NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (CDF review of TA446) [ID1366]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (CDF review of TA446) [ID1366]

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 treating CD30-positive Hodgkin's lymphoma (CDF review of TA446) [ID1366]

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

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Abbreviations

Allo-SCT	Allogeneic stem cell transplant
ASCT	Allogeneic stem cell transplant
BV	Brentuximab vedotin
CDF	Cancer Drugs Fund
HL	Hodgkin lymphoma
PET	Positron emission tomography
r/r	Relapsed or refractory
r/r HL	Relapsed or refractory Hodgkin lymphoma
SCT	Stem cell transplant

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Description of the technology

Technology	Brentuximab vedotin (Adcetris, Takeda UK)
Marketing authorisation	For treating relapsed or refractory CD30-positive Hodgkin lymphoma in adults: • after autologous stem cell transplant or • after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option or • at increased risk of relapse or progression after autologous stem cell transplant
Mechanism of action	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.
Administration & dosage	1.8 mg/kg administered by intravenous infusion over 30 minutes every 3 weeks.
Price	£2,500 for a 50-mg vial (There is a PAS simple discount applied to the list price)

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From Table 2, page 12-13 of company submission.

TA446 Recommendations

1. Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:
   - they have relapsed or refractory disease after autologous stem cell transplant and
   - the company provides brentuximab vedotin at the price agreed with NHS England in the commercial access agreement.

2. Brentuximab vedotin is ***recommended for use within the Cancer Drugs Fund*** as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:
   - they have relapsed or refractory disease after at least 2 previous therapies and
   - they cannot have autologous stem cell transplant or multi-agent chemotherapy and
   - the conditions of the managed access agreement are followed.

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TA446 Rationale for CDF recommendation (1)

- Company presented a UK observational study (retrospective) in adult patients with:
  - relapsed or refractory Hodgkin lymphoma
  - two prior lines of therapy
  - ineligible for stem cell transplant (SCT) due to insufficient remission.
- Following treatment 58% patients received a SCT.
- Committee was concerned that the SCT rate following treatment might not be generalisable beyond the 10 centres that contributed to this dataset.

Outcome	Results (n=78)
ORR	51% (CR = 24%, PR = 27%)
Post BV SCT rate	58%
PFS	5.68 months (95% CI 4.21 - 17.05)
OS	37.2 months (95% CI 17.8 - not reached)

Key: ORR, overall response rate; SCT, stem cell transplant; CR, complete response; PR, partial response.

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From Table 4, page 19 of company submission.

Rationale for CDF recommendation (2)

- the ICER for brentuximab vedotin compared with single-agent chemotherapy was approximately £40,000 per QALY gained (between £28,332 and £53,998 per QALY gained).
- The key cost-effectiveness drivers were:
  - Model structure
  - Relative rate of post-chemotherapy and brentuximab vedotin SCT
  - Modelled estimates of progression free survival
- End-of-life not met for this population.
- Committee concluded not to recommend for routine commissioning but had plausible potential for cost-effectiveness
- Therefore committee required further data collection on:
  - SCT rates after brentuximab vedotin treatment

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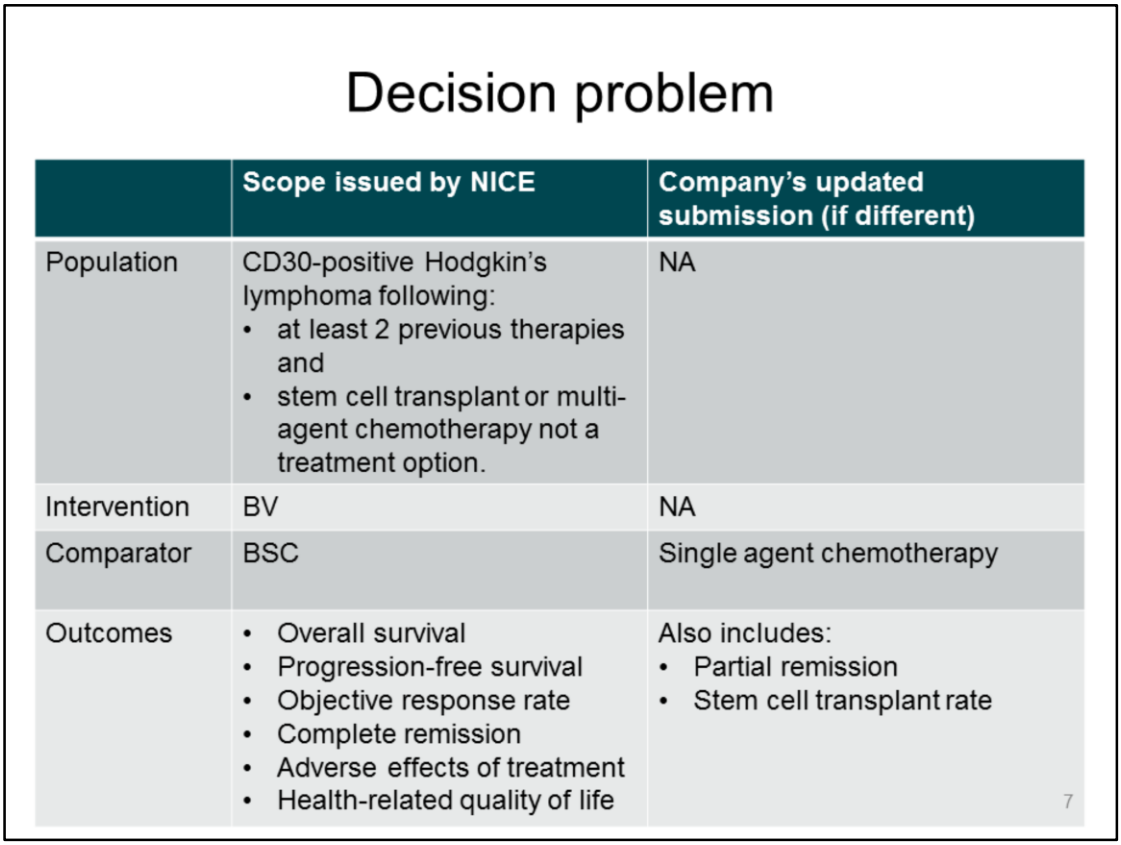

