Use, E59 | 1250 | Table 5.40 | 1000 |
| Gem-P, dose (mg) | Resource Use, E60 | 25 | Table 5.40 | 100 |
| GCSF Administration, cost (£) | Costs, F227 | 166 | Table 5.57 | 66 |
| Specialist nurse for filgrastim admin (d5), cost (£) | SCT, F87 | N/A | Table 5.58 | 36 |
| Specialist nurse for filgrastim admin (d5), cost (s.e./LQ) | SCT, H87 | N/A | Table 5.58 | 4 |
| Weighted average cost of allo-SCT (£) | SCT, H120 | 108,241 | Table 5.61 | 108,052 |
| ASCT, cost (£) | Sum of SCT; H38, H46, H56 | 10,573 | pg. 150 | 10,884 |

Key: ASCT: autologous stem cell transplant; GCSF: Granulocyte-colony stimulating factor; s.d: standard deviation; se: standard error; LQ: lower quartile

The impact of applying all the values reported in the CS report (rather than model values) to the economic model, reduced the ICER by only £13. Whilst a number of discrepancies were identified between the model and the report, the ERG notes that

these have not had a material impact on the ICER, and therefore do not impact on cost-effectiveness conclusions. As such, the ERG are confident that the company's models pass the internal consistency and error checks applied.

Given the companies approach of disaggregating the no SCT and SCT subgroups of SG035-0004 for modelling, the ERG also cross checked the weighted aggregation of the modelled OS curves with the observed OS KM curve for the whole cohort (n=58) of SG035-0004. This showed that the model in fact slightly under-predicted the observed OS at 5 years (47% Vs 60%) and 7 years (46% Vs 56%)

### *5.3 Exploratory and sensitivity analyses undertaken by the ERG*

This section details the additional work completed by the ERG, and the associated impact on the ICER. For all cases the ERG have considered their revisions according to the revised, corrected version of the economic model submitted by the company on March 22nd, 2017. Section 5.3.1 describes the rectification of minor technical errors identified in the company submission. Section 5.3.2 outlines a number of scenario analyses explored by the ERG to address what we have determined as weak or questionable assumptions in the model or to explore the impact of using different sources of parameter estimates on the ICER. The impact of our exploratory analyses are applied to two alternative base cases (i.e. 'trial based' and 'expert based' distribution of post-progression therapy). The section concludes with a discussion of the ERG's preferred base case ICER.

#### 5.3.1 Model corrections

The ERG identified two technical errors in the company submission and have implemented corrections to remedy these. First, as noted in Section 5.2.5, there was an error in discounting of post-progression therapy costs, whereby discounted costs from one section of the trace were recycled into another part and re-discounted. The ERG considers that all costs should be discounted, once, relative to time 0 in the model (i.e. time from model commencement, not start of post-progression therapy).

The second error relates to the PSA. The distributions of chemotherapy component treatments was incorporated probabilistically, but no correction was applied to ensure that the values actually sum to 1 for each individual simulation. Table 40 reports the impact of the removal of double discounting on the deterministic ICER.

**Table 40 Errors identified in the company submission and ERG corrections applied**

| Model parameter | Model reference | Error identified | Correction applied by ERG | Revised ICER | Change in ICER |
|---|---|---|---|---|---|
| **Base case company ICER** (trial based post-progression therapy distribution) | | | | £19, 470 | N/A |
| Post progression treatments | Tabs: 'TraceChemo' & 'TraceBV)<br><br>Cells: (Col: BH, BR, CB) | Double discounting of post progression therapy costs | Remove double discounting, ensuring costs are discounted once only (from week 1 of the model) | £19, 534 | +0.33% |



### 5.3.2 ERG scenario analyses

The ERG have undertaken a number of further scenario analyses. The objective of these analyses is to explore uncertainty surrounding key model parameters and to identify the assumptions to which the model is most sensitive. We focus on assumptions which may be questionable, or where a judgement call is required. In particular, a number of multi-variate sensitivity analyses are conducted to more fully explore the range of uncertainty in the ICER. Exploratory analyses are applied to the ERG's preferred 'trial based' distribution of post-progression therapies using the model submitted by the company on 22/3/17 as an erratum to clarification response, with the ERG performed correction for double discounting. The ERG have added further switches to the company's model where necessary for ease of implementation. Table 41 outlines the analyses carried out together with a justification for each and Table 42 presents the results.

**Table 41 Additional scenario analyses, including justifications performed by the ERG**

| | Parameter / Analysis | Base case Assumption | Scenario explored | Justification | Relevant section of the ERG report |
|---|---|---|---|---|---|
| **Company models in response to clarification queries** | | | | | |
| BC1 | Post progression therapy distribution | Model assuming trial based distribution of post-progression survival therapy. ERG preferred analysis Errors and bugs corrected from Table 40. | | | Section 5.2.9.2 |
| BC2 | Post progression therapy distribution | Model assuming clinical expert based distribution of post-progression survival therapy. Company preferred analysis. Errors and bugs corrected from Table 40. | | | Section 5.2.9.2 |
| **ERG exploratory analyses** | | | | | |
| ***Methodological choices*** | | | | | |
| 1 | Time horizon | 60 years | 10 years | This analysis explores the scenario of using a shorter time horizon than the base-case, to minimise the uncertainties with the longer term extrapolation curves | Section 5.2.5 |
| 2 | Time horizon | 60 years | 20 years | Alternative exploratory time horizon | Section 5.2.5 |
| 3 | Discounting of costs and QALYs | 3.5% | 0% | To reflect lower range of NICE reference case | Section 5.2.5 |
| 4 | Discounting of costs and QALYs | 3.5% | 6% | To reflect upper range of NICE reference case | Section 5.2.5 |
| 5 | Method of utility incorporation | | Gen. pop norms incorporated multiplicatively. | Exploratory analysis to investigate the impact of applying multiplicative utilities (in accordance with NICE DSU recommendations) | Section 5.2.7 |
| ***Costs*** | | | | | |
| 6 | Number of treatment cycles on brentuximab vedotin (No SCT cohort) | Mean =8 | 4 cycles | Scenario analysis reflects company and ERG clinical expert opinion that brentuximab vedotin treatment would be used over a shorter time period in clinical practice than evidenced in the trial | Section 5.2.8 |
| 7 | Number of treatment cycles on brentuximab vedotin (No SCT cohort) | Mean =8 | 16 cycles | Scenario analysis to reflect the upper bound of possible brentuximab vedotin cost, reflecting the scheduled dosage. | Section 5.2.8 |
| 8 | Costs of administering BV | Weekly | 3-weekly as per dosage guidelines. | This scenario analysis explores the effect of changing the method of calculation to reflect the real life prescription method for brentuximab vedotin | Section 5.2.8 |
| 9 | Costs of adverse events in chemo trace | Cost of adverse events in the chemotherapy (no SCT) and | Adverse event costs of brentuximab vedotin (ASCT) was also applied to | This analysis explored the scenario that all patients receiving ASCT are attached additional costs associated with adverse events. In the company's model, patients receiving brentuximab vedotin (ASCT) are assumed to receive | Section 5.2.8 |

| | Parameter / Analysis | Base case Assumption | Scenario explored | Justification | Relevant section of the ERG report |
|---|---|---|---|---|---|
| | | chemotherapy (ASCT) cohort are equal | chemotherapy (ASCT) | additional costs associated with adverse events, however, patients receiving chemotherapy (ASCT) are attached the same costs as chemotherapy (no SCT). | |
| 10 | Post progression therapy distribution | Distribution allows more than one post-progression therapy | Rescaling the distribution to allow post-progression therapies to sum to 100% | Analysis conducted to explore the impact of allowing only one post-progression therapy according to the 'trial based' distribution. Ensures comparability with the assumed chemotherapy distribution which assumes only one post-progression therapy. | Section 5.2.8 |
| 11 | Source of ASCT costs | Clinical expert | NHS reference costs | This analysis explores the impact of using alternative data for costs of ASCT | Section 5.2.8 |
| 12 | Source of allo-SCT costs | Clinical expert | NHS reference costs | This analysis explores the impact of using alternative data for costs of allo-SCT | Section 5.2.8 |
| 13 | Combined scenarios 11 & 12 | | | All SCT costs based on NHS reference cost data. | Section 5.2.8 |
| ***Utilities*** | | | | | |
| 14 | Long term utility gain past the cured time point | Cured time point – 5 years | Cured time point – 100 years | This analysis is conducted to explore the impact of equalising the utility benefit of long term survivors in both the brentuximab vedotin and chemotherapy cohorts, assuming that all patients who have long term survival will have a utility depending on their state (PFS / PPS), rather than their baseline treatment. | Section 5.2.7 |
| 15 | Adverse event disutilities | Adverse event disutilities in the chemotherapy (no SCT) and chemotherapy (ASCT) cohort are equal | Adverse event utilities of brentuximab vedotin (ASCT) was also applied to chemotherapy (ASCT) | This scenario was explored to see the effect of added utility decrement of adverse events in the chemotherapy (ASCT) (compared to chemotherapy (no SCT)) | Section 5.2.7 |
| 16 | Combined Scenarios 9 & 15 | | | Applying alterations to adverse events (to include additional cost and dis-utility) for ASCT following chemotherapy. | Section 5.2.7 |
| 17 | Utility decrement (versus general population) of patients achieving complete response | 5% | 0% | This analysis explores the scenario that patients achieving complete remission may have no additional utility decrement compared to the general population. | Section 5.2.7 |

| | Parameter / Analysis | Base case Assumption | Scenario explored | Justification | Relevant section of the ERG report |
|---|---|---|---|---|---|
| 18 | Utility decrement (versus general population) of patients achieving complete response | 5% | 20% | This analysis explores the scenario that patients achieving complete remission may have a greater utility decrement compared to the general population. | Section 5.2.7 |
| 19 | Long term utility decrement vs gen pop. | 5% | 0% | Analysis to reflect uncertainty in clinical expert opinion regarding long term survivor utility decrements. | Section 5.2.7 |
| 20 | Long term utility decrement vs gen pop. | 5% | 20% | Analysis to reflect uncertainty in clinical expert opinion regarding long term survivor utility decrements. | Section 5.2.7 |
| 21 | Utility values | Swinburn et al[89] | Doorduijn et al[94] (as per NICE TA 370, FAD) | Explores an alternative utility source based directly on EQ-5D values. | Section 5.2.7 |
| ***Survival parameters*** | | | | | |
| 22 | Excess mortality risk | 5% for brentuximab vedotin and 7% for chemotherapy | Equal (5% for all) | This analysis was conducted to explore the impact of the mortality risk being equal in both arms as the data source of mortality risk in the company's base case is based on one clinical expert, therefore, there is little evidence to support that brentuximab vedotin is superior to chemotherapy | Section 5.2.6.5 |
| 23 | Excess mortality risk | 5% for brentuximab vedotin and 7% for chemotherapy | Equal, (25% for all) | An exploratory analysis to illustrate the impact of assuming a higher long term mortality risk, relative to the general population for cancer survivors. | Section 5.2.6.5 |
| 24 | PFS & OS hazard | No adjustment (OS as per data sources) | -25% | Company explored analysis | Section 5.2.6 |
| 25 | PFS & OS hazard | No adjustment (OS as per data sources) | -50% | ERG explored analysis to judge sensitivity of model to differences in OS curves between treatments in the No SCT cohorts | Section 5.2.6 |
| 26 | PFS & OS hazard | No adjustment (OS as per data sources) | -75% | ERG explored analysis to judge sensitivity of model to differences in OS curves between treatments in the No SCT cohorts | Section 5.2.6 |
| 27 | Brentuximab vedotin PFS data source | Investigator based | IRF based | This analysis was conducted to minimise the inherent bias towards brentuximab vedotin associated with per INV assessment | Section 5.2.6.2 |

| | Parameter / Analysis | Base case Assumption | Scenario explored | Justification | Relevant section of the ERG report |
|---|---|---|---|---|---|
| 28 | Progression free survival for brentuximab vedotin | Log-logistic (cure) | Gamma (standard) | This scenario looks at the effect of using a standard gamma model instead of a cure model for brentuximab vedotin and attempts to neutralise any bias created due to the fact that there may be a small proportion of long term survivors of chemotherapy treatment. Furthermore, the assumption of cure is based on INV data which may be biased. | Section 5.2.6.2 |
| 29 | Overall survival for brentuximab vedotin | Log logistic (Cure) | Lognormal (standard) | To explore the impact of removing the cure model assumption from the assessment of OS for brentuximab vedotin | Section 5.2.6.3 |
| 30 | Progression free survival for chemotherapy | Self-control (SG035-0004) | (PS<2) data source [72] | This analysis explores the impact of using alternative data for PFS, which does not bias towards brentuximab vedotin as when using the self-controls from the SG035-0004 trial. Using the subgroup of patients (PS<2) also presents less heterogeneity between the cohorts in the SG-35-0004 trial and the Mak et al dataset. | Section 5.2.6.2 |
| 31 | Overall survival distribution for chemotherapy | Lognormal (standard) | Kaplan-Meier | Best case data for chemotherapy for OS. | Section 5.2.6.3 |
| 32 | Combined scenarios 27 to 31 | | | Assuming IRF assessed data with standard models (PFS and OS) for brentuximab vedotin with Mak et al. data [72] applied to PFS and OS for chemotherapy | Section 5.2.6 |
| ***SCT parameters*** | | | | | |
| 33 | Rates of SCT across the cohorts | Differential rates applied | Equal in both arms [72] | Analysis provided by the company to explore the impact of SCT rates on the ICER. | Section 5.2.6.1 |
| 34 | Combined scenarios 32 & 33 | | | Most pessimistic assumptions applied to brentuximab vedotin. | Section 5.2.6 |

Key: AE: adverse events; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BC: base case; BV: brentuximab vedotin; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression free survival; PS: performance status; QALY: quality adjusted life year.

**Table 42 Impact of alternative scenario analyses on cost-effectiveness results**

| | | BV | | Chemo | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analysis** | **Description** | **Cost** | **QALY** | **Cost** | **QALY** | **Inc. Cost** | **Inc. QALY** | **Deterministic ICER** |
| **Company submitted models (response to clarification)** | | | | | | | | |
| BC1 | Post progression therapy distribution (trial based, with correction applied) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,534 |
| BC2 | Post progression therapy distribution (expert based, with correction applied) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £12,840 |
| **ERG explored analyses (All applied to BC1)** | | | | | | | | |
| ***Methodological choices*** | | | | | | | | |
| 1 | Time horizon (10) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £48,025 |
| 2 | Time horizon (20) | | | | | | | £27,303 |
| 3 | Discount 0% | | | | | | | £11,189 |
| 4 | Discount 6% | | | | | | | £26,598 |
| 5 | Multiplicative utilities used to incorporate age specific gen pop norms | | | | | | | £15,931 |
| ***Costs:*** | | | | | | | | |
| 6 | No.treatment cycles on brentuximab vedotin (No SCT cohort) =4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £13,131 |
| 7 | No.treatment cycles on brentuximab vedotin (No SCT cohort) =16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,477 |
| 8 | Applying the cost of BV every 3 weeks | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,826 |
| 9 | Apply additional cost to AE for ASCT following chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,525 |
| 10 | Rescaling trial-based post progression therapy distributions (to sum up to 100%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £16,588 |
| 11 | Source of ASCT costs: NHS reference costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,449 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12 | Source of allo-SCT costs: NHS reference costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £17,616 |
| 13 | Combined scenarios 11 & 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £16,531 |
| ***Utilities*** | | | | | | | | |
| 14 | Cure point = 100 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,235 |
| 15 | Apply additional disutility to AE for ASCT following chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,531 |
| 16 | Combined scenarios 9 & 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,525 |
| 17 | Utility decrement of CR: 0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,894 |
| 18 | Utility decrement of CR: 20% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,260 |
| 19 | Utility decrement (Vs. General population) – 0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,847 |
| 20 | Utility decrement (vs. general population) – 20% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,933 |
| 21 | Doorduijn utilities applied in the model. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £17,411 |
| ***Survival*** | | | | | | | | |
| 22 | Equal excess mortality for both arms (5%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,535 |
| 23 | Equal excess mortality for both arms (25%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,958 |
| 24 | PFS & OS hazard (-25%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,200 |
| 25 | PFS & OS hazard (-50%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £31,631 |
| 26 | PFS & OS hazard (-75%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| 27 | BV PFS based on IRF data | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,408 |
| 28 | BV PFS (standard gamma model) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,346 |
| 29 | BV OS (standard gamma model) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,119 |
| 30 | Chemo PFS (KM data from Mak et al PS<2)[72] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,336 |
| 31 | Chemo OS (KM data from Mak et al)[72] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,794 |
| 32 | Combined scenarios 27 to 31 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £38,927 |
| ***SCT*** | | | | | | | | |
| 33 | Equal rates of SCT progression in both arms | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,528 |
| 34 | Combined scenarios 32 & 33 (worst case for BV) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £50,190 |

Key: AE: adverse events; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BC: base case; BV: brentuximab vedotin; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression free survival; PS: performance status; QALY: quality adjusted life year.