Decision problem

	Scope issued by NICE	Company's updated submission (if different)
Population	CD30-positive Hodgkin's lymphoma following: • at least 2 previous therapies and • stem cell transplant or multi-agent chemotherapy not a treatment option.	NA
Intervention	BV	NA
Comparator	BSC	Single agent chemotherapy
Outcomes	• Overall survival • Progression-free survival • Objective response rate • Complete remission • Adverse effects of treatment • Health-related quality of life	Also includes: • Partial remission • Stem cell transplant rate

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From Table 1, pages 10-11 of company submission.

Patient organisations comments: Lymphoma Association and Bloodwise

- HL symptoms are debilitating and distressing.
- Life-expectancy with chemotherapy or palliative care is severely limited
- Achieving a cure for these patients would have a profound positive impact on physical and psychological health.
- Brentuximab vedotin offers greater effectiveness, ease of administration, fewer side effects, less toxicity and increased life expectancy. In patients having this as a 'bridge' to allogeneic transplant, some may eventually be cured.
- Brentuximab vedotin is much less intensive and exhausting than conventional chemotherapy.
- Brentuximab vedotin is only administered once every 3 weeks meaning patients only need to be in hospital for 2 days in each 3-week cycle. This is beneficial for those with mobility or other issues which make it difficult to travel to hospital on a more regular basis.

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Professional Group comments: NCRI-ACP-RCP

- When brentuximab vedotin was first introduced it was considered a step-change in the management of HL (it had the highest demonstrated single agent activity in HL).
- In most clinical trials or real world data collection, brentuximab vedotin in HL shows 60-70% overall response rate and 25-30% complete response rate. Irrespective of when the drug is used and what patient group
- Peripheral neuropathy is a common side effect. This can be severe. However brentuximab vedotin has been used now for some years and centres are used to monitoring for it.
- In patients with relapsed disease it is imperative to induce remission prior to stem cell transplantation, to maximise the chance of cure. Both UK published data (Eyre *et al*, Brit J Haematol) and the national CDF data collection exercise show that brentuximab vedotin is effective at doing this in a significant proportion of patients.

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Clinical effectiveness: CDF data collection methods

Method	• Questionnaire sent to 223 consultants across 106 trusts in England. 496 HL patients received CDF funding for BV treatment (6 week data collection period)

Questions	• To determine whether the:
	  • patient was SCT-naïve and whether or not they received BV
	  • patients had been given BV with the intention of bridging to an SCT, if the patient had an SCT or not, and whether the patients required salvage chemotherapy after BV to bridge to an SCT

Results	• Response rate = 88% (436/496) no data for 60 patients
Main cohort	• 219 patients treated with BV with intention of a SCT
Sensitivity analysis (i)	• Main cohort + n=60 with no data
Sensitivity analysis (ii)	• Main cohort + n=93 who had BV with no intention of a SCT
Sensitivity analysis (iii)	• Main cohort + (i) & (ii)

Takeda base case analysis is all SCT-naïve patients who received brentuximab vedotin and subsequently bridged to a SCT, regardless of whether or not the initial intention was to bridge to SCT (i.e. Sensitivity analysis 2).

Please see Brentuximab Vedotin Re-Appraisal, Public Health England Report pages 9-15.

Clinical effectiveness: Results

Number and percentage of patients having a SCT for the different scenarios

	Main cohort: BV with intention of getting a SCT	Main cohort + patients with no data (i)	Main cohort + those given BV with no intention of a SCT (ii)	Main cohort + combination of (i) and (ii)
Denominator for each cohort	219	279	312	372
Underwent an allogeneic SCT	45 (21%)	45 (16%)	45 (14%)	45 (12%)
Underwent an autologous SCT	33 (15%)	33 (12%)	33 (11%)	33 (9%)
Had salvage CT after BV before SCT	50 (23%)	50 (18%)	50 (15%)	50 (13%)
Underwent SCT after BV[a]	78 (36%)	78 (28%)	**78 (25%)**	78 (21%)
Underwent SCT after BV +/- salvage[b]	128 (58%)	128 (46%)	128 (41%)	128 (34%)

[a] Patients who had BV and then a SCT straight afterwards; [b] Patients who had BV then a SCT or BV then salvage chemotherapy and then a SCT

From Table 5, page 24 of company submission.
In order to keep the analysis focused on the effectiveness of brentuximab vedotin alone, the SCT rate of 25% (red text) was selected as the input for the base case in the revised health economic model. This avoids any confounding effect of salvage chemotherapy on the base case economic analysis, although a scenario analysis is also provided using the SCT rate of 41% and including the cost of salvage chemotherapy.

Please see Brentuximab Vedotin Re-Appraisal, Public Health England Report page 15.

Clinical effectiveness: SCT rate following single-agent chemotherapy

- In TA446 committee preferred an SCT rate with chemotherapy of **14.3%** (2/14) from Zinzani et al (2000).
- Company asked HL study group what the SCT rate would be following single-agent chemotherapy
- None of the group have any experience of using single-agent chemotherapy in the SCT-naïve setting with the intention to bridging a patient to a SCT. This is because combination chemotherapy regimens would routinely be used.
- Group stated that:
  - *" it would strongly caution against taking the Zinzani et al. paper as somehow more representative than the others……...there is no scientific basis for doing this."* And *"there is an argument for saying that the Zinzani et al. paper is unrepresentative of the transplantation rate we might see today with this agent"* (gemcitabine).
  - *"The group feels the overall SCT rate of **5.3%*** (rate originally submitted by Takeda in TA446) *is more representative than taking the Zinzani et al. paper alone. It is also the sort of transplant rate the group would expect using a single agent chemotherapy, apart from brentuximab vedotin, in this setting".*

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Clinical effectiveness: ERG's comments on CDF data collection

- agrees with the company that, to capture the full benefit of brentuximab vedotin the rate of SCT post-brentuximab should be based on patients that did and did not have salvage therapy after brentuximab
- the proportion of missing data is large and introduces uncertainty in the estimated post-brentuximab vedotin SCT rate
- considers the most relevant population to be based on sensitivity analysis (iii) which includes:
  - Missing data (60 patients)
  - Patients who had BV with no intention of a SCT
  - All those who received salvage therapy after brentuximab vedotin to bridge to SCT
- ERG preferred SCT rate is **34%** (128/372).
- ERG accepts company's rationale for a SCT rate post chemotherapy of 5.3% and have included a scenario analysis using the rate form the Zinzani paper (14.3%)

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New outcomes data after Allo-SCT

	TA446	ID1366
Dataset	• Sureda et al. (2012)	• Reyal et al. (2016)
Patients	• 78 patients with r/r HL who received an allo-SCT at 10 European centres between the years 2000 and 2007 • 4-year overall survival 24%	• 116 patients with r/r HL undergoing allo-SCT at 4 UK transplant centres between 2005 and 2014 • 4-year overall survival 77.5% for PET negative
Company comments	• 86% of the patients included in the trial had failed a previous ASCT prior to receiving allo-SCT	• Used a subgroup (Peggs analysis) of 86 patients (74% of the total cohort) who were receiving allo-SCT as their first SCT (matching population in this re-appraisal) • dataset uses the PET-response-adjusted transplantation strategy that is now routinely used across the UK

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New outcomes data after ASCT

	TA446	ID1366
Dataset	• Sureda et al. (2001).	• Thompson et al (2013).
Patients	• 494 patients with r/r HL who received an ASCT between 1984-1998 at one of 46 Spanish centres. • 5-year overall survival 54.5%	• 28 patients with r/r HL treated at University College London with an ASCT and followed up over 5 years. • 3-year overall survival 92.9%
Company comments	• Not representative of UK clinical practice • PET-response-adjusted transplantation strategy was not followed in the dataset, meaning only 41% of patients in that dataset were in complete response prior to their ASCT while 15% had resistant disease prior to ASCT.	• UK study following UK clinical practice • dataset uses the PET-response-adjusted transplantation strategy that is now routinely used across the UK

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Clinical-effectiveness: ERG's comments on overall survival

Company's new outcomes data	ERG comment
Allo-SCT – Reyal (2016)	• agrees that this study provides outcome data for allo-SCT that is highly relevant to current UK transplant practice
ASCT – Thompson (2013)	• sample size is small (28 patients), and data immature with substantial censoring • ERG prefers outcomes data from Reyal 2016 which is more mature and has larger samples size. • Outcomes for patients after ASCT are better than those for patients after allo-SCT • therefore the ERG's preferred outcome data for allo-SCT to inform the outcomes after ASCT, provides a more robust, although conservative, estimate