The ERG found that the ICER was most sensitive to the time horizon employed in the model, the discount rate applied, the cost of brentuximab vedotin (i.e. the number of cycles of treatment) and assumptions regarding the relative treatment effectiveness (PFS and OS) for brentuximab vedotin relative to chemotherapy. The ERG notes that the model was not particularly sensitive to assumptions surrounding utility inputs.

As discussed in Section 5.2.6, Figure 9, there were substantial differences between the PFS curves depending on the source of data for brentuximab vedotin (INV or IRF) and chemotherapy (self-controls vs. Mak et al.). As such, the ERG considers that a plausible but conservative estimate of the ICER can be obtained using IRF data for PFS and standard parametric models for both PFS and OS for brentuximab vedotin, together with Mak et al data (PTCL subgroup, PS<2, N=47) for chemotherapy (OS and PFS).[72] The resultant ICER, increased from £19, 534 to £38,927. A worst case scenario for brentuximab might result from combining this analysis with the assumption of equal rates of progression to SCT for both chemotherapy and brentuximab vedotin. The resultant deterministic ICER in this more pessimistic scenario increases to £50,190 per QALY gained. The probabilistic ICER is £54,202 per QALY gained and the probability of cost-effectiveness falls to 7%, 22% and 48% at a willingness to pay for a QALY gain of £20,000, £30,000 and £50,000 respectively.



With regards to costs, the ICER was most sensitive to the cost of brentuximab vedotin and the number of treatment cycles required. The ERG note that there is uncertainty regarding the number of cycles that would be offered in practice, with clinical experts noting that treatment could be for 4-6 cycles, and the scheduled dosage being 16 cycles. A judgement call is required as to the most appropriate number of cycles for inclusion in the model. As noted in the response to clarification queries, the ICER is also sensitive to the costs of post progression therapy and the respective distributions applied. It is the ERGs view that the distribution based on trial data from SG035-0004 is the most appropriate, hence its use in all the exploratory analyses above.

Discount rates and time horizon had a relatively large impact on the ICER. This is because most of the costs are incurred in the early part of the model with treatment

effectiveness accruing and sustaining over the longer term (particularly due to the use of mixture cure models in the brentuximab vedotin patients). The ERG notes that whilst uncertainty exists with respect to the values selected for these parameters, the analysis is in line with the NICE reference case.

*ERG preferred base case*

The ERG has considered the range of alternative analyses presented in the company's submission together with further exploratory analyses conducted at clarification stage and additional ERG exploratory analyses.

The ERG prefers the use of the 'trial based' distribution of post-progression therapy costs, stripping the costs of brentuximab vedotin out of the chemotherapy comparator. The ERG also prefers the use of data from Mak et al for both PFS and OS. [72] The deterministic ICER for the ERG preferred analysis (£21,336) is provided in Table 42 above, analysis no.30. Table 43 presents the probabilistic results, with an ICER of £20,720, with a 53%, 78% and 99% probability of cost-effectiveness at threshold values of willingness to pay for a QALY gained of £20,000, £30,000 and £50,000 respectively.



**Table 43 ERG preferred base case analysis (probabilistic results)**

| Comparator | Costs | QALYs | ICER | P (C/E) @ £20k | P (C/E) @ £30k | P (C/E) @ £50k |
|---|---|---|---|---|---|---|
| Brentuximab vedotin | [redacted] | [redacted] | | | | |
| Chemotherapy | [redacted] | [redacted] | | | | |
| Incremental | [redacted] | [redacted] | £20,720 | 53% | 78% | 99% |

### *5.4 Conclusions of the cost effectiveness section*

The company's base case ICER (original submission) was £8,829 per QALY. A revised submission, correcting a violation of post-progression therapies resulted in an increased ICER of £19,470 (trial based post-progression therapy distribution) and £12,873 (clinical expert opinion post-progression therapy distribution). Following correction of a bug in discounting of post-progression therapy by the ERG, these ICERs increased slightly to £19,534 and £12,840 respectively. The ERG's preferred

analysis applies the 'trial based' post progression therapy distribution, corrects the minor technical error (removing double discounting of post-progression therapy costs), and uses data from Mak et al. [72] (as opposed to internal self-controls from SG035-0004) to model PFS for chemotherapy. The resultant deterministic ICER (£21,336) is considered to offer a plausible alternative to the company's base case analysis. The probabilistic analysis shows that under this revised base case, there is a 53%, 78% and 99% probability of cost-effectiveness at a willingness to pay per QALY of £20,000, £30,000 and £50,000 respectively.

The ERG considers the following to represent key issues of uncertainty for decision making:

- The true rate of stem cell transplantation following brentuximab vedotin or chemotherapy is unclear. The higher the rate of SCT following brentuximab vedotin, the higher the resultant ICER. This is due to progression to a high cost treatment for minimal additional survival gain over the No SCT cohort.
- The method of assessment used to gauge progression in brentuximab vedotin. The use of longer term INV data are suggestive of cure/long-term remission (without SCT) for a proportion of patients. However, the likely less biased per IRF data report a higher proportion progressing with no evidence of cure (albeit at a shorter follow up).
- A related point of uncertainty is therefore whether it is appropriate to use a mixture cure model for brentuximab vedotin, but not for chemotherapy, given the conflicting evidence from per INV and per IRF assessment.
- The model is sensitive to the costs of brentuximab vedotin and the most appropriate number of cycles in the model (observed in trial: 8 cycles; expert opinion: 4-6 cycles; scheduled dosage: 16 cycles).
- The distribution of post-progression therapy. The ERG considers the initial model (assuming 80% of chemotherapy patients receive brentuximab vedotin) to be outwith the scope of the appraisal. However, a judgement call is required as to whether the revised 'trial based' distribution or 'expert based' distribution is most appropriate. The ERG takes the view that the former should be preferred.

- The appropriateness of using Swinburn et al as a source of utility, based on health state vignettes with emotionally charged, condition specific language. The ERG offers an alternative source (Doorduijn et al) based on EQ-5D data in an older population in Belgium / Netherlands, which does not differentiate by clinical response. As such the alternative source provides utilities only for progressed and non-progressed disease.

# 6 Overall conclusions

The company's submission considered brentuximab vedotin for treating people with R/R sALCL. The comparator was established clinical management without brentuximab vedotin. In UK clinical practice, this equates to salvage chemotherapy regimens either on their own or with consolidating ASCT or allo-SCT. Brentuximab vedotin has been adopted as the standard of care in the UK for R/R sALCL since 2012.

The company's systematic review identified six studies which addressed the decision problem. The company based their clinical effectiveness evidence mainly on the SG035-0004 study, a prospective, open-label, single-arm, interventional multicentre study which was sponsored by Seattle Genetics and had links to Takeda Pharmaceuticals. The study included 58 patients with relapsed or refractory sALCL and at least one prior multi-agent chemotherapy regimen. The remaining five studies included in the company's review of clinical effectiveness included two retrospective case series and three NPPs, one of which did not fulfil the inclusion criterion of at least 20 patients with sALCL; its inclusion is questioned by the ERG. Otherwise, the ERG considered that the company's systematic review of clinical evidence was broadly adequate.

The company did not conduct any meta-analyses as only non-randomised single-arm studies were identified in the systematic review. The results of the six included studies provided evidence that brentuximab vedotin was effective in producing objective responses in the majority of patients, including complete remission in at least half. A substantial number of adverse events were reported, with every patient in the SG-035-0004 study experiencing at least one adverse event. The most common adverse events of any grade were peripheral sensory neuropathy, nausea, fatigue and pyrexia. The most common adverse events of grade 3 or above were neutropenia, thrombocytopenia, peripheral sensory neuropathy and anaemia. There were some cases of adverse events leading to treatment discontinuation or dose delays. No deaths were attributable to brentuximab vedotin.

The company submitted a *'de novo'* partitioned-survival model. Progression free survival (PFS), post-progression survival (PPS) and death were modelled, with health state occupancy based on the area under the modelled PFS and OS curves. The original company submission predicted additional costs for brentuximab vedotin of [redacted] additional life years of 6.18 and additional QALYs of [redacted] over chemotherapy. The ICER was £8,829. After adopting the revised 'trial based' post progression therapy distribution, stripping out the costs of brentuximab vedotin in the chemotherapy arm, and correction of a minor technical error, the ICER increased to £19,470 per QALY gained after response to clarification queries. The probabilistic ICER was £19,034 per QALY gained, with a probability of cost effectiveness of 58%, 83% and 100% at a willingness to pay per QALY gained of £20k, £30k and £50k respectively.



The ERG considers the submitted model to be generally of good quality, with an appropriate model structure given the lack of comparative data. There are however a number of uncertainties, and a judgement call will be required to determine which parameter inputs and data sources are most appropriate in the UK setting. In the ERG's view, the most important areas of uncertainty are:

- The most likely rate of SCT following brentuximab vedotin and chemotherapy
- The most appropriate assessment data (INV or IRF) to consider for brentuximab vedotin PFS
- The appropriateness of using a mixture cure model for brentuximab vedotin, compared to a standard model for chemotherapy (PFS and OS).
- The most appropriate distribution of post-progression therapy used in the model.

The ERG conducted a range of exploratory analyses (including multi-variate analyses) to explore the impact of key uncertainties on the ICER. The ERG's preferred base case analysis uses Kaplan Meier data from Mak et al. for chemotherapy PFS instead of the internal self-controls from SG035-0004, applied to the company's 'trial based' distribution of post-progression therapy. The associated ICER was £21,336 per QALY gained (probabilistic ICER: £20,720). The probability that

brentuximab vedotin is cost-effective under the ERG's preferred base case assumptions is 53%, 78% and 99% at a willingness to pay for a QALY gain of £20,000, £30,000 and £50,000 respectively. A worst-case scenario for brentuximab vedotin (IRF data and Mak et al for brentuximab vedotin and chemotherapy PFS respectively; with equal rates of SCT across arms) increases the ICER to £50,190 per QALY gained in the most pessimistic scenario considered. The ERG further note that rreducing the hazard of progression and mortality in the chemotherapy arm, significantly increases the ICER for brentuximab vedotin.

### *6.1 Implications for research*

There are a number of activities ongoing as part of the company's conditional marketing authorisation from brentuximab vedotin. These include the long-term follow-up (for OS) of patients from SG035-0004. This will in time help to assess the validity of the long-term survival assumptions underpinning the cost-effectiveness modelling for this submission. Further ongoing research relates to the post authorisation safety study (PASS) currently being conducted, which is due to report in 2018. Further research which could help to address uncertainties in the economic model include: 1) studies to assess health state utilities (using a generic validated instrument) of patients being treated for R/R sALCL – including long-term responders with and without SCT; and 2) if possible, further retrospective analyses of registry data for the relevant patient populations who received salvage chemotherapy for R/R sALCL. The latter type of study will depend on the identification of a suitable data source, and should ideally compare outcomes whilst matching on known prognostic factors with patients in SG035-0004.

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# 8 Appendices

**Appendix 1 Additional search undertaken by ERG for HRQoL for non-Hodkin's lymphoma**

Database: Embase <1996 to 2017 Week 13>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Date of search: 14th March 2017

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1 lymphoma, non-hodgkin/ or lymphoma, t-cell/ or lymphoma, large-cell, anaplastic/ or lymphoma, t-cell, peripheral/ or nonhodgkin lymphoma/

2 (lymphoma$ adj3 (anaplastic or t-cell or non-hodgkin)).ti,kw.

3 1 or 2

4 quality adjusted life year/

5 (qaly? or qald? or qale? or qtime?).tw,kf.

6 (euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).tw,kf

7 (eq-sdq or eqsdq).tw,kf

8 (hye or hyes).tw,kf.

9 health$ year$ equivalent$.tw,kf.

10 (hui or hui1 or hui2 or hui3).tw,kf.

11 (quality adjusted or adjusted life year$).tw,kf

12 disability adjusted life.tw,kf.

13 daly?.tw,kf.

14 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).tw,kf.

15 (multiattribute$ or multi attribute$).tw,kf.

16 (utility adj3 (score? or scoring or valu$ or measur$ or evaluat$ or scale? or instrument? or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure? or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).tw,kf.

17 utility.ab. /freq=2

18 utilities.tw,kf.
19 disutili$.tw,kf.
20 (hsuv or hsuvs).tw,af.
21 (illness state$ or health state$).tw,kf.
22 (shortform$ or short form$).tw,kf
23 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).tw,kf.
24 (sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).tw,kf.
25 (sf12 or sf 12 or sf twelve or sftwelve).tw,kf.
26 (sf16 or sf 16 or sf sixteen or sfsixteen).tw,kf.
27 (sf20 or sf 20 or sf twenty or sftwenty).tw,kf.
28 (15d or 15-d or 15 dimension).tw,kf.
29 standard gamble$.tw,kf.
30 (time trade off$ or time tradeoff$ or tto or timetradeoff$).tw,kf.
31 (case report or editorial or letter).pt.
32 case report/
33 or/4-30
34 3 and 33
35 34 not (31 or 32)

# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

**Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]**

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 20 April 2017** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

**Issue 1** **Sections 1, 2 and 3.2**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Pages 1, 11, 16<br>Location of Takeda UK Ltd., listed as Taastrup, Denmark | Change to Wooburn Green, UK | This is the address for the part of the business that is responsible for placing brentuximab vedotin onto the market in the UK and for this NICE appraisal | Text amended as suggested, and erratum pages provided |

**Issue 2** **Section 1**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 1<br>Individual funding requests for Scotland and Wales incorrectly referred to as independent funding requests | Replace ‘independent’ with ‘individual’ | Incorrect terminology | Text amended as suggested and erratum pages provided |

**Issue 3** **Sections 1.2, 2 and 3.1**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Pages 2, 13 and 16<br>The patient population is relapsed or refractory sALCL and not relapsed or recurrent sALCL as | Replace ‘recurrent’ with ‘refractory’ | Incorrect terminology | Text amended as suggested and erratum pages provided |

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| stated in the text | | | |

**Issue 4** **Section 4.2**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 44<br><br>In the section 4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)<br><br>It states that the company's submission reported CR of 59% (34/58) and PR of 28% (16/58). In contrast, the Pro et al 2012 publication reports a CR rate of 57% (33/58) and PR of 29% (17/58). The Pro et al 2016 poster of five-year survival data reports that 34 patients achieved CR per independent review and 38 per investigator.[79] The reason for these discrepancies is unclear to the ERG. | Suggested amendment:<br><br>The company's submission reported CR of 59% (34/58) and PR of 28% (16/58). In contrast, the Pro et al 2012 publication reports a CR rate of 57% (33/58) and PR of 29% (17/58). This discrepancy can be accounted for by a late conversion from a PR to a CR in one patient.<br><br>The Pro et al 2016 poster of five-year survival data reports that 34 patients achieved CR per independent review and 38 per investigator. Concordance assessment between the investigator and IRF outcomes was found to be 93%, while ORR was 86% in both groups. | The Pro 2012 publication reflected the initial report (in which the ORR met its primary end point). The discrepancy in CR rate with the Pro 2016 can be accounted for by a late conversion from a PR to a CR in one patient.<br><br>Small discrepancy between IRF and investigator outcomes is not unexpected. Overall concordance assessment between the investigator and IRF outcomes was found to be 93% and the primary outcome of ORR was found to be 86% in both groups. | Text amended as suggested and erratum pages provided |

**Issue 5** **Section 4.2**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 46<br>Patient numbers for ALK+ve and ALK-ve from the SG035-0004 study are incorrect.<br>It currently states 'There were 16 patients with ALK- disease and 42 patients with ALK+ disease' | The correct wording is 'There were 16 patients with ALK+ve disease and 42 patients with ALK-ve disease' | Incorrect data | Text amended as suggested and erratum pages provided |

**Issue 6** **Section 5.2.4**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 67<br>Orphan status designation is incorrectly stated.<br>It currently states 'Brentuximab vedotin has been designated as an orphan drug by the European Medicines Agency [41] prescribed for patients with no other salvage therapy available to them; i.e. following ASCT or for patients who had already undergone a minimum of two other therapies (in which ASCT or multi-agent chemotherapy failed)' | There is no requirement either in the orphan designation or the marketing authorisation for brentuximab vedotin in relapsed or refractory sALCL for patients to have no other salvage therapy available to them. The wording 'i.e. following ASCT or for patients who had already undergone a minimum of two other therapies (in which ASCT or multi-agent chemotherapy failed) is related to the marketing authorisation in relapsed or refractory Hodgkin lymphoma.<br><br>Suggested amendment:<br>'Brentuximab vedotin has been designated as an orphan medicinal product by the European Medicines Agency [41] for the treatment of | Inaccurate information | The ERG accept this correction (please see erratum, pg. 67) |

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| | sALCL’ | | |

## Issue 7 Section 5.2.4

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 67<br>The Cancer Drugs Fund listing is incorrect and not consistent with the current requirements. | Suggested amendment:<br>‘Brentuximab vedotin has been approved for use on the national Cancer Drugs Fund (CDF) since 2013 for R/R sALCL’ | The initial recommendation by the CDF in 2013 that limited the use of brentuximab vedotin in RR sALCL to patients where no other salvage treatment is available was changed following discussion between Takeda and NHS England. As there was no clinical justification or evidence to support this limitation it was removed by NHS England and the listing changed to be consistent with the marketing authorisation (i.e. R/R sALCL) | The ERG accept this correction for clarity, but note that the text was taken from the company original submission (p35). (please see erratum, pg. 67) |

## Issue 8 Section 5.2.6.2

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 75<br>In Section 5.2.6.2 Progression Free Survival it states ‘The primary endpoint for the trial was per IRF, with per Investigator as a secondary | Suggested amendment:<br>‘Disease progression in the SG035-0004 trial was assessed by two alternative methods: as per investigator (INV) decision and as per independent review facility (IRF) decision. | Both endpoints were pre-specified and were secondary/exploratory endpoints. Neither were the primary endpoint. PFS per IRF was determined by blinded CT/PET-CT scan only whereas Per INV also | The ERG were referring to the main analysis in the trial pertaining to PFS (as per the section heading in the ERG assessment report). However, the ERG accepts |

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| analysis'.<br><br>This suggests that the primary endpoint of the study was PFS by IRF. The primary end point was objective response rate (ORR) by IRF. PFS by IRF and per Investigator were pre-specified secondary/exploratory endpoints. | PFS per IRF was a pre-specified secondary endpoint and PFS per INV a pre-specified exploratory endpoint.' | included clinical assessment in addition to CT/PET-CT scan. In the CSR (dated 29/11/11), the median PFS per IRF and per INV were similar (14.3 and 14.5 months respectively). For patients in long term remission (>2 years) who are at low risk of subsequent progression of their disease it would not be appropriate to expose them to unnecessary CT or PET-CT scans. For this reason a protocol amendment was implemented in October 2013 stipulating that a CT scan would only be performed if progression was suspected clinically. Therefore, long term follow up (5 years) of patients was per INV criteria and not per IRF. Per INV is a relevant endpoint as it more closely reflects how relapse is detected and documented in clinical practice. | that the phrasing may have been misleading and have accepted the company's suggested amendment (please see erratum, pg. 75). |

## Issue 9 Section 1.4 Summary of cost-effectiveness evidence submitted by the company

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 3<br>"Six cohorts were modelled according to assumptions regarding progression to stem | Modification of statement to "Six cohorts were modelled according to assumptions regarding the proportion of patients who proceed to stem cell transplantation following each | Use of "progression" is incorrect in this context. Patients typically receive SCT following salvage therapy in the absence of disease progression. | This is not an inaccuracy, progression in this context refers to movement to SCT and not disease progression. No amendment has |

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| cell transplantation following each treatment." | treatment." | | been made to the ERG report. |
| Page 4<br>"The base case analysis of chemotherapy PFS was informed using internal self-control data from the single arm, open label, non-randomised SG035-0004 study for a subset of 39/58 (67%) of patients who had previously had a salvage chemotherapy for R/R disease." | Modification of statement to "The base case analysis of chemotherapy (no SCT) PFS was informed using internal self-control data from the single arm, open label, non-randomised SG035-0004 study for a subset of 39/58 (67%) of patients who had previously had a salvage chemotherapy for R/R disease." | The current statement is incorrect. Chemotherapy (no SCT) PFS was informed by the self-control dataset. | The statement is correct, but the ERG have added '(no SCT)' for clarity. (Please see erratum, pg. 4) |
| Page 4<br>"It was assumed that chemotherapy would not be curative with subsequent stem cell transplant, therefore standard parametric survival models were used for both PFS and OS in the chemotherapy cohort." | Modification of statement to "Standard parametric models were used to model PFS and OS for the chemotherapy (no SCT) cohort as conventional chemotherapies were not considered curative." | Use of "it was assumed that chemotherapy would not be curative with subsequent stem cell transplant" is incorrect in this context. In the base case, 7% and 7% of chemotherapy patients receive the outcomes associated with ASCT and alloSCT respectively which are curative treatments.<br>The company believe that the ERG is referring to the chemotherapy (no SCT) cohort. | Thank you for pointing out this typographical error. The text is amended to read:<br>"It was assumed that chemotherapy would not be curative without subsequent stem cell transplant, therefore standard parametric survival models were used for both PFS and OS in the chemotherapy (No SCT) cohort."<br>(Please see erratum, pg. 4) |
| Page 4<br>"In all cases, an additional 5% excess mortality risk was applied to general population life-table estimates to model | Modification of statement to "General population mortality was applied as a competing risk to all parametric extrapolations for all cohorts. Excess mortality risks based on clinical expert opinion were also applied to general | This is incorrect. A 5% excess mortality risk was applied to the brentuximab (no SCT) cohort only. | The figure of 5% was mistakenly entered in the text here and has now been removed. The revised text reads:<br>"An additional excess mortality risk |

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| long-term survival in those assumed to be cured." | population life-table estimates (brentuximab vedotin no SCT [5%], brentuximab + SCT [10%], chemotherapy no SCT [7%], chemotherapy + SCT [10%])." | | was applied to general population life-table estimates for all cohorts."<br>(Please see erratum, pg. 4) |

## Issue 10 Section 1.7 Summary of explanatory and sensitivity analyses undertaken by the ERG

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 8<br>"Further uncertainty relates the magnitude of the survival benefit for brentuximab vedotin versus chemotherapy, which is based on an unadjusted naïve indirect comparison between independent single arm studies with heterogeneous cohorts." | Modification of statement to "Further uncertainty relates the magnitude of the survival benefit for brentuximab vedotin (no SCT) versus chemotherapy (no SCT), which for OS is based on a naïve indirect comparison between SGN35-0004 and Mak et al. (2013), with observed heterogeneity with respect to age and stage of disease." | As highlighted in the original CS and on page 48 of the ERG report, heterogeneity between SGN35-0004 and Mak et al. (2013) was evident for age, disease stage and performance status. Given OS for chemotherapy (no SCT) is informed by the subgroup of PTCL patients in Mak et al. (2013) with performance status <2 (n = 47), any bias induced through differences in performance status has been accounted for. | The ERG accepts this correction. (Please see erratum, pg. 8) |

## Issue 11 Section 4.4 Critique of the indirect comparison and/or multiple treatment comparisons

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 47<br>"However, the economic modelling relied on a number of sources to make unadjusted | Modification of statement to "However, the economic modelling relied on unanchored indirect comparisons between brentuximab vedotin (no | The current statement is incorrect. Unanchored comparisons were made between brentuximab vedotin (no SCT) and chemotherapy (no SCT). | Text amended as suggested<br>(Please see erratum) |

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| comparisons between brentuximab vedotin and chemotherapy." | SCT) and chemotherapy (no SCT)." | | |
| Page 48<br>"In terms of overall survival, unadjusted indirect comparisons in the economic model are made between the results of the SG035-0004 trial and results reported be Mak et al 2013." | Modification of statement to "In terms of overall survival for the no SCT cohorts, unanchored indirect comparisons in the economic model are made between the results of the SG035-0004 trial and results reported by Mak et al 2013." | The current statement is incorrect. Unanchored indirect comparisons were made between brentuximab vedotin (no SCT) and chemotherapy (no SCT). | Text amended as suggested<br>(Please see erratum) |

## Issue 12 Section 5.2 Summary and critique of company's submitted economic evaluation by the ERG

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 69<br>"A minor error was noted by the ERG with respect to the apparent double discounting of post progression treatment costs." | Modification of statement to "A methodological note was made by the ERG with respect to the double discounting of post-progression costs." | Use of the term "error" is incorrect.<br>The ERG is correct in stating that all costs and outcomes must be discounted back to time zero. The model does so by:<br>1) discounting the full stream of post-progression treatment costs deriving the NPV of these costs at the point of progression<br>2) assigning this discounted sum (the NPV at time of progression) to progressing patients at the time they progress<br>3) discounting (using the discount factor relevant to time of progression) the NPV of post-progression costs at the time of progression to derive the NPV at time zero.<br>The company wished to clarify the basis of double discounting in the model, and highlight that the ERG's adjustment may be inappropriate. However, the company recognise that the modification impacts both treatment arms, and hence has minimal impact on the results. | The ERG thank the company for their explanation, which now provides clarity on the discounting approach. On reflection, the ERG agrees that it is inappropriate to label the company's approach as an error. The ERG has amended the text to remove reference to an error.<br>(Please see erratum, pg. 69 - 70) |
| Page 69-70<br>"The ERG has corrected this error and finds that the impact of removing the second | Modification of statement to "The ERG explored removing the second discounting of post-progression therapy costs and found the impact | Use of the term "error" is incorrect.<br>Following inspection of the amended model supplied by the ERG, it appears that the removal of 'second discounting' refers to the costs accrued | The ERG removes reference to an error.<br>Additionally, an incorrect |

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| discounting of post-progression therapy costs is minimal." | to be minimal." | in post-progression phase; discounting of which is covered by step 1 cited above.<br><br>Thus, the removal of the 'second discounting' results in undiscounted post-progression costs being subject to partial discounting (step 3 above) back to time zero; therefore under discounting these costs. | spelling of brentuximab has been corrected on pg. 70<br><br>(Please see erratum, pg. 69-70). |
| Page 80<br><br>"The company therefore relied on a naïve unadjusted indirect comparison when using data from Mak et al to model PFS." | Modification of statement to "The company therefore relied on a naïve indirect comparison when using data from Mak et al to model PFS for chemotherapy (no SCT)." | The current statement is incorrect. Data from Mak et al was used to model PFS for chemotherapy (no SCT). | The section heading clearly states "Chemotherapy (No SCT)".<br><br>No amendment required. |
| Page 81<br><br>"The CS uses standard parametric models rather than cure models to extrapolate chemotherapy PFS, using the self-control data from SG035-0004." | Modification of statement to "The CS uses standard parametric models rather than cure models to extrapolate chemotherapy (no SCT) PFS, using the self-control data from SG035-0004." | The current statement is incorrect. Chemotherapy (no SCT) PFS was informed by the self-control dataset and extrapolated using standard parametric models. | The statement is correct. The section heading clearly states "Chemotherapy (No SCT)".<br><br>No amendment required. |
| Page 83<br><br>"Figure 9 presents six different survival curves for PFS that could be implemented in the model to illustrate the range of uncertainty underpinning the choice of data:<br><br>1. Brentuximab vedotin, no SCT (per INV assessment) using a log-logistic cure model | Modification of statement to "Figure 9 presents seven different survival curves for PFS that could be implemented in the model to illustrate the range of uncertainty underpinning the choice of data:<br><br>1. Brentuximab vedotin, no SCT (per INV assessment) using a log-logistic cure model (CS base case model)<br><br>2. Brentuximab vedotin, no | The current text is incorrect. PFS for chemotherapy (no SCT) can be informed by Mak et al. (2013) using the subgroup of patients with ALCL (n=17). | The text is correct. The company refers to the potential for a further analysis. There are many others which could have been considered. The ERG considered the six curves presented in figure 9 to be most informative. No amendment required. |

| | | | |
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| (CS base case model)<br>2. Brentuximab vedotin, no SCT (per IRF assessment) using a log logistic cure model<br>3. Brentuximab vedotin, no SCT (per INV assessment) using a standard, non-cure gamma model;<br>4. Brentuximab vedotin, no SCT (per IRF assessment) using a standard non-cure Log normal model<br>5. Chemotherapy, no SCT (self-control data) using a standard log normal model<br>6. Chemotherapy, no SCT (Mak et al cohort, PS<2) using KM curve | SCT (per IRF assessment) using a log logistic cure model<br>3. Brentuximab vedotin, no SCT (per INV assessment) using a standard, non-cure gamma model;<br>4. Brentuximab vedotin, no SCT (per IRF assessment) using a standard non-cure Log normal model<br>5. Chemotherapy, no SCT (self-control data) using a standard log normal model<br>6. Chemotherapy, no SCT (Mak et al cohort, PS<2) using KM curve<br>7. Chemotherapy, no SCT (Mak et al cohort, ALCL) using KM curve | | |
| Page 84<br>Figure 9 | Chemo, Mak ALCL, KM should be added to this figure. | The figure does not illustrate that chemotherapy (no SCT) can be informed by Mak et al. (2013) using the subgroup of patients with ALCL (n=17). | This is not an error. The ERG did not intend to present the data to which the company refer. No amendment required. |
| Page 84<br>"The company's preferred base case assumptions (per INV | Removal of statement | This is incorrect. An exponential parametric cure model was the most optimistic scenario to model PFS for brentuximab (no SCT). | The ERG report intended to refer to the analyses conducted in Figure 9. This |