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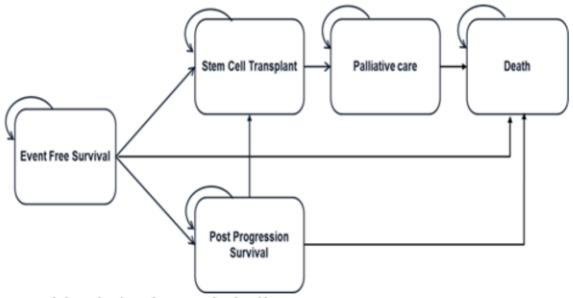
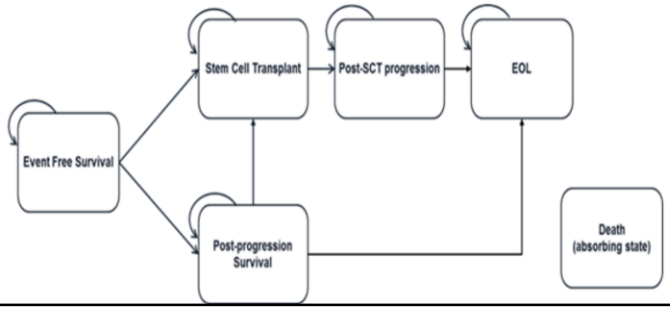
Cost-effectiveness: Company's updated model

- Original model diagram (TA446). Time horizon of 70 years; 1-week model cycle



- Updated model diagram



- Company have updated the model structure
- New model includes:
  - 28 day model cycle
  - a *post-SCT progression state* to account for the structural flaw identified in TA446 and
  - tunnel states to correct an error identified by the company in the way transitions between health states were calculated.

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Cost-effectiveness: HRQoL & costs in the new post-SCT progression state

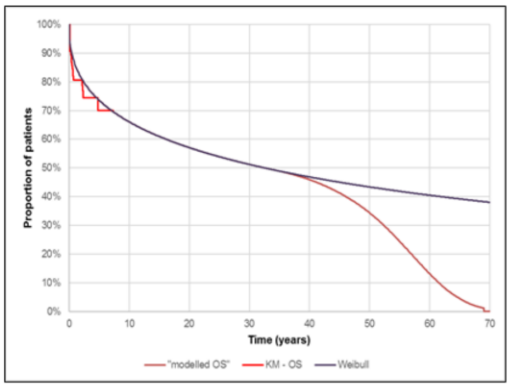
Utility value *(value used in TA466 in the PPS state)*	0.38	
Costs of disease progression after ASCT	**% Pts.**	**£ per cycle**
GEM-P (Gemcitabine, cisplatin, methylprednisolone)	33%	£119
IVE (Ifosfamide, epirubicin, etoposide)	33%	£1,659
Bendamustine + steroids (assumed dexamethasone)	33%	£6,240
Treatment administration	100%	£322
Total	-	**£8,340**
Weighted total	-	**£2,995**
Costs of disease progression after Allo-SCT		
Gemcitabine & methylprednisolone	25%	£101
Bendamustine + steroids (assumed dexamethasone)	25%	£6,240
Donor lymphocyte infusion	50%	£7,100
Treatment administration	50%	£322
Total	-	**£5,457**
Weighted total	-	**£5,296**

Company's costs informed by clinical expert opinion. Assumed treatment duration 2 months 18

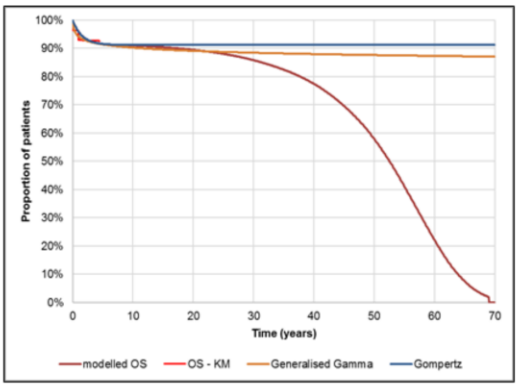
From Page 27, tables 2 & 3 of ERG report.
PPS = post-progression survival

Cost-effectiveness: Overall survival after allo-SCT and ASCT

Overall survival KM data from Reyal *et al*. 2016 and modelled curves (allo-SCT)



Overall survival KM data from Thomson *et al*. 2013 and modelled curves (ASCT)



- For allo-SCT company used a Weibull curve. The Weibull curve was capped by the general population background survival curve, with divergence in the curves from about 40 years onwards.
- For ASCT company used a Gompertz curve which was also capped by the general population background survival curve from about 5-years

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Cost-effectiveness: ERG's comments on updated model (1)

Issue	ERG comment
Model functionality	Could not properly validate the updated model because of the volume of code, size of the model and its running time
Changes in risk of death (tunnel states)	No justification for the company's rationale behind the changes in the model to account for changes in risk of death overtime. The change in the risk of death over time after SCT is accounted for in the underlying hazard of the best fitting survival curve.
Cost of salvage chemotherapy	Company included costs of salvage chemotherapy in the comparator arm of the economic model. Patients receiving chemotherapy cannot receive subsequent salvage chemotherapy to bridge to SCT, therefore ERG does not see a clinical rationale for including these costs.