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| assessment, using a log-logistic mixture cure model) was the most optimistic scenario for modelling brentuximab vedotin PFS." | | | is now clarified in the text.<br><br>(Please see erratum). |
| Page 85<br>"In order to reflect that there may be an additional residual mortality risk, the company applied an additional 5% excess mortality, based on clinical expert opinion, to all parametric OS extrapolations." | Modification of statement to "In order to reflect that there may be an additional residual mortality risk, the company applied an additional 5% excess mortality, based on clinical expert opinion, to all parametric OS extrapolations for the brentuximab (no SCT) cohort." | The current statement is incorrect. A 5% excess mortality risk was applied to the brentuximab (no SCT) cohort only. | The statement is correct. The section heading clearly states that the ERG refers to "Brentuximab vedotin (No SCT)".<br>No amendment required. |
| Page 88<br>"It should also be noted that the cohort used by Hux et al. comes from the same source as the data reported by Mak et al. and the company were asked to comment on the overlap between these cohorts. However, they noted that they had insufficient time to ascertain this." | Modification of statement to "It should also be noted that the cohort used by Hux et al. comes from the same source as the data reported by Mak et al. and the company were asked to comment on the extent of overlap between these cohorts. However, they noted that they had insufficient time to ascertain this." | The current statement is incorrect. The company provided some detail on the overlap in the responses to the clarification questions; the company could not determine the extent of the overlap. | The statement is correct. The exact wording of the clarification query sent to the company was<br>*"Please clarify, if possible, the overlap between the data used in Hux et al. and the data reported by Mak et al, which is used in the company submission".*<br>No amendment required. |
| Page 94<br>"The excess applied mortality did not depend on the estimated cure fraction in the model or the type of extrapolation model used (i.e. | Modification of statement to "The excess applied mortality in the model was treatment-dependent (brentuximab vedotin no SCT [5%], brentuximab + SCT [10%], chemotherapy no SCT [7%], chemotherapy + SCT [10%]), and | Use of "the excess applied mortality did not depend on the estimated cure fraction" is misleading; the estimated cure fraction is likely to be dictated by treatment, and the excess mortality applied was dependent on treatment. | The statement is correct. As the company correctly point out, excess mortality risks were treatment dependent. The ERG report clearly states this on page 94: |

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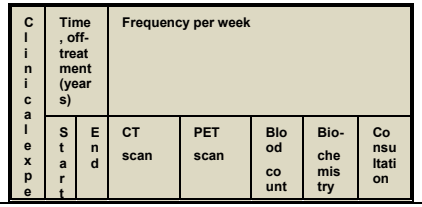
| cure or standard)." | was independent of the type of extrapolation model used (i.e. cure or standard)." | | *"The company added excess mortality risks (5% brentuximab vedotin, 7% chemotherapy, 10% SCT) to reflect the remaining risk of secondary malignancies due to residual effects of therapy, even among those who have long term remission."*<br><br>No amendment required. |
| Page 99<br>"The ERG are concerned that by assuming a cured time point of 5 years in the brentuximab vedotin arm but not the chemotherapy arm, the model assigns different utility decrements to longer term survivors across the different cohorts. This creates a scenario which biases against chemotherapy survivors." | Removal of statement | This is incorrect. A cured time-point is applied in the model for the chemotherapy (no SCT) cohort. | The ERG accepts that this statement is misleading. The statement is amended as follows:<br>"The ERG are concerned that by assuming a cured time point of 5 years, the model may over-estimate QALY gains. This potential over-estimation is greater for brentuximab vedotin (No SCT) than for chemotherapy (No SCT) given the higher proportion experiencing progression in the latter cohort."<br>(Please see erratum). |
| Page 110 | Modification of statement to "The cost of ASCT includes the cost of | The current statement is incorrect. | Text amended as suggested |

<table>
<tr>
<td>“The cost of SCT includes cost of donation, BEAM conditioning, transplant and follow-up care for both ASCT and allo-SCT.”</td>
<td>donation, BEAM conditioning and transplant. The cost of allo-SCT includes the cost of preparation, donation, conditioning, transplant and immunosuppressives.”<br><br>Revised statement should be moved to after “In both cases, the company provided an alternative sensitivity analysis, based on national unit costs for key components of the transplant process.”</td>
<td></td>
<td>(Please see erratum)</td>
</tr>
<tr>
<td>Page 115<br><br>“For both brentuximab vedotin and chemotherapy, patients in the model incur costs associated with follow-up both on and off treatment.”</td>
<td>Modification of statement to “For both the brentuximab vedotin (no SCT) and chemotherapy (no SCT) cohorts, patients in the model incur costs associated with follow-up both on and off treatment.”</td>
<td>The current statement is incorrect. This text refers explicitly to the no SCT cohorts.</td>
<td>Text amended as suggested<br><br>(Please see erratum)</td>
</tr>
<tr>
<td>Page 115<br><br>“Follow-up care for the first three years off-treatment was costed as one CT and one PET scan over the three year period. Blood counts, biochemistry and consultations were converted to weekly frequencies (0.07 per week). From year three (post treatment) onwards, no follow up was assumed for the pre-progression state in the base case analysis. Frequencies</td>
<td>Modification of statement to “Follow-up care for the first three years off-treatment was costed as one CT and one PET scan over the three year period. Blood counts, biochemistry and consultations were converted to weekly frequencies (0.07 per week). From year three (post treatment) onwards, no follow up was assumed for the pre-progression state in the base case analysis. Frequencies were based on two clinical experts’ opinions.”</td>
<td>The current statement may be misleading as two clinical experts were consulted. Frequencies of CT and PET scans provided by both experts align (see below).<br><br> 
<table>
<tr><th rowspan="2">Clinical expe</th><th colspan="2">Time, off-treatment (years)</th><th colspan="5">Frequency per week</th></tr>
<tr><th>Start</th><th>End</th><th>CT scan</th><th>PET scan</th><th>Blood count</th><th>Bio-chemistry</th><th>Consultation</th></tr>
</table></td>
<td>The statement is correct. In the interest of clarity, two clinical experts were consulted by the company. The resource use provided by clinical expert no.1 was used in the base case analysis. The model included functionality to allow the data from expert no. 2 to be considered as an alternative. There was no attempt to synthesise or merge the data from the experts in any way.</td>
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<td>were based on one clinical expert's opinion."</td>
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<table>
<tr><th>rt</th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></tr>
<tr><td rowspan="2">1</td><td>0</td><td>3</td><td>One post-treatment</td><td>One post-treatment</td><td>0.07</td><td>0.07</td><td>0.07</td></tr>
<tr><td>3</td><td>6.5</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td></tr>
<tr><td rowspan="2">2</td><td>0</td><td>2</td><td>One post-treatment</td><td>One post-treatment</td><td>0.07</td><td>0.07</td><td>0.07</td></tr>
<tr><td>2</td><td>5.5</td><td>0.00</td><td>0.00</td><td>0.04</td><td>0.04</td><td>0.04</td></tr>
</table>
</td>
<td>Therefore, the base case analysis is based on the opinion of a single clinical expert as stated in the ERG report.<br><br>No amendment required.</td>
</tr>
<tr>
<td>Page 116<br><br>"First, it is inappropriate to include discounted costs, and re-discount them again."</td>
<td>Modification of statement to "First, the ERG believes it is inappropriate to include discounted costs, and re-discount them again."</td>
<td>Use of "it is inappropriate" is incorrect (see response to previous double discounting query).</td>
<td>Text amended to remove the statement regarding inappropriate discounting.<br><br>(Please see erratum)</td>
</tr>
<tr>
<td>Page 116<br><br>"Follow-up care post receiving ASCT was also based on clinical expert opinion. Patients were followed-up with two CT scans and one PET scan post-transplant and 0.07 blood counts, biochemistry and consultations per week (until year 5)."</td>
<td>Modification of statement to "Follow-up care post receiving ASCT was also based on two clinical experts' opinions. Patients were followed-up with two CT scans and one PET scan post-transplant and 0.07 blood counts, biochemistry and consultations per week (until year 5)."</td>
<td>The current statement may be misleading as two clinical experts were consulted (see below).
<table>
<tr><th rowspan="2">Clinical expert</th><th colspan="2">Time, off-treatment (years)</th><th colspan="5">Frequency per week</th></tr>
<tr><th>Start</th><th>End</th><th>CT scan</th><th>PET scan</th><th>Blood count</th><th>Bio-chemistry</th><th>Consultation</th></tr>
<tr><td rowspan="2">1</td><td>0</td><td>5</td><td>Two post-transplant</td><td>One post-transplant</td><td>0.07</td><td>0.07</td><td>0.07</td></tr>
<tr><td>5</td><td>8.5</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td></tr>
<tr><td rowspan="2">2</td><td>0</td><td>2</td><td>0.00</td><td>One post-treatment</td><td>0.07</td><td>0.07</td><td>0.07</td></tr>
<tr><td>2</td><td>5.5</td><td>0.00</td><td>0.00</td><td>0.04</td><td>0.04</td><td>0.04</td></tr>
</table>
</td>
<td>The statement is correct. In the interest of clarity, two clinical experts were consulted by the company. The resource use provided by clinical expert no.1 was used in the base case analysis. The model included functionality to allow the data from expert no. 2 to be considered as an alternative. There was no attempt to synthesise or merge the data from the experts in any way. Therefore, the base case analysis is based on the opinion of a single clinical</td>
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<td></td>
<td></td>
<td></td>
<td>expert as stated in the ERG report.<br><br>No amendment required.</td>
</tr>
<tr>
<td>Page 116<br><br>“Follow-up treatment post allo-SCT was assumed over a longer duration, (see Table 5.50 and 5.51 of the CS). Resource use was dependent on time from transplant. One CT scan, one PET scan and bi-weekly blood count, biochemistry and consultations were assumed in the first 3 months follow up. Frequency was reduced in a stepped manner between 3 months and 2 years, and again between 2-3 years. Beyond 3 years, patients were assumed to be followed up with a consultation, blood count and biochemistry every 6 months until progression or death.”</td>
<td>Modification of statement to “Follow-up care off-treatment was informed by two clinical experts. Follow-up treatment post allo-SCT was assumed over a longer duration, (see Table 5.50 and 5.51 of the CS). Resource use was dependent on time from transplant. One CT scan, one PET scan and bi-weekly blood count, biochemistry and consultations were assumed in the first 3 months follow up. Frequency was reduced in a stepped manner between 3 months and 2 years, and again between 2-3 years. Beyond 3 years, patients were assumed to be followed up with a consultation, blood count and biochemistry every 6 months until progression or death.”</td>
<td>The current statement may be misleading as two clinical experts were consulted (see below).<br><br>
<table>
<tr><th rowspan="2">Clinical expert</th><th colspan="2">Time, off-treatment (years)</th><th colspan="5">Frequency per week</th></tr>
<tr><th>Start</th><th>End</th><th>CT scan</th><th>PET scan</th><th>Blood count</th><th>Bio-chemistry</th><th>Consultation</th></tr>
<tr><td rowspan="4">1</td><td>0</td><td>0.25</td><td>One post-transplant</td><td>One post-transplant</td><td>0.5</td><td>0.5</td><td>0.5</td></tr>
<tr><td>0.25</td><td>2</td><td>0.06</td><td>0.04</td><td>0.23</td><td>0.23</td><td>0.23</td></tr>
<tr><td>2</td><td>3</td><td>0.02</td><td>0.02</td><td>0.08</td><td>0.08</td><td>0.08</td></tr>
<tr><td>3</td><td>60</td><td>0.00</td><td>0.00</td><td>0.04</td><td>0.04</td><td>0.04</td></tr>
<tr><td>2</td><td>0</td><td>0.25</td><td>One post-transplant</td><td>One post-transplant</td><td>1</td><td>1</td><td>1</td></tr>
</table>
</td>
<td>The statement is correct. In the interest of clarity, two clinical experts were consulted by the company. The resource use provided by clinical expert no.1 was used in the base case analysis. The model included functionality to allow the data from expert no. 2 to be considered as an alternative. There was no attempt to synthesise or merge the data from the experts in any way. Therefore, the base case analysis is based on the opinion of a single clinical expert as stated in the ERG report.<br><br>No amendment required.</td>
</tr>
</table>

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 0.25 | 2 | 0.00 | 0.01 | 0.23 | 0.23 | 0.23 | |
| | | | 2 | 3 | 0.00 | 0.00 | 0.08 | 0.08 | 0.08 | |
| | | | 3 | 5 | 0.00 | 0.00 | 0.04 | 0.04 | 0.04 | |
| Page 125<br>"Table 32 shows that, under the company's conducted analyses, the ICER was most sensitive to changing the discount rate to 1.5% (26% decrease), using IRF as data for PFS on brentuximab vedotin instead of investigator assessed progression (41% increase), and using an exponential function instead of log-logistic for estimating PFS in the brentuximab vedotin arm (no SCT) (29% increase)." | Modification of statement to, "Table 32 shows that, under the company's conducted analyses, the ICER was most sensitive to changing the discount rate to 1.5% (26% decrease), using IRF as data for PFS on brentuximab vedotin instead of investigator assessed progression (41% increase), and using an exponential function instead of log-logistic for estimating PFS per IRF in the brentuximab vedotin arm (no SCT) (29% increase)." | The current statement is incorrect. Use of an exponential function to estimate PFS per IRF for brentuximab vedotin (no SCT) led to a 29% increase in the ICER. | Text amended as suggested<br>(Please see erratum) |
| Page 130<br>"The ICERs ranged from £14,492 to £29,296, and as per the base case were most sensitive to the choice of PFS data used for brentuximab vedotin in the model." | Modification of statement to, "The ICERs ranged from £14,492 to £29,296, and as per the base case were most sensitive to the choice of PFS data used for brentuximab vedotin (no SCT) in the model." | The current statement is misleading. This relates to the choice of PFS data used for brentuximab vedotin (no SCT) cohort. | Text amended as suggested<br>(Please see erratum) |

## Issue 13 Section 5.3 Exploratory and sensitivity analyses undertaken by the ERG

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 140<br>"First, as noted in Section 5.2.5, there was an error in discounting of post-progression therapy costs, whereby discounted costs from one section of the trace were recycled into another part and re-discounted." | Modification of statement to "First, as noted in Section 5.2.5, the ERG believes that the company made an error in discounting of post-progression therapy costs, whereby discounted costs from one section of the trace were recycled into another part and re-discounted." | Use of the term "error" is incorrect (see response to previous double discounting query). | Text amended to remove reference to inappropriate discounting.<br>A further reference to inappropriate discounting is removed from pg 141.<br>Table 40 removes reference to a discounting error and now reflects the impact of correcting the error in the psa on the probabilistic ICER.<br>Table 42 (pg 146 / 147) are updated to reflect all ICERs based on the assumption that the company's approach to discounting is not an error.<br>However, in the interests of clarity, all associated analyses in the ERG report have been updated (including probabilistic analyses) to remove reference to a double discounting error. The ERG notes that the impact of removing the amendment to discounting has a minimal impact on the ICERs and does not change the conclusions of the ERGs report.<br>(Please see erratum to text and ICERs, pg. 8,140, 141, 146, 147, 148, 149, 150, 153, 154) |

## Issue 14 Section 5.4 Conclusions of the cost-effectiveness section

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 149<br>"Following correction of a bug in discounting of post-progression therapy by the ERG, these ICERs increased slightly to £19,534 and £12,840 respectively." | Modification of statement to "Following correction of a potential bug in discounting of post-progression therapy by the ERG, these ICERs increased slightly to £19,534 and £12,840 respectively." | This is incorrect (see response to previous double discounting query). | See response to issue 13 above |
| Page 150<br>"The ERG's preferred analysis applies the 'trial based' post progression therapy distribution, corrects the minor technical error (removing double discounting of post-progression therapy costs)," | Modification of statement to ""The ERG's preferred analysis applies the 'trial based' post progression therapy distribution, removes the double discounting of post-progression therapy costs," | Use of the term "error" is incorrect (see response to previous double discounting query). | See response to issue 13 above |
| Page 150<br>"and uses data from Mak et al. (as opposed to internal self-controls from SG035-0004) to model PFS for chemotherapy." | Modification of statement to "and uses data from Mak et al. (as opposed to internal self-controls from SG035-0004) to model PFS for chemotherapy (no SCT)." | The current statement is incorrect. Chemotherapy (no SCT) PFS was informed by the self-control dataset. | Text amended as suggested<br>(Please see erratum) |

## Issue 15 Section 6 Overall conclusions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response / comment |
|---|---|---|---|
| Page 153<br>"After adopting the revised 'trial based' post progression therapy distribution, stripping out the costs of brentuximab vedotin in the chemotherapy arm, and correction of a minor technical error, the ICER increased to £19,470 per QALY gained after response to clarification queries." | Modification of statement to "After adopting the revised 'trial based' post progression therapy distribution, stripping out the costs of brentuximab vedotin in the chemotherapy arm, and removal of the double discounting of post-progression therapy costs, the ICER increased to £19,470 per QALY gained after response to clarification queries." | Use of the term "error" is incorrect (see response to previous double discounting query). | The error referred to on pg 153 relates to the error corrected by the company as an erratum at clarification stage (i.e. subtraction rather than addition of adverse events in the QALY calculations). In order to be clear, the text in the ERG report is amended to read:<br>"….and correction of a minor technical error by the company regarding adverse event QALYs"<br><br>Further amendment to revise ICERs at bottom of page 153 to remove the impact of the ERGs amendment to discounting in the model on the ERG's preferred base case analysis.<br><br>(Please see erratum). |
| Page 153<br>"The ERG's preferred base case analysis uses Kaplan Meier data from Mak et al. for chemotherapy PFS instead of the internal self-controls from SG035-0004, applied to the | Modification of statement to "The ERG's preferred base case analysis uses Kaplan Meier data from Mak et al. for chemotherapy (no SCT) PFS instead of the internal self-controls from SG035-0004, applied to the company's 'trial based' distribution of | The current statement is incorrect. Chemotherapy (no SCT) PFS was informed by the self-control dataset. | Text amended as suggested<br>(Please see erratum) |

| | | | |
|---|---|---|---|
| company's 'trial based' distribution of post-progression therapy." | post-progression therapy." | | |

# Aberdeen HTA Group

# Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma

# Erratum

**Completed** 26 April, 2017

**Source of funding:** This report was commissioned by the NIHR HTA Programme as project number 16/51/14.

This document is intended to replace pages 1, 2, 4, 8, 11, 13, 16, 44, 46-48, 67, 69, 70, 75, 84, 99, 110, 115, 116, 125, 130, 140, 141, 146-150, 153 and 154 of the original ERG assessment report for *Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma,* which contained some typographical errors and potentially misleading statements. The main issue relates to the ERG's mis-understanding of the company's approach to discounting post progression costs. The original ERG report stated that the company's approach was an error. However, on reflection, the company's approach uses an alternative methodology to that suggested by the ERG, and as such, is not an error. Therefore, in the interest of clarity, the ERG have updated all its exploratory analyses to remove this correction. All related ICERs have been updated. It should be noted that the impact on the ICER is minimal and does not alter the conclusions of the ERG's report. In addition, we amended a number of further minor typographical inaccuracies or statements which the company have identified as misleading. These primarily relate to explicitly adding the text 'No SCT' when we refer to either the brentuximab (No SCT) or chemotherapy (No SCT) cohorts. The amended pages follow in order of page number below.

# 1 Summary

Anaplastic large cell lymphoma (ALCL) is a rare, aggressive peripheral T-cell lymphoma which occurs most commonly in children and young people. The two main types are systemic ALCL (sALCL) and primary cutaneous ALCL. There are two distinct subtypes of sALCL: ALK-positive and ALK-negative. Patients with ALK-positive ALCL tend to be younger than those diagnosed with ALCL-negative disease, and there are more males than females with both types. The prognosis of ALK-positive ALCL is better than that of ALK-negative disease, with significantly longer failure-free survival and overall survival then ALK-negative patients. Standard front-line treatment has traditionally been multi-agent chemotherapy but up to two-thirds of patients developed refractory disease, and a proportion are refractory. There has been no standard treatment for recurring or refractory (R/R) sALCL and the outcome for these patients has been, in general, very poor.

Brentuximab vedotin (Adcetris®, Takeda UK Ltd, Wooburn Green, UK) is a CD-30 directed antibody-drug conjugate, which consists of an antibody against a cancer cell marker, covalently linked to a drug that kills the target cell. The mechanism of action involves the active drug's attachment to the antibody, which seeks out cancer cells. The linker binds the drug to the cancer cells, where it is internalised into the cells. The microtubule network is disrupted, leading to cell cycle arrest and apoptosis of the cell. Non-randomised single-arm trials and Named Patient Programmes have shown high rates of objective response with an acceptable safety profile. Brentuximab vedotin has had conditional authorisation in the EU since October 2012 and has become adopted as the standard of care for R/R sALCL in the UK, with funding from the Cancer Drugs Fund in England and via individual funding requests in Scotland and Wales.

## *1.1 Critique of the decision problem in the company submission*

The NICE scope for this appraisal considered the clinical and cost-effectiveness of brentuximab vedotin within its licensed indication for the treatment of R/R sALCL. The decision problem addressed in the company's submission was consistent with the NICE final scope.

### *1.2 Summary of clinical effectiveness evidence submitted by the company*

The company did not conduct any meta-analyses as only non-randomised single-arm studies were identified in the systematic review.

The company's clinical effectiveness evidence focused upon the Phase II, open-label, single-arm, multi-centre trial by Pro et al 2012, examining the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory sALCL after treatment failure of at least one prior therapy. The primary outcome was objective response rate, defined as the proportion of patients with complete response or partial response, as determined by an independent review facility. Objective response rate was 86% (range across included studies: 60% to 100%); complete remission rate was 59% (range across included studies: 48% to 63%); partial remission rate was 28% (range across included studies: 29% to 50%).

Adverse events were common. Every patient in the Pro et al 2012 study experienced at least one adverse event. Overall, the most common adverse events of any grade were peripheral sensory neuropathy, nausea, fatigue and pyrexia. The most common adverse events of grade 3 or above were neutropenia, thrombocytopenia, peripheral sensory neuropathy and anaemia. There were some cases of adverse events leading to treatment discontinuation or dose delays. No deaths were attributable to brentuximab vedotin.

### *1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted*

The company's systematic review identified the prospective interventional study by Pro et al 2012 and further identified two retrospective studies (Gopal 2014, Chihara 2015) and three named patient programmes (Gibb 2013, Lamarque 2016, Pellegrini 2016) involving use of brentuximab vedotin in patients with R/R sALCL. The study by Gibb et al 2103 included only five participants with ALCL, which did not fulfil the company's relevant eligibility criterion (i.e. at least 20 patients with ALCL). At clarification, the company justified the study's inclusion with the explanation that that the study reports outcomes for the UK which are relevant to the decision problem. The ERG agrees that the Gibb et al 2013 study reports relevant UK-specific outcomes but is of the opinion that this study should not have been included in the company's submission as it does not fulfil the eligibility criteria.

observed in the SG035-0004 study, per investigator (INV) assessment, max follow up: 76 months in the base case, or per independent review facility (IRF) assessment, max follow up: 40 months as a sensitivity analysis. Per INV data show a long plateau on the Kaplan Meier curves. Therefore mixture cure models were used for PFS in the base case analysis. Per IRF assessment showed substantially poorer outcomes for brentuximab vedotin, with insufficient evidence (perhaps due to insufficient follow up) to determine the plausibility of long-term remission. OS data for brentuximab were extrapolated from data observed from the SG035-0004 study and similar cure assumptions were applied. The base case analysis of chemotherapy (No SCT) PFS was informed using internal self-control data from the single arm, open label, non-randomised SG035-0004 study for a subset of 39/58 (67%) of patients who had previously had a salvage chemotherapy for R/R disease. This inherently excludes any long term remissions following chemotherapy. With the respect to OS on chemotherapy, a subgroup of patients with PTCL, PS < 2, reported by Mak et al. was used. The same source was considered as a sensitivity analysis for PFS. It was assumed that chemotherapy would not be curative without subsequent stem cell transplant, therefore standard parametric survival models were used for both PFS and OS in the chemotherapy (No SCT) cohort. PFS and OS data for SCT adopted a similar approach to brentuximab vedotin, assuming mixture cure models due to the plateaus observed in the KM curves. Data from a single study were used for both ASCT and AlloSCT and the treatment effectiveness of SCT was not dependent upon the initial salvage therapy (brentuximab vedotin or chemotherapy). An additional excess mortality risk was applied to general population life-table estimates for all cohorts.

Utility data were sourced from a single study (Swinburn et al.) that elicited time trade-off values for health state vignettes describing CR, PR, SD and PD. Additional utility decrements, based on clinical expert opinion, were applied to general population norms to reflect the fact long term cancer survivors may not regain full utility. Utility data associated with adverse events had minimal impact on the model.

Costs included drug acquisition, administration, concomitant medications, SCT treatment, follow up care and post progression therapy. Modelled costs were sensitive to the number of treatment cycles on brentuximab vedotin and a judgement is required.

approach adheres to the NICE reference case with regards to time horizon and discounting.

The model was particularly sensitive to additional ERG exploratory analyses around assumptions regarding the treatment effectiveness (PFS and OS) for brentuximab vedotin relative to chemotherapy. This applies particularly to the extrapolated PFS data for brentuximab vedotin and chemotherapy under optimistic and pessimistic assumptions *(See Figure 9).* The ERG's preferred base case analysis uses Kaplan Meier data from Mak et al. for chemotherapy PFS instead of the internal self-controls from SG035-0004, applied to the company's 'trial based' distribution of post-progression therapy. The associated ICER was £21,267 per QALY gained (probabilistic ICER: £20,667). The probability that brentuximab vedotin is cost-effective under the ERG's preferred base case assumptions is 53%, 77% and 99% at a willingness to pay for a QALY gain of £20,000, £30,000 and £50,000 respectively.

The ERG considers that an exploratory analysis using the more conservative IRF data for PFS and standard parametric models for both PFS and OS, and avoiding the use of self-control data for chemotherapy (i.e. using Mak et al data for both OS and PFS) in the No SCT cohorts, presents a plausible and more conservative estimate of the ICER (£38,783). A worst case scenario, combining this analysis with the further assumption that rates of progression to SCT are equal following both treatments (at 20% overall) pushes the ICER to £49,994 per QALY gained. Further uncertainty relates the magnitude of the survival benefit for brentuximab vedotin (no SCT) versus chemotherapy (no SCT), which for OS is based on a naïve indirect comparison between SGN35-0004 and Mak et al. (2013), with observed heterogeneity with respect to age and stage of disease. Reducing the hazard of progression and mortality in the chemotherapy arm, significantly increases the ICER for brentuximab vedotin.

The standard front-line treatment for aggressive lymphomas, including ALCL, is considered to be CHOP (cyclophosphamide, doxorubicin, vincristine [Oncovin®], prednisone) or CHOP-type multi-agent chemotherapy. Of all the PTCLs, only ALK-positive ALCL tends to respond positively to CHOP (or other anthracycline-based regimens).[4, 31-34] In general, ALK-positive ALCL benefits from chemotherapy more than ALK-negative disease.[18, 31]

A review of 138 patients with sALCL between 1997 and 2010 (46% ALK-positive, 54% ALK-negative) reported that the most common regimen was ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by sequential consolidation with methotrexate, ifosfamide, etoposide and cytarabine (plus high dose chemotherapy and ASCT for some patients). The outcomes of people with ALK-positive disease were superior to those with ALK-negative disease.[25]

Up to around two-thirds of patients with sALCL develop refractory disease following front-line chemotherapy.[4, 15] In the absence of brentuximab vedotin, treatment options for these patients, or for those refractory to front-line chemotherapy, depend on individual patient characteristics. High-dose chemotherapy (HDC) with autologous SCT is recommended for people with relapsed chemotherapy-sensitive disease who are eligible for transplant. For patients who have relapsed after HDC with autologous SCT, or who are not eligible for that combination, options are generally limited to non-curative treatments including GDP or DHAP. Single-agent alkylator-based regimens may be an option for people who are older and/or unfit. Prior to the introduction of brentuximab vedotin, there was a need for less toxic treatments for these patients and, in general, for R/R sALCL, a disease for which there was no standard treatment and poor outcomes.[15, 31, 33, 35-37]

Brentuximab vedotin (Adcetris®, Takeda UK Ltd, Wooburn Green, UK) is a CD30-directed antibody-drug conjugate (ADC).[26] Antibody-drug conjugates are a novel class of drugs for the selective treatment of cancer, consisting of an antibody against a cancer cell marker, covalently linked to a drug that kills the target cell.[38, 39] There are three components of brentuximab vedotin: (1) antibody (cAC10chimeric anti-human CD30 monoclonal antibody), (2) linker (a protease-cleavable linker composed of a maleimidocaproyl attachment group, a valine-citrulline dipeptide and a spacer), and

brentuximab vedotin, which is manageable and tolerable in the conditionally approved indications. The final study report of MA25101 is due in December 2018.

The company's submission appropriately refers to The British Committee for Standards in Haematology guidelines for management of mature T-cell and NK-cell neoplasms, which makes the following recommendations for ALCL:[42]

- The International Prognostic Index (IPI) has predictive value in ALCL but ALK positivity is the most important prognostic factor
- Patients with limited stage ALCL and no adverse prognostic features by IPI should be treated with four cycles of CHOP chemotherapy and involved field radiography
- All other patients should be entered into a clinical trial or receive six to eight cycles of CHOP chemotherapy
- Patients with ALK-negative ALCL should be treated as for peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
- Primary cutaneous ALCL (ALK-negative) should be managed with local excision +/- radiotherapy and chemotherapy reserved for those patients with systemic disease (note: primary cutaneous ALCL is out with the scope of this appraisal)
- At relapse, patients should receive platinum-based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemo-sensitive disease should be considered for transplant.

These guidelines do not specify treatment for refractory disease.

### *2.1 Critique of company's description of underlying health problems*

The company's description of sALCL in terms of histology, prognosis and prevalence appears accurate and appropriate to the decision problem. The ERG further notes that some young, fit patients with ALK-negative disease would be considered for autograft in first remission. This option subsequently appears in the company's simplified treatment pathway (reproduced below; Figure 1).

# 3 Critique of company's definition of decision problem

## *3.1 Population*

Both the NICE final scope and the company's submission specify the population for this appraisal as "*people with relapsed or refractory systemic anaplastic large cell lymphoma*".

The company's submission focuses upon the evidence of one trial,[46] a Phase II, open-label, single-arm, multi-centre study which examines the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory sALCL after treatment failure of at least one prior therapy (front-line chemotherapy; CHOP or multi-agent chemotherapy regimens) with curative intent. The study CSR reported an inclusion criterion of age greater than or equal to 18 years, with a codicil that patients of at least 12 years could be enrolled at US and Canadian sites.