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Cost-effectiveness: ERG's comments on updated model (2)

Issue	ERG comments
Post progression state	Duration of time spent in this health state is determined from the extrapolated OS and PFS outcomes following ASCT and allo-SCT: • The proportion of time spent alive but also progressed was calculated by comparing the total time spent alive (area under the OS curve) with the total time spent progression-free (area under the PFS curve), with the difference being the total time spent in this new post-SCT progression state. • The company justify this approach because it avoids further multiplication of tunnel states which reinforces ERGs view that the use of tunnel states in the model is not suitable.
Conclusion	ERG's preferred analyses uses original model from TA446 and includes: • Use of Reyal et al 2016 to inform OS and PFS after allo-SCT and ASCT and to update the estimated costs and QALYs expected after SCT. • 34% post BV SCT rate • 5.3% post chemotherapy SCT rate

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Cost-effectiveness: ERG's updated cost estimates

- To use the updated costs presented by the company in the original model the ERG added the new mean progressed disease costs to the total costs for brentuximab vedotin and chemotherapy
- The ERG calculated the number of newly progressed patients in each model cycle, after SCT, and multiplied the proportion of newly progressed patients in each cycle by the total cost of progressed disease after ASCT and allo-SCT.
- Newly progressed patients were estimated through the manipulation of the OS and PFS data provided by the company for SCT (fitted with the Gompertz model and adjusted to reflect the 7-days model cycle length in the previous model).
- Finally, the ERG discounted, and summed all the cycle costs and then weighted the final sum by the proportion of patients receiving ASCT (42.2%) and allo-SCT (57.8%) and subsequently, by the proportion of patients bridging to SCT in the brentuximab arm and in the chemotherapy treatment arm, respectively.

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Cost-effectiveness: ERG's updated utility estimates

- The ERG estimated the progressed disease curve by subtracting the PFS from the OS curve from Reyal *et al*. 2016, in order to estimate the proportion of progressed patients after alloSCT in each model cycle (same data used ASCT).
- The ERG estimated mean time spent in the progression-free state and in the progression state (taken from the PFS and progressed disease curves) after SCT. This was 30 years for progression-free and 3 years for progression.
- These values were then used to generate a weighted post-SCT progressed disease utility value of 0.73.
- This value compares with the company's previous utility value of 0.77 and the ERG's previous exploratory utility value of 0.50. The key driver of the ERG's weighted utility estimate is the mean time spent in the PFS and in the progressed disease sates.
- Considering that the company's new data for survival outcomes after SCT show a considerable survival benefit compared with the ones used in the previous submission (Sureda *et al*. 2012), the ERG's estimated utility value increased substantially

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Cost-effectiveness: Summary of changes to the company's and ERG's models (1)

Issue	TA446	Company's new model	ERG preferred (using TA446 model)
Changes in risk of death (tunnel states)	NA	transitions from health states in the model did not take into account the change in risk over time.	change in the risk of death over time is accounted for in the underlying hazard of the survival curve fitted, therefore the tunnel states were not necessary
New post-SCT progression health state	Structural flaw that patients could not experience disease progression following SCT.	New post-SCT progression with higher resource use and lower quality of life compared with the pre-progression health state.	Not suitable. ERG used post-SCT OS/PFS from Reyal 2016 to update the company's previous model and replace the Sureda 2012 data.

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Cost-effectiveness: Summary of changes to the company's and ERG's models (2)

Issue	TA446	Company's new model	ERG preferred (using TA446 model)
Updated utility values	Company utility = 0.77 ERG preferred = 0.50 *(in original model)*	0.38 (Swinburn 2015) expected that these patients would have a similar HRQoL to those in the post-progression survival from TA446	0.73 (weighted post-SCT in progressed disease state).
SCT rate following BV	58% (UK observational dataset)	25% (CDF data)	34% (includes people who received salvage chemo *before* SCT).
SCT rate following chemotherapy	14.3% (Zinzani 2000)	5.3% (UK NCRI Hodgkin study group)	5.3% and scenario analysis using 14.3%

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Cost-effectiveness: Company's base case results with PAS

- Company's cost-effectiveness results using new model updated to correct following errors identified by the ERG at clarification:
  - applying age-related utility decrements
  - Using relative risks for time to SCT
- Company's base case pairwise results (including PAS)

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Standard care	[redacted]	[redacted]			
Brentuximab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	£16,535

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From table 2, Page 2 of the Company clarification response Appendix F

Cost-effectiveness: Company's scenario analyses

Scenario	Company rationale
SCT rate with BV 41%	In the CDF study an additional 50 patients proceeded to SCT following treatment with BV **and** salvage chemotherapy. This lead to an overall SCT rate of 128/312 (41%) among patients who received treatment with BV
Post-progression utilities from the Checkmate 205 study	0.715 from Checkmate 205 (nivolumab for r/r classical Hodgkin lymphoma after ASCT). 74% patients had received prior treatment with BV
Lower discount rate of 1.5% applied for costs and QALYs	Long-term health benefits (approx. 20% patients alive at 30 years).
TA446 model (25% SCT rate with BV)	Model used in TA446 updated with CDF data only.
TA446 model (41% SCT rate with BV)	Model used in TA446 updated with CDF data only.