## *3.2 Intervention*

Brentuximab vedotin is a potent CD30-directed ADC, a class of drugs which facilitate the provision of a cytotoxic drug to a target malignant cell.[32, 46] The lymphocyte activation marker CD30 is a member of the tumour necrosis family and is highly expressed on the cell surface in anaplastic large cell lymphoma, while its expression on healthy cells is limited to activated T and B cells.[14, 47-49] Brentuximub vedotin comprises three elements: the chimeric monoclonal antibody cAC10 specific for CD30; the potent cytotoxic antitubulin agent monomethyl auristatin E (MMAE); and a stable valine-citrulline dipeptide linker, acting as the protease-cleavage site attaching MMAE to cAC10.[26, 50] The mechanism of action of brentixumab vedotin involves, first, the CD30 receptor binding to the surface of malignant cells. The brentixumab vedotin-CD30 complex is then internalised and carried to lysosomes, where MMAE is released, disrupting the microtubule network and leading to cell apoptosis.[26]

Brentuximab vedotin (Adcetris®, Takeda Pharma, Wooburn Green, UK) is formulated as a powder for concentrate for solution for infusion. Each vial contains 50mg of brentuximab vedotin and, after reconstitution, each ml contains 5mg of brentuximab

Median OS had not yet been reached in two studies.[46, 55] Objective response rates (ORRs) across studies ranged from 60%[75] to 100%,[55] complete remission (CR) rates ranged from 48%[56] to 63% [58] and partial remission (PR) rates from 29%[46] to 50%.[55] The company's submission reported CR of 59% (34/58) and PR of 28% (16/58). In contrast, the Pro et al 2012 publication reported a CR rate of 57% (33/58) and PR of 29% (17/58).[46] This discrepancy can be accounted for by a late conversion from a PR to a CR in one patient. The Pro et al 2016 poster[79] of five-year survival data reports that 34 patients achieved CR per independent review and 38 per investigator. Concordance assessment between investigator and IRF outcomes was 93%, while ORR was 86% in both groups. The results reported by Pro et al 2012 were at the higher end of the range across studies for ORR and CR but at the low end of the range for PR, albeit only three studies reported those data. Median progression-free survival ranged from 5.2 months (after first salvage therapy)[54] to 15.6 months,[55] with Pro et al 2016 reporting 13.3 months.[79]

Rate of stem cell transplantation was reported by three studies: Pro et al 2016[79] reported that 8 of the 38 patients who achieved CR per investigator (21%) underwent consolidative allogeneic SCT and 8 (21%) underwent consolidative autologous SCT. Chihara et al 2015[54] reported that 30 patients underwent autologous SCT and 15 patients underwent allogeneic SCT after salvage chemotherapy. In the study by Gibb et al 2013,[75] two of the five patients (40%) with ALCL underwent allogeneic transplant. The remaining three studies did not report this information.[55, 56, 58]

While it was not all reported in the company submission, several exploratory subgroups were considered in the SG-35-0004 trial. A subgroup analysis on age did not identify any clear differences in ORR and CR between age groups. There was 100% complete response for all individuals in the 12-17 age group while in the 18-64 and 65 and above age groups 56% had a complete response. However, there were only 4 patients in the 12-17 category, and the ORRs vary less between the groups. A second age subgroup analysis was also undertaken and showed similar ORR between those aged 12-40 and those older than 40. The CR rate was however lower in the older than 40 group (54% compared to 71%). Overall, the ERG do not believe there is sufficient data to inform differences in outcomes between children (12-18 years) and adults, and so feel it is appropriate to base the economic modelling on the whole trial sample.

There were 16 patients with ALK+ disease and 42 patients with ALK- disease. The ORR was slightly higher in the ALK- group. There was a larger difference in CR (69% for ALK+ compared to 55% for ALK-) which was expected as patients with ALK- disease have a poorer prognosis. The durations of OR and PFS were similar in the two subgroups.

The subgroups on prior therapies were 1 prior therapy (n=8) compared to more than 1 prior therapy (n=50). Whilst the categories were uneven, both ORR (90% in comparison to 63%) and CR (64% compared to 25%) were higher in the group which had received more than 1 prior therapy.

Subgroups were also formed for patients who had not achieved an objective response to any prior therapy and patients who had responded to at least one prior therapy. The ORR (89% v 77%) and CR (64% v 38%) were both slightly higher in the subgroup who had responded to a prior therapy. Amongst patients who received an SCT as their first therapy after stopping treatment with brentuximab vedotin the ORR and CR were 94% and 88%. These are higher than in the group who did not receive SCT post treatment (83% and 48% respectively).

Overall, whilst these exploratory subgroup-analyses suggest there may be differences in outcomes driven by certain patient characteristics and treatment history (particularly refractory versus relapsed disease), the small overall numbers and in many cases unequal distribution between subgroup categories, make it difficult to draw any firm conclusions. The ERG believe that given the limited data, it is appropriate to consider the cohort as a whole for the purposes of economic modeling.

### *4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison*

The ERG considers Pro et al 2012 to be an appropriate source of evidence for the clinical effectiveness of Brentuximab vedotin.[46] As detailed in the scope, the objective was to consider the effect on adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL) and, as Pro et al 2012 has 58 participants all with R/R sALCL, it certainly fulfils the second of these requirements.[46] The company's clarification that only 4 out of the 58 patients were

aged between 12 and 17 and their statement that the trial results are generalisable to the specified population and clinical practice and including these 4 participants will not significantly influence the results satisfies the ERG that an appropriate population has been used. The ERG does not have any concerns with the population in the SG035-0004 trial. It is noted by the ERG that the trial was sufficiently powered.

The ERG agree with the company's statement that the rarity of the disease and the lack of a standard comparator make a randomised controlled trial unfeasible and are therefore open to considering the outcomes from the single-arm trial. The reported outcomes of an 86% objective response rate (CR + PR), 59% complete remission (CR) and 28% partial remission (PR) all support the efficacy of the treatment. The ERG note that these outcomes were assessed by independent review. The overall survival, progression free survival, duration of response and observation times for patients still on the study and in remission again suggest long-term efficacy from the treatment.

While the Gopal and Gibb studies only involve a small number of ALCL patients,[55, 75] the results support those of Pro et al 2012.[46]

The company reports the list of adverse events experienced by patients in the SG035-0004 trial. The list is extensive with every patient experiencing at least one adverse event. The adverse event rates are similar to those presented in the Gopal and Gibb studies and appear consistent with expectation based on the ERGs clinical expert advice.

### *4.4 Critique of the indirect comparison and/ or multiple treatment comparison*

The company did not present an indirect comparison in the clinical effectiveness chapter of their submission. However, the economic modelling relied on a number of sources to make unadjusted comparisons between brentuximab vedotin (no SCT) and chemotherapy (no SCT). These are discussed further in chapter 5

Briefly, the clinical response rates and progression free survival estimates for chemotherapy were derived from the past history of a subgroup of patients enrolled in SG035-0004 whose most recent treatment (prior to brentuximab) had been for R/R

disease (n=39). The company's justification for this is that it will minimise bias which would be associated with an unanchored indirect comparison. The ERG are concerned that this data comes from a sample of patients who did not respond to chemotherapy and hence were enrolled in the trial of brentuximab vedotin. The selection excludes any long-term responders to salvage chemotherapy who do not require a subsequent line of therapy, and also excludes any patients who die prior to progression or are otherwise deemed to be unfit for subsequent therapy. Therefore, the ERG are of the opinion that this choice of data may bias the results against chemotherapy, and that it may not be appropriate for chemotherapy response rates and PFS in the economic model.

In terms of overall survival for the no SCT cohorts, unanchored indirect comparisons in the economic model are made between the results of the SG035-0004 trial and results reported be Mak et al 2013.[72] While the Mak et al 2013 study was described in the cost effectiveness section of the CS, the ERG were surprised that it was not summarised in the clinical effectiveness section given its pivotal role in determining the incremental effects of brentuximab.[72]

Mak et al. present data on progression free survival and overall survival for a historical cohort of patients on the British Colombia Cancer Agency Lymphoid Cancer database (diagnosed between December 1976 and October 2010) who had relapsed or experienced progressive disease after primary therapy. For purposes of making comparisons with SG035-0004, the company focusses on a subset of the Mak et al 2013 data.[72] This subset includes 89 patients who received chemotherapy for R/R disease. The company provided a table comparing baseline characteristics for this subgroup [72] with those of patients in SG035-0004 in their original submission. The company identifies heterogeneity in age, stage III-IV disease and performance status. However, in the economic model, the comparison with Mak et al [72] is restricted to the subset of SG035-0004 patients who do not go on to receive a SCT. At clarification, the company provided an additional table comparing baseline characteristics for this subgroup of SG035-0004 participants with the n=89 patients from Mak et al (Table 9). [72] While the age heterogeneity is slightly reduced, there is still considerable difference in stage III-IV disease and in performance status. The company explored the possibility of conducting a matching adjusted indirect

### 5.2.4 Interventions and comparators

The intervention is brentuximab vedotin, available as a 50 mg vial. The summary of Product Characteristics (SPC) states that the recommended dosage for R/R sALCL is 1.8 mg/kg intravenous infusion over 30 minutes every 3 weeks[51] For patients weighing over 100kg, the dose calculation should use 100kg. The marketing licence for brentuximab vedotin was granted on the basis of the results from the single Phase II (SG035-0004) trial of 58 patients having R/R sALCL. The SmPC states that patients who achieve stable disease or better should receive a minimum of eight cycles and up to a maximum of 16 cycles (almost one year) (SmPC). The mean number of cycles received by patients in the SG035-0004 was eight, ranging from one to 16; treatment was recommended to continue until disease progression or unacceptable toxicity. The intervention was costed on this basis in the economic model, though the ERGs clinical advice suggests that in practice, patients may receive fewer cycles of treatment with brentuximab vedotin than in the SG035-0004 trial. Patients may proceed to transplant after best response which is often seen by 4-6 cycles. Others will stop early because of toxicity and / or progression. Brentuximab vedotin has been designated as an orphan drug by the European Medicines Agency for the treatment of sALCL.[41] Brentuximab vedotin was approved for use on the national Cancer Drugs Fund (CDF) since 2013 for R/R sALCL. In the context of the current model, the ERG notes that brentuximab vedotin is modelled according to the inclusions and exclusion criteria from SG035-0004 for a mixed cohort of patients who have progressed following either primary treatment (first line CHOP (Cyclophosphamide, Hydroxydaunomycin, Oncovin®, Prednisolone) chemotherapy), prior salvage therapy, or a previous ASCT. Prior allo-SCT were excluded.

The modelled comparator consisted of multi-agent chemotherapy treatments given as salvage therapy. The multi-agent therapies were ICE (ifosfamide, carboplatin, etoposide), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), DHAP (dexamethasone, high-dose cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin) and Gem-P (gemcitabine, methylprednisolone, cisplatin). The ERG's clinical expert agrees that these treatment regimens are an appropriate comparator for

means that patients are modelled to a maximum age of 108 years. It is not clear how realistic this is for a population with aggressive disease receiving brentuximab vedotin (or comparator therapies). The ERG notes that 99% of the brentuximab vedotin modelled patients have died by 50 years (age 98) whereas 99% of modelled chemotherapy patients have died by 43 years (age 91). Furthermore, residual differences in PFS and OS are maintained between treatment arms over the entire time horizon of the model. The adopted time horizon may therefore introduce a small overestimation of the QALY gains associated with brentuximab relative to chemotherapy. However, the ERG also acknowledges that the impact on the ICER is negligible since the majority of QALY gains for brentuximab are realised in the first 20 years of the model time horizon. A more important determinant of the QALY gain is the adopted approach to modelling PFS and OS in the intervention and comparator arms, particularly in those who do not receive a SCT (see section 5.2.6).

Discounting was applied in the model at a constant rate of 3.5% per annum to costs life years and QALYs in the base case analysis. This is appropriate and in line with the NICE reference case.[53] A methodological note was made by the ERG with respect to the double discounting of post progression treatment costs. That is, the post progression treatment costs are sourced from the discounted values of the original treatment course and recycled into the model at a later date and re-discounted. Given that the discount factor references time since the model commencement, the ERG considered that this may over-discount post-progression treatment costs in both arms of the model. The ERG queried the approach at clarification stage and the company responded that:

> *"PPS therapy costs have been double-discounted intentionally". The discounting which is calculated in cells BB5:BE5 in the TraceBV and TraceChemo tabs reflects time elapsing from initiation to discontinuation of treatment. These are then discounted back to t = 0 in the model to reflect the time at which patients enter the PPS state (which differs across treatment arms) and therefore begin to accrue the associated costs."*

Upon reflection the ERG are satisfied with this response.

### 5.2.6 Treatment effectiveness and ***extrapolation***

Treatment effectiveness in the company's economic model is based on a combination of clinical response rates (complete response, partial response, stable and progressed disease), stem cell transplant rates by response categories, and PFS and OS by transplant status (no SCT, ASCT and allo-SCT). It should be noted that for those who receive a transplant, PFS and OS is modelled to be equivalent irrespective of treatment arm. However, for those who receive no transplant, there are substantial differences in PFS and OS between the brentuximab vedotin and chemotherapy which are based on a naïve indirect comparison. Thus the key drivers of life-year and QALY gains with brentuximab vedotin are: 1) the increased proportion of patients who received a SCT; and 2) improved progression free and overall survival over salvage chemotherapy in those who do not receive a SCT.

*5.2.6.1. Clinical outcomes – data sources used in the model*

**Response rates & proportions receiving SCT**

Clinical response rates have three important functions within the model. They are used to 1) determine the proportion of patients who enter the PFS state post treatment *(See the following section)*; 2) to calculate response based utilities *(See Section 5.2.7)*; and 3) to determine the proportion of patients receiving a SCT.

The company noted that only a proportion of complete and partial responders intended for SCT will actually receive a SCT. Data for clinical response rates and subsequent SCT rates (by response rates) for brentuximab vedotin were sourced from SG035-0004 in the base case analysis, including the ratio of ASCT to allo-SCT (47%: 53%). This results in 29% of brentuximab vedotin treated patients receiving SCT (14% ASCT; 16% allo-SCT). In addition, the company also provided 2 scenario analyses, 1) where SCT rates (by clinical response rate) were based on expert opinion about the percentage of CRs and PRs that would be intended for treatment (100% and 50% respectively) and 2) where data from Mak et al.[72] about the percentages of those intended for SCT actually receiving SCT were assumed.

Disease progression in the SG035-0004 trial was assessed by two alternative methods: as per investigator (INV) decision and as per independent review facility (IRF) decision. PFS per IRF was a pre-specified secondary endpoint and PFS per INV was a pre-specified exploratory endpoint. However, per INV was used for the base case model analysis as longer term follow up data (71.4 months (range 0.8 to 82.4)) have recently become available.[79] Specifically, for the 'no SCT' subgroup, maximum INV follow-up was 76 months compared to 40 months for IRF data. Figure 3 shows the KM curves illustrating important differences between the INV and IRF assessments for the N=41 patients in SG035-0004 who did not receive SCT.

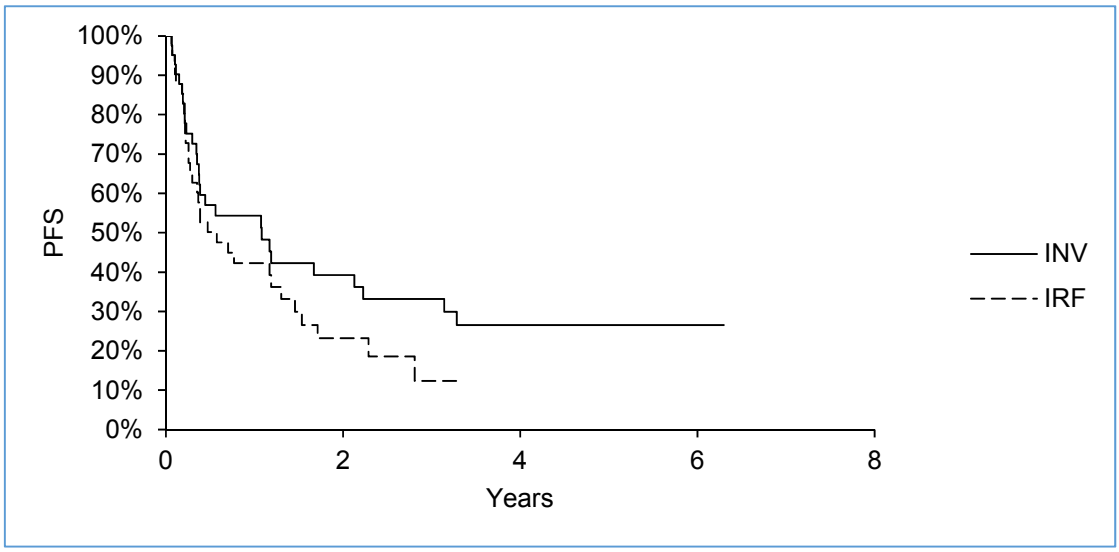
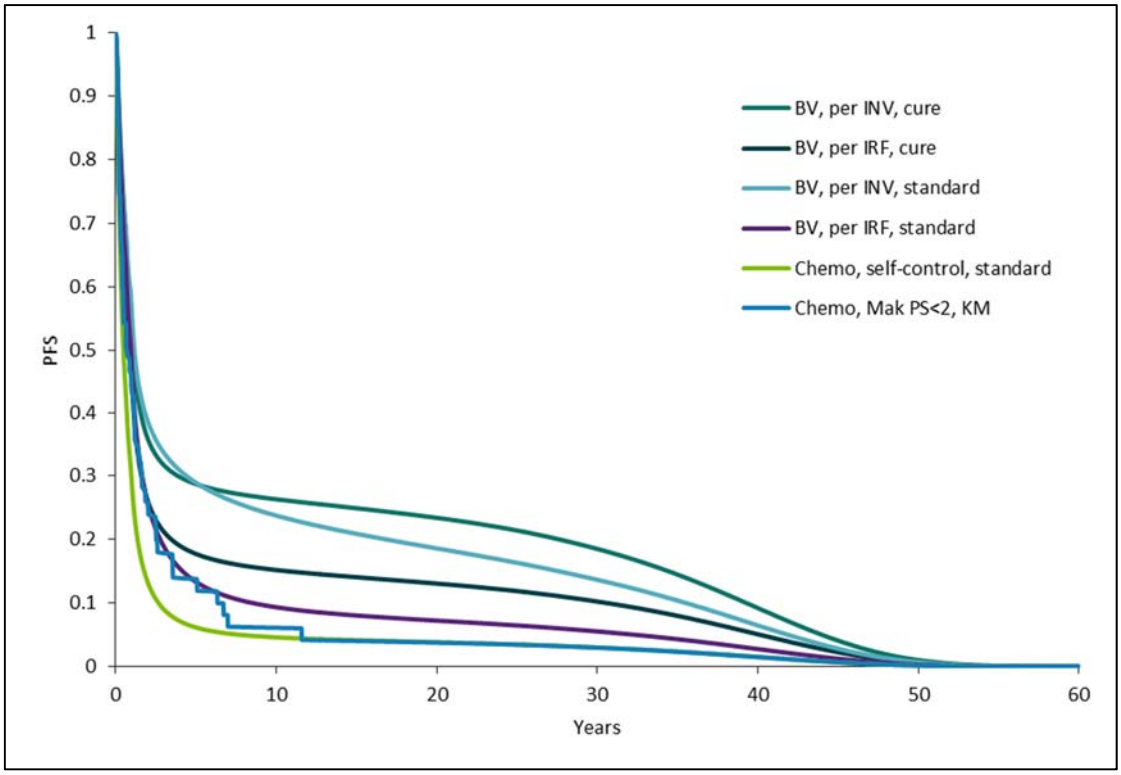



**Figure 3 Kaplan Meier curves for Brentuximab Vedotin (no SCT) PFS (Source: CS Figure 5.3, page 94).**

The ERG notes advantages and disadvantages with each approach. The IRF assessment is likely to be more objective and have a lower risk of bias. However, the ERG also acknowledges that the INV assessment provides the best available long term data.[79]The company state in response to clarification that per INV assessment is also more consistent with the approach taken for the self-controls. The ERG further note that both assessments are subject to a high rate of censoring at later follow-up time points. Therefore, the tails of the Kaplan Meier curves are subject to a high degree of uncertainty and need to be interpreted with caution.




Key: BV: Brentuximab vedotin; INV: Investigator; IRF: Independent review facility; KM: Kaplan Meier; PS: Performance Status

**Figure 9 Exploration of the impact of alternative data choices on PFS curves**

Among the analyses reported in Figure 9 above, the company's preferred base case assumptions (per INV assessment, using a log-logistic mixture cure model) was the most optimistic scenario for modelling brentuximab vedotin PFS. By contrast, PFS modelled on the basis of IRF assessment with a standard non-cure parametric model represents a worst case for brentuximab vedotin. Conversely, in the chemotherapy arm, the base case uses a standard parametric log-normal model fitted to the self-control data, which represents the most pessimistic approach for chemotherapy PFS. Overall, the ERG notes that there is a substantial difference in the excess PFS benefit of brentuximab vedotin, depending on the sources of data and extrapolation approach used. The impact of this uncertainty on the ICER is explored further in Section 5.3.2.

*5.2.6.3. Overall survival (OS)*

**Brentuximab vedotin (No SCT)**

*Trial based data*

As with PFS, OS data were reported according to the SG035-0004 study for the subset of n=41 patients who did not receive SCT. The estimated 5 year OS rate for

chemotherapy) were rescaled (removing progressive disease) to weight utility in the PFS state.

Patients achieving a CR were assigned the utility of 0.91, based on the general population norm for mean age 38 from Swinburn et al. [89] To reflect a decrement of utility for CR vs. general population, a further 5% decrement was applied. The base utility was therefore 0.95. The ERG are concerned that a 5% decrement may not be sufficient to capture the health state of patients obtaining a CR, as they recover from cancer, in the short term in particular.

Patients who do not progress by an assumed cure time point (5 years in the base case analysis) are assumed to follow age adjusted population norm utilities, with the same additional 5% decrement applied based on clinical expert opinion. Patients experiencing progressive disease were assumed to receive the appropriate decrement from Swinburn et al.[89] The ERG are concerned that by assuming a cured time point of 5 years, the model may over-estimate QALY gains. This potential over-estimation is greater for brentuximab vedotin (No SCT) than for chemotherapy (No SCT) given the higher proportion experiencing progression in the latter cohort. The impact of removing the cured time point (setting this parameter to 100 years in the model, allowing long term utility to follow a similar trajectory for all long term progression-free survivors) and varying the general population decrement on the ICER is explored in Section 5.3.

In general, the ERG found that the CS lacked clarity on assumptions, calculations or methods of implementing utility data within the model. The ERG's understanding of the modelling approach is that the decrements from Table 18 are subtracted from the age and gender specific population EQ-5D norms,[97] which change over time in the economic model. The ERG notes that it may be inappropriate to apply decrements from a vignette study to EQ-5D based norms, noting the different methodologies may add uncertainty. The ERG considers using an indexed multiplicative approach, rather than an additive utility model would have been preferable, but note also that there is limited empirical evidence to validate either approach. The ERG have explored the impact of using a multiplicative approach based on multiplying the respective utilities by an age adjustment index based on population norms (rather than applying a constant utility decrement to age adjusted population norms) in the model. Whilst not

guidelines. Concomitant medications were dependent on anti-emesis risk. Table 5.43 to 5.46 of the CS provide further details of costing methods. The average weekly cost of concomitant medication (weighted according to the assumed proportions receiving each chemotherapy treatment) was £41 (£984 over 24 weeks).

*SCT treatment costs*

The base case analysis assumes a total cost of £53,790 and £108,241 (stated in CS as £108,052) for ASCT and allo-SCT respectively. These costs were sourced from the BMT Unit at the Beatson West of Scotland Cancer Centre (WoSCC). No further details were provided regarding the resource use assumed to generate these costs. For example, it was not clear if the costs of treating associated adverse events were included. As such, it was not possible for the ERG to determine the appropriateness of these costs for ASCT or allo-SCT.

In both cases, the company provided an alternative sensitivity analysis, based on national unit costs for key components of the transplant process. The cost of ASCT includes the cost of donation, BEAM conditioning and transplant. The cost of allo-SCT includes the cost of preparation, donation, conditioning, transplant and immunosuppressives. The resultant costs were £10,573 (stated in CS as £10,884) and £57,550 for ASCT and allo-SCT respectively, substantially lower than the costs sourced from the Beatson WoSCC. The company justified their rejection of this NHS reference costing approach as the base case because it was felt to substantially under-estimate the true costs of SCT.

The ERG note that the base case analysis uses an approach that is inconsistent with the costing of other cost parameters in the model. Whilst in general, it would be preferable to use NHS reference costs where possible, the base case chosen by the company may be justified on the grounds that the NHS reference costs appear to substantially underestimate costs of SCT. The details provided in the submission with regards to the elicited base case costs are insufficient for the ERG to determine the most appropriate approach. Given the uncertainty, the ERG accepts that the approach used by the company can be considered conservative (in favour of chemotherapy) in the base case analysis.

The cost of multi-agent therapy was based on the cost of GDP (presenting the second highest total cost of all chemotherapy treatments). The cost of single-agent chemotherapy was based on the cost of Gemcitabine. The cost of inhibitors was based on the cost of multi-agent chemotherapy as none of the inhibitors used in the SG035-0004 trial were licensed in the UK. These decisions were based on clinical expert opinion. The post-progression therapy treatment costs used in the original and revised submissions are compared in Table 26.

**Table 26 Post-progression therapy costs (Source: Table 13 of the company's response to clarification queries.)**

| Therapy | Company Original Submission | Company response to clarification |
|---|---|---|
| Allo-SCT | Not included | £111,551 |
| ASCT | Not included | £52,737 |
| Brentuximab vedotin | [redacted] | [redacted] |
| Single-agent chemotherapy | [redacted] | [redacted] |
| Multi-agent chemotherapy | | [redacted] |
| Inhibitor treatments | Not included | £12,310 |
| BSC | Not included | £0 |

Key: ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BSC: best supportive care.

*Follow-up care*

Patients in all cohorts require follow up care (both pre and post progression).

For both brentuximab vedotin (No SCT) and chemotherapy (No SCT), patients in the model incur costs associated with follow-up both on and off treatment. The CS costed follow-up care (on treatment) as follows: CT scan (3), PET scan (2), consultation (1 per treatment cycle), blood count (1 per treatment cycle) and biochemistry (1 per treatment cycle). Follow-up care for the first three years off-treatment was costed as one CT and one PET scan over the three year period. Blood counts, biochemistry and consultations were converted to weekly frequencies (0.07 per week). From year three (post treatment) onwards, no follow up was assumed for the pre-progression state in the base case analysis. Frequencies were based on one clinical expert's opinion. Costs of pre-progression follow-up were slightly higher in the chemotherapy group. This is

driven by slightly higher weekly costs for CT and PET scans for chemotherapy, due to differing time on treatment in the model.

Post progression follow up costs were based on discounted pre-progression follow up care costs, weighted according to the proportion of patients receiving each treatment post-progression. The ERG noted a minor formula error in the chemotherapy trace providing this weighting. As the formula referenced brentuximab vedotin following progression on chemotherapy (i.e. 0% in the revised model), the error didn't impact on cost-effectiveness in the revised model. Therefore, the ERG do not consider this issue further.

Follow-up care post receiving ASCT was also based on clinical expert opinion. Patients were followed-up with two CT scans and one PET scan post-transplant and 0.07 blood counts, biochemistry and consultations per week (until year 5).

Follow-up treatment post allo-SCT was assumed over a longer duration, *(see Table 5.50 and 5.51 of the CS).* Resource use was dependent on time from transplant. One CT scan, one PET scan and bi-weekly blood count, biochemistry and consultations were assumed in the first 3 months follow up. Frequency was reduced in a stepped manner between 3 months and 2 years, and again between 2-3 years. Beyond 3 years, patients were assumed to be followed up with a consultation, blood count and biochemistry every 6 months until progression or death.

The ERG notes some uncertainty in follow up treatment resource use, driven by variation in opinion between clinical experts. However, the resources applied in the model appear reasonable and are considered plausible by the ERG's clinical expert.

Table 32 shows that, under the company's conducted analyses, the ICER was most sensitive to changing the discount rate to 1.5% (26% decrease), using IRF as data for PFS on brentuximab vedotin instead of investigator assessed progression (41% increase), and using an exponential function instead of log-logistic for estimating PFS per IRF in the brentuximab vedotin arm (no SCT) (29% increase).

In relation to SCT, basing the SCT rate on clinical expert opinion instead of the SG035-0004 trial increased the ICER by 61%. It is worth noting that the greater the difference in rates of SCT for brentuximab vedotin over chemotherapy, the higher the resultant ICER for brentuximab vedotin. This is due to the favourable OS and PFS modelled for brentuximab vedotin (no SCT) without the substantial costs of SCT. There is a greater benefit to be accrued from progressing chemotherapy patients to SCT than there is for progressing brentuximab vedotin patients to SCT, given the higher cure percentage and superior survival assumptions applied to the brentuximab vedotin (No SCT) cohort under the base case assumptions. Given the assumptions applied in the model, the ERG considers these findings to be plausible, however it is noted that increasing progression to SCT increases the ICER for brentuximab vedotin. Decreasing the rate of SCT on brentuximab vedotin to equate with chemotherapy substantially lowers the base case ICER.

Finally, using data from Mak et. al. 2013[72] (ALCL patients) or (PTCL patients with PS<2) for PFS on chemotherapy (no SCT), rather than the self-controls from SG035-0004, leads to a 20% and 19% increase in the ICER respectively.

Whilst the company presented many deterministic scenario analyses, the ERG are not convinced that the original submission sufficiently tested the aspects of the model which generate the greatest uncertainty in the ICER, namely the distribution of post-progression therapy as well as the comparative effectiveness (PFS and OS) between brentuximab vedotin and chemotherapy. In particular, the scenarios chosen for two-way, combined analyses by the company were based on analyses with minimal impact on the ICER. Sections 5.2.9.2 and 5.3, report a range of further analyses conducted by both the company (in response to clarification) and the ERG respectively.

*Revised deterministic sensitivity analyses*

The ERG reproduced the company's set of deterministic analyses using the revised post-progression therapy ('trial based') distribution (*Table 35)*. The ICERs ranged from £14,492 to £29,296, and as per the base case were most sensitive to the choice of PFS data used for brentuximab vedotin (no SCT) in the model. The ERG notes that in the revised set of analyses, 12/38 (32%) of analyses push the ICER above £20,000, though none rise above £30, 000 per QALY gained. The ERGs concerns and critique remain as per Section 5.2.9.1 above.