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Cost-effectiveness: Company's scenario analyses results with PAS

Scenario	Inc. Costs	Inc. QALYs	Pairwise ICER
SCT rate with BV 41% (includes people who received salvage chemo after BV but before SCT)	[redacted]	[redacted]	£13,503
post-progression utilities from the Checkmate 205 study	[redacted]	[redacted]	£16,584
lower discount rate of 1.5% applied for costs and QALYs	[redacted]	[redacted]	£11,269
TA 466 model (25% SCT rate with BV)	[redacted]	[redacted]	£35,449
TA 466 model (41% SCT rate with BV)	[redacted]	[redacted]	£29,825

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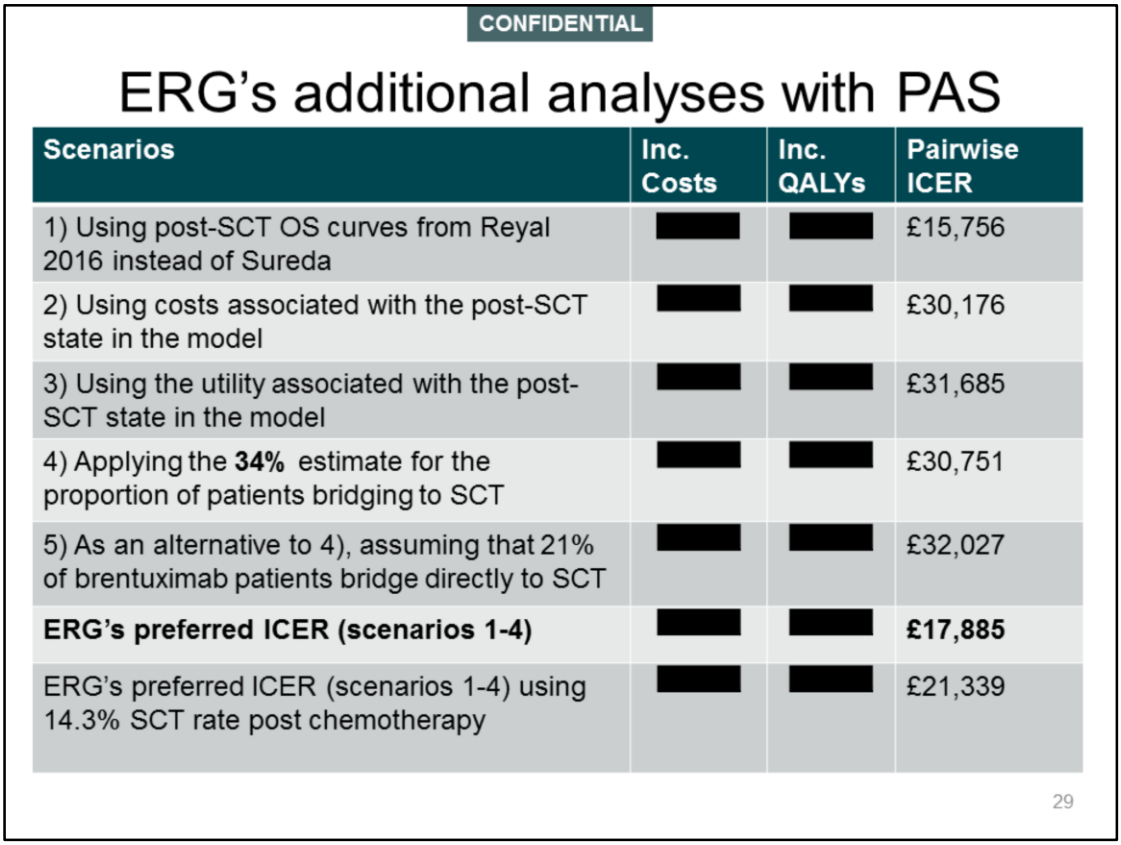
Tables 7-12 of company's clarification response Appendix F



From page 37, Table 10 of ERG report (updated in erratum) and page 2 of the ERG addendum

Innovation – Company (1)

- Targeted therapy with a mechanism of action that is unique within r/r HL.
- Based on the high response rates achieved and its ability to bridge a significant proportion of patients to a potentially curative stem cell transplant (SCT), brentuximab vedotin is viewed by physicians and patient interest groups as a real "step-change" in the management of r/r HL. This is recognised in section 4.3 of TA446.
- Over the past 5 years (through its continuous availability on the CDF), it has become firmly established as the preferred treatment option for patients with r/r HL following at least two prior therapies when SCT or multi-agent chemotherapy is not a treatment option (Population 3 within TA446). This represents a patient group that had a very high unmet need and limited survival outcomes in the pre-brentuximab vedotin era.

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Innovation – Company (2)

- Offers other benefits, at least some of which may not be adequately captured within the cost-effectiveness estimates. These include:
  - a convenient administration schedule (one 30-minute infusion every 3 weeks) that means it can be administered on an out-patient basis. This allows patients to live a more normal life and spend less time in hospital during treatment.
  - improved tolerability compared to traditional, non-targeted chemotherapy. As a result, brentuximab vedotin delivers patients to SCT in better condition that is the case after other bridging agents (less cumulative toxicity etc.).
  - a potentially positive impact on the quality of life of caregivers and family members. Given the young age of patients with HL (and hence likely young age of partners / caregivers) this could be substantial in terms of its impact on activities such as work.

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Innovation – Professional groups

- When first introduced, brentuximab vedotin was indeed innovative. It has now become standard of care however within its licensed indications

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Equality issues

- Patient groups
  - Brentuximab vedotin is only administered once every 3 weeks meaning patients only need to be in hospital for 2 days in each 3-week cycle. This is beneficial for those with mobility or other issues which make it difficult to travel to hospital on a more regular basis.
  - Hodgkin lymphoma has twin peaks of incidence in those under 30 and those over 65 years old. If access to treatment is denied to these patients, then there is potentially an issue of age discrimination against both young and old people
- Company
  - No additional equality issues concerning the use of brentuximab vedotin that have arisen since the initial NICE appraisal

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Key Issues

- What is the most appropriate SCT rate to use in the base case following treatment with brentuximab vedotin?
- Do the committee accept the rate of SCT post chemotherapy proposed by the company and accepted by the ERG?
- Do the committee accept the use of new data sources for outcomes post SCT to replace the Sureda et al data in TA446?
- Do the committee accept the structural changes made to the model by the company.
- What is the most plausible ICER for brentuximab vedotin vs single-agent chemotherapy?

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  Technical Lead
- **Nicola Hay**
  Technical Adviser
- with input from the Lead Team (Peter Selby, Paul Tappenden and David Chandler)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma (CDF review of TA446) [ID1366]

Document B

Company evidence submission

18 January 2018

File name	Version	Contains confidential information	Date
		Yes/no	

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long, it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

List of Abbreviations

ACD	Appraisal consultation document
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
ASH	American Society of Haematology
BCSH	British Committee for Standards in Haematology
BSBMT	British Society of Blood and Marrow Transplantation
BV	Brentuximab vedotin
CDF	Cancer Drugs Fund
CI	Confidence interval
COMP	Committee for Orphan Medicinal Products
CR	Complete remission
CSGs	Clinical Study Groups
DCA	Data Collection Agreement
DLI	Donor lymphocyte infusions
EFS	Event-free survival
EMA	European Medicines Agency
EOL	End of life
ERG	Evidence Review Group
EU	European Union
FAD	Final Appraisal Document
GEL/TAMO	Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea
HL	Hodgkin lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LY	Life year
MAIC	Matching Adjusted Indirect Comparison
MMAE	Molecule monomethyl auristatin E
NCRAS	National Cancer Registration Analysis Service
NCRI	National Cancer Research Institute
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NPP	Named Patient Programme
ORR	Objective response rate
OS	Overall survival

PAS	Patient access scheme
PbR	Payment by results
PET	Positron emission tomography
PFS	Progression-free survival
PHE	Public Health England
PPS	Post-progression survival
PR	Partial response
PSA	Probability sensitivity analysis
QALY	Quality adjusted life year
r/r	Relapsed or refractory
r/r HL	Relapsed or refractory Hodgkin lymphoma
SACT	Systemic Anti-Cancer Therapy
sALCL	Systemic anaplastic large cell lymphoma
SCT	Stem cell transplant
SmPC	Summary of Product Characteristics
vs.	Versus

Executive Summary

Brentuximab vedotin has been available continuously across England since April 2013 through the national Cancer Drugs Fund (CDF) for the indication under review (i.e. the treatment of patients with relapsed/refractory Hodgkin lymphoma (r/r HL) following at least two prior therapies when stem cell transplant (SCT) or multi-agent chemotherapy is not a treatment option). During that time, it has become established as the preferred treatment option and has transformed the management and outcomes of these patients. This submission is the CDF review of TA446 following the conclusion of data collection.

Prior to the availability of brentuximab vedotin, if a r/r SCT-naïve HL patient did not respond to, or was intolerant of multi-agent chemotherapy, their only treatment option was palliation with single-agent chemotherapy. The use of brentuximab vedotin has given patients who were ineligible for a SCT and were headed for palliation an opportunity for a potentially curative stem cell transplant. Maintaining access for patients to brentuximab vedotin in this indication is regarded as a priority not just by Takeda, but by all clinicians involved in treating these otherwise difficult to manage patients.

In June 2017, at the conclusion of appraisal TA446, the NICE appraisal committee recommended that brentuximab vedotin be included within the CDF for this particular indication (referred to as "Population 3" within TA446). The rationale for inclusion within the CDF was to maintain access for patients while additional data was collected to address the two areas of clinical uncertainty that had been identified by the NICE committee. The first area of clinical uncertainty related to what proportion of patients would subsequently become eligible to receive a SCT following treatment with brentuximab vedotin; while the second related to what percentage of patients treated with the comparator, single-agent chemotherapy, would become eligible for a SCT.

A Data Collection Agreement (DCA) was concluded between Takeda UK and NHS England in which it was agreed that the first question would be addressed through a retrospective collection of outcomes for all relevant patients who had previously received brentuximab vedotin through the original CDF, the data collection being led and reported by Public Health England (PHE). The data on SCT rates after brentuximab vedotin provided by Takeda previously during TA446 was based on a sample of CDF patients from 10 centres in England, rather than all centres. According to the DCA, the second question on the post-comparator SCT rate would be addressed by seeking the advice of clinical experts from the National Cancer Research Institute (NCRI) Hodgkin lymphoma clinical study subgroup.