**Table 35 Deterministic sensitivity analyses applied to trial based post-progression therapy distribution**

| Analysis | Parameter | Base case | Scenario | ICER | Change vs. base case |
|---|---|---|---|---|---|
| | **Base case** | | | **£19,470** | |
| 1 | Discount rate (costs, benefits) | 3.5% | 1.5% | £14,492 | -26% |
| 2 | Assessment type | Investigator | IRF | £29,296 | 50% |
| 3 | Source of response data for brentuximab patients receiving SCT | SGN35-0004 (self-control) | Equivalent to chemotherapy | £19,549 | 0% |
| 4 | Brentuximab (no SCT) PFS per INV distribution | Log-logistic | Exponential | £19,222 | -1% |
| 5 | Brentuximab (no SCT) PFS per IRF distribution | Log-logistic | Exponential | £26,912 | 38% |
| 6 | Brentuximab (no SCT) OS distribution | Log-logistic | Kaplan-Meier | £18,974 | -3% |
| 7 | Brentuximab (no SCT) PFS and OS distribution | Log-logistic cure model | Gamma standard model | £21,934 | 13% |
| 8 | Source of chemotherapy (no SCT) PFS data | Self-control | ALCL (n=17)[72] | £21,495 | 10% |
| 9 | Source of chemotherapy (no SCT) PFS data | Self-control | PS<2 (n=47)[72] | £21,267 | 9% |
| 10 | Chemotherapy (no SCT) PFS distribution | Lognormal | Log-logistic | £19,663 | 1% |
| 11 | Chemotherapy (no SCT) PFS hazard | Original data | Increased 25% | £18,989 | -2% |
| 12 | Chemotherapy (no SCT) PFS hazard | Original data | Decreased 25% | £20,550 | 6% |
| 13 | Source of chemotherapy (no SCT) OS data | PS<2 (n=47)[72] | ALCL (n=17)[72] | £18,594 | -4% |
| 14 | Combined scenarios 8 and 13 | | | £20,593 | 6% |

these have not had a material impact on the ICER, and therefore do not impact on cost-effectiveness conclusions. As such, the ERG are confident that the company's models pass the internal consistency and error checks applied.
Given the companies approach of disaggregating the no SCT and SCT subgroups of SG035-0004 for modelling, the ERG also cross checked the weighted aggregation of the modelled OS curves with the observed OS KM curve for the whole cohort (n=58) of SG035-0004. This showed that the model in fact slightly under-predicted the observed OS at 5 years (47% Vs 60%) and 7 years (46% Vs 56%)

### *5.3 Exploratory and sensitivity analyses undertaken by the ERG*

This section details the additional work completed by the ERG, and the associated impact on the ICER. For all cases the ERG have considered their revisions according to the revised, corrected version of the economic model submitted by the company on March 22nd, 2017. Section 5.3.1 describes the rectification of minor technical errors identified in the company submission. Section 5.3.2 outlines a number of scenario analyses explored by the ERG to address what we have determined as weak or questionable assumptions in the model or to explore the impact of using different sources of parameter estimates on the ICER. The impact of our exploratory analyses are applied to two alternative base cases (i.e. 'trial based' and 'expert based' distribution of post-progression therapy). The section concludes with a discussion of the ERG's preferred base case ICER.

#### 5.3.1 Model corrections

The ERG identified one technical error in the company submission and have implemented a correction to remedy this. The error relates to the PSA. The distributions of chemotherapy component treatments was incorporated probabilistically, but no correction was applied to ensure that the values actually sum to 1 for each individual simulation. Table 40 shows that correction of this error has no impact on the deterministic ICER.

**Table 40 Errors identified in the company submission and ERG corrections applied**

| Model parameter | Model reference | Error identified | Correction applied by ERG | Revised deterministic ICER | Revised probabilistic ICER |
|---|---|---|---|---|---|
| **Base case company ICER** (trial based post-progression therapy distribution) | | | | £19, 470 | £19,034 |
| Chemotherapy acquisition, breakdown of regiments | Tabs: 'Resource Use'<br><br>Cells: (G23: G27) | Regiments do not sum to 1 in the PSA | Apply a correction to ensure that probabilities sum to 1. | N/A* | £19,096 |

**Note that there is no change to the deterministic ICER as the identified error impacts only on the PSA.*

### 5.3.2 ERG scenario analyses

The ERG have undertaken a number of further scenario analyses. The objective of these analyses is to explore uncertainty surrounding key model parameters and to identify the assumptions to which the model is most sensitive. We focus on assumptions which may be questionable, or where a judgement call is required. In particular, a number of multi-variate sensitivity analyses are conducted to more fully explore the range of uncertainty in the ICER. Exploratory analyses are applied to the ERG's preferred 'trial based' distribution of post-progression therapies using the model submitted by the company on 22/3/17 as an erratum to clarification response. The ERG have added further switches to the company's model where necessary for ease of implementation. Table 41 outlines the analyses carried out together with a justification for each and Table 42 presents the results.

**Table 42 Impact of alternative scenario analyses on cost-effectiveness results**

| | | BV | | Chemo | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analysis** | **Description** | **Cost** | **QALY** | **Cost** | **QALY** | **Inc. Cost** | **Inc. QALY** | **Deterministic ICER** |
| **Company submitted models (response to clarification)** | | | | | | | | |
| BC1 | Post progression therapy distribution (trial based) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,470 |
| BC2 | Post progression therapy distribution (expert based) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £12,873 |
| **ERG explored analyses (All applied to BC1)** | | | | | | | | |
| ***Methodological choices*** | | | | | | | | |
| 1 | Time horizon (10) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £47,867 |
| 2 | Time horizon (20) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,212 |
| 3 | Discount 0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £11,208 |
| 4 | Discount 6% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £26,421 |
| 5 | Multiplicative utilities used to incorporate age specific gen pop norms | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £15,879 |
| ***Costs:*** | | | | | | | | |
| 6 | No.treatment cycles on brentuximab vedotin (No SCT cohort) =4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £13,090 |
| 7 | No.treatment cycles on brentuximab vedotin (No SCT cohort) =16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,321 |
| 8 | Applying the cost of BV every 3 weeks | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,764 |
| 9 | Apply additional cost to AE for ASCT following chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,463 |
| 10 | Rescaling trial-based post progression therapy distributions (to sum up to 100%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £16,544 |
| 11 | Source of ASCT costs: NHS reference costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,389 |
| 12 | Source of allo-SCT costs: NHS reference costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £17,576 |
| 13 | Combined scenarios 11 & 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £16,496 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***Utilities*** | | | | | | | | |
| 14 | Cure point = 100 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,138 |
| 15 | Apply additional disutility to AE for ASCT following chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,467 |
| 16 | Combined scenarios 9 & 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,460 |
| 17 | Utility decrement of CR: 0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,832 |
| 18 | Utility decrement of CR: 20% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,193 |
| 19 | Utility decrement (Vs. General population) – 0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,785 |
| 20 | Utility decrement (vs. general population) – 20% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,861 |
| 21 | Doorduijn utilities applied in the model. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £17,354 |
| ***Survival*** | | | | | | | | |
| 22 | Equal excess mortality for both arms (5%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,470 |
| 23 | Equal excess mortality for both arms (25%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,892 |
| 24 | PFS & OS hazard (-25%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,127 |
| 25 | PFS & OS hazard (-50%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £31,530 |
| 26 | PFS & OS hazard (-75%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| 27 | BV PFS based on IRF data | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,296 |
| 28 | BV PFS (standard gamma model) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,276 |
| 29 | BV OS (standard gamma model) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,052 |
| 30 | Chemo PFS (KM data from Mak et al PS<2)[72] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,267 |
| 31 | Chemo OS (KM data from Mak et al)[72] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,728 |
| 32 | Combined scenarios 27 to 31 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £38,783 |
| ***SCT*** | | | | | | | | |
| 33 | Equal rates of SCT progression in both arms | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,448 |
| 34 | Combined scenarios 32 & 33 (worst case for BV) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £49,994 |

Key: AE: adverse events; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BC: base case; BV: brentuximab vedotin; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression free survival; PS: performance status; QALY: quality adjusted life year.

The ERG found that the ICER was most sensitive to the time horizon employed in the model, the discount rate applied, the cost of brentuximab vedotin (i.e. the number of cycles of treatment) and assumptions regarding the relative treatment effectiveness (PFS and OS) for brentuximab vedotin relative to chemotherapy. The ERG notes that the model was not particularly sensitive to assumptions surrounding utility inputs.

As discussed in Section 5.2.6, Figure 9, there were substantial differences between the PFS curves depending on the source of data for brentuximab vedotin (INV or IRF) and chemotherapy (self-controls vs. Mak et al.). As such, the ERG considers that a plausible but conservative estimate of the ICER can be obtained using IRF data for PFS and standard parametric models for both PFS and OS for brentuximab vedotin, together with Mak et al data (PTCL subgroup, PS<2, N=47) for chemotherapy (OS and PFS).[72] The resultant ICER, increased from £19, 470 to £38,783. A worst case scenario for brentuximab might result from combining this analysis with the assumption of equal rates of progression to SCT for both chemotherapy and brentuximab vedotin. The resultant deterministic ICER in this more pessimistic scenario increases to £49,994 per QALY gained. The probabilistic ICER is £54,082 per QALY gained and the probability of cost-effectiveness falls to 8%, 22% and 48% at a willingness to pay for a QALY gain of £20,000, £30,000 and £50,000 respectively.

With regards to costs, the ICER was most sensitive to the cost of brentuximab vedotin and the number of treatment cycles required. The ERG note that there is uncertainty regarding the number of cycles that would be offered in practice, with clinical experts noting that treatment could be for 4-6 cycles, and the scheduled dosage being 16 cycles. A judgement call is required as to the most appropriate number of cycles for inclusion in the model. As noted in the response to clarification queries, the ICER is also sensitive to the costs of post progression therapy and the respective distributions applied. It is the ERGs view that the distribution based on trial data from SG035-0004 is the most appropriate, hence its use in all the exploratory analyses above.

Discount rates and time horizon had a relatively large impact on the ICER. This is because most of the costs are incurred in the early part of the model with treatment

effectiveness accruing and sustaining over the longer term (particularly due to the use of mixture cure models in the brentuximab vedotin patients). The ERG notes that whilst uncertainty exists with respect to the values selected for these parameters, the analysis is in line with the NICE reference case.

*ERG preferred base case*

The ERG has considered the range of alternative analyses presented in the company's submission together with further exploratory analyses conducted at clarification stage and additional ERG exploratory analyses.

The ERG prefers the use of the 'trial based' distribution of post-progression therapy costs, stripping the costs of brentuximab vedotin out of the chemotherapy comparator. The ERG also prefers the use of data from Mak et al for both PFS and OS. [72] The deterministic ICER for the ERG preferred analysis (£21,267) is provided in Table 42 above, analysis no.30. Table 43 presents the probabilistic results, with an ICER of £20,667, with a 53%, 77% and 99% probability of cost-effectiveness at threshold values of willingness to pay for a QALY gained of £20,000, £30,000 and £50,000 respectively.

**Table 43 ERG preferred base case analysis (probabilistic results)**

| Comparator | Costs | QALYs | ICER | P (C/E) @ £20k | P (C/E) @ £30k | P (C/E) @ £50k |
|---|---|---|---|---|---|---|
| Brentuximab vedotin | [redacted] | [redacted] | | | | |
| Chemotherapy | [redacted] | [redacted] | | | | |
| Incremental | [redacted] | [redacted] | £20,667 | 53% | 77% | 99% |

### *5.4 Conclusions of the cost effectiveness section*

The company's base case ICER (original submission) was £8,829 per QALY. A revised submission, correcting a violation of post-progression therapies resulted in an increased ICER of £19,470 (trial based post-progression therapy distribution) and £12,873 (clinical expert opinion post-progression therapy distribution). The ERG's preferred

analysis applies the 'trial based' post progression therapy distribution and uses data from Mak et al. [72] (as opposed to internal self-controls from SG035-0004) to model PFS for chemotherapy (No SCT). The resultant deterministic ICER (£21,267) is considered to offer a plausible alternative to the company's base case analysis. The probabilistic analysis shows that under this revised base case, there is a 53%, 77% and 99% probability of cost-effectiveness at a willingness to pay per QALY of £20,000, £30,000 and £50,000 respectively.

The ERG considers the following to represent key issues of uncertainty for decision making:

- The true rate of stem cell transplantation following brentuximab vedotin or chemotherapy is unclear. The higher the rate of SCT following brentuximab vedotin, the higher the resultant ICER. This is due to progression to a high cost treatment for minimal additional survival gain over the No SCT cohort.
- The method of assessment used to gauge progression in brentuximab vedotin. The use of longer term INV data are suggestive of cure/long-term remission (without SCT) for a proportion of patients. However, the likely less biased per IRF data report a higher proportion progressing with no evidence of cure (albeit at a shorter follow up).
- A related point of uncertainty is therefore whether it is appropriate to use a mixture cure model for brentuximab vedotin, but not for chemotherapy, given the conflicting evidence from per INV and per IRF assessment.
- The model is sensitive to the costs of brentuximab vedotin and the most appropriate number of cycles in the model (observed in trial: 8 cycles; expert opinion: 4-6 cycles; scheduled dosage: 16 cycles).
- The distribution of post-progression therapy. The ERG considers the initial model (assuming 80% of chemotherapy patients receive brentuximab vedotin) to be outwith the scope of the appraisal. However, a judgement call is required as to whether the revised 'trial based' distribution or 'expert based' distribution is most appropriate. The ERG takes the view that the former should be preferred.

The company submitted a *'de novo'* partitioned-survival model. Progression free survival (PFS), post-progression survival (PPS) and death were modelled, with health state occupancy based on the area under the modelled PFS and OS curves. The original company submission predicted additional costs for brentuximab vedotin of [redacted], additional life years of 6.18 and additional QALYs of [redacted] over chemotherapy. The ICER was £8,829. After adopting the revised 'trial based' post progression therapy distribution, stripping out the costs of brentuximab vedotin in the chemotherapy arm, and correction of a minor technical error by the company regarding adverse event QALYs, the ICER increased to £19,470 per QALY gained after response to clarification queries. The probabilistic ICER was £19,034 per QALY gained, with a probability of cost effectiveness of 58%, 83% and 100% at a willingness to pay per QALY gained of £20k, £30k and £50k respectively.

The ERG considers the submitted model to be generally of good quality, with an appropriate model structure given the lack of comparative data. There are however a number of uncertainties, and a judgement call will be required to determine which parameter inputs and data sources are most appropriate in the UK setting. In the ERG's view, the most important areas of uncertainty are:

- The most likely rate of SCT following brentuximab vedotin and chemotherapy
- The most appropriate assessment data (INV or IRF) to consider for brentuximab vedotin PFS
- The appropriateness of using a mixture cure model for brentuximab vedotin, compared to a standard model for chemotherapy (PFS and OS).
- The most appropriate distribution of post-progression therapy used in the model.

The ERG conducted a range of exploratory analyses (including multi-variate analyses) to explore the impact of key uncertainties on the ICER. The ERG's preferred base case analysis uses Kaplan Meier data from Mak et al. for chemotherapy (no SCT) PFS instead of the internal self-controls from SG035-0004, applied to the company's 'trial based' distribution of post-progression therapy. The associated ICER was £21,267 per QALY gained (probabilistic ICER: £20,667). The probability that

brentuximab vedotin is cost-effective under the ERG's preferred base case assumptions is 53%, 77% and 99% at a willingness to pay for a QALY gain of £20,000, £30,000 and £50,000 respectively. A worst-case scenario for brentuximab vedotin (IRF data and Mak et al for brentuximab vedotin and chemotherapy PFS respectively; with equal rates of SCT across arms) increases the ICER to £49,994 per QALY gained in the most pessimistic scenario considered. The ERG further note that rreducing the hazard of progression and mortality in the chemotherapy arm, significantly increases the ICER for brentuximab vedotin.

### *6.1 Implications for research*

There are a number of activities ongoing as part of the company's conditional marketing authorisation from brentuximab vedotin. These include the long-term follow-up (for OS) of patients from SG035-0004. This will in time help to assess the validity of the long-term survival assumptions underpinning the cost-effectiveness modelling for this submission. Further ongoing research relates to the post authorisation safety study (PASS) currently being conducted, which is due to report in 2018. Further research which could help to address uncertainties in the economic model include: 1) studies to assess health state utilities (using a generic validated instrument) of patients being treated for R/R sALCL – including long-term responders with and without SCT; and 2) if possible, further retrospective analyses of registry data for the relevant patient populations who received salvage chemotherapy for R/R sALCL. The latter type of study will depend on the identification of a suitable data source, and should ideally compare outcomes whilst matching on known prognostic factors with patients in SG035-0004.