Both data collection exercises have been completed, and provide more extensive evidence on the rate of SCT following treatment with brentuximab vedotin or single-agent chemotherapy. The evidence on the SCT rate after brentuximab vedotin is now based on a total of 312 patients treated in England between April 2013 and March 2016 in more than 100 Trusts across the whole country. Reassuringly, the overall SCT rate among this expanded dataset is similar to what was reported previously for 78 patients in 10 Trusts. In patients where the intent was to bridge to SCT, in both the PHE data and the data from 10 Trusts, 58% of patients had a SCT following treatment with brentuximab vedotin (128/219 in the PHE data, 44/76 patients with evidence in the 10 Trust data).

Of the information available in the PHE report, notable findings are:

- 25% of all patients who received brentuximab vedotin were bridged directly to SCT, regardless of intent to transplant;

- 41% of all patients who received brentuximab vedotin were bridged to a SCT, including patients who received additional salvage chemotherapy.

The clinical specialists from the Hodgkin lymphoma subgroup of the NRCI have endorsed 5.3% as an appropriate SCT rate following treatment with single-agent chemotherapy. This rate is based on a literature review of the limited evidence available in this setting, and was presented by Takeda to NICE previously during TA446.

The SCT rates derived from the data collection have been incorporated into an updated health economic model. At the same time, the structure of the model and some of its inputs (i.e. in relation to clinical outcomes following SCT) have been revised in order to address issues raised in TA446. Compared with the previous health economic model, this revised model now more accurately reflects: (1) the patient pathway following progression post-SCT (via inclusion of a post-SCT progression health state); and (2) the clinical outcomes that are currently achieved with SCT in the UK. The SCT outcomes data are now based on data for patients being treated in accordance with UK guidelines for the management of r/r HL as published in 2014 (i.e. following a PET-response adjusted transplant strategy that is now used by all UK transplant centres). By contrast, the publications previously used for SCT outcomes were based on outdated approaches to SCT with transplants dating back to 1980, were not from the UK, and were not reflective of current UK transplant practice or outcomes.

Based on the comprehensive SCT rates from the PHE report, revision of the model structure to address the committee's previous issues, and the more representative SCT outcomes data used, we believe the current cost-effectiveness estimates are now more accurate than those in TA446. The justification for all changes to the model are provided in this resubmission. The results derived from the revised economic model clearly demonstrate that brentuximab vedotin is cost-effective at standard thresholds. The base case takes a conservative approach by using the lower SCT rate of 25% for brentuximab vedotin, which gives an ICER (with PAS) of £14,101/QALY.

A range of scenario analyses are undertaken, many of which lower the ICER further. Using the higher SCT rate of 41% (patients who received additional salvage prior to SCT) the ICER is £11,658/QALY. The only scenario that leads to an ICER in excess of £30,000 is the previous version of the model used with an SCT rate of 25% for brentuximab vedotin (ICER of £32,749). If the SCT rate is increased to the observed 41% then even the previous model has an ICER of £27,803. We would caution against using the previous model however as it contains both a structural flaw identified by the committee, and uses outdated SCT outcomes data that do not reflect current UK transplant practice.

In this post CDF review, we would encourage the committee to ensure that patients in England can retain access to brentuximab vedotin for this indication by recommending it as cost-effective for routine NHS use.

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

B.1.1 Decision problem

The decision problem for this technology appraisal is an evaluation of the clinical and cost-effectiveness of brentuximab vedotin for the treatment of CD30-positive Hodgkin's lymphoma (HL) (CDF review of TA446) [ID1366]. This resubmission covers the indication which was referred by NICE to the Cancer Drugs Fund (CDF) in June 2017 for further data collection.

The evaluation covers the following indication:

People with CD30-positive HL following at least 2 previous therapies when stem cell transplant or multi-agent chemotherapy is not a treatment option (the so called "two lines ineligible population" or Population 3 from TA446).

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

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Re-appraisal following data collection for Population 3 from single technology appraisal of brentuximab vedotin for Lymphoma (Hodgkin, CD-30 positive) [TA446], recommended by NICE for the CDF within the context of a managed access agreement: People with CD30-positive Hodgkin's lymphoma following at least 2 previous therapies when stem cell transplant or multi-agent chemotherapy is not a treatment option.	The population addressed by the current submission is as defined by the final scope issued by NICE.	None
Intervention	Brentuximab vedotin	Brentuximab vedotin	None
Comparator(s)	Following at least 2 previous therapies when stem cell transplant (SCT) or multi-agent chemotherapy is not a treatment option: • Best supportive care	Patients with r/r HL who are not suitable for SCT due to chemo-refractory disease, advanced age or co-morbidities and are not eligible for multi-agent chemotherapy have few treatment options. Prior to the availability of brentuximab vedotin on the CDF, the only option for such patients was single-agent chemotherapy, palliative care (which may include radiotherapy for local relapse) or to attempt an ASCT with a very low probability of success. Based on the Marketing Authorisation for	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		brentuximab vedotin, single-agent chemotherapy was accepted by the NICE committee during TA446 as the appropriate comparator in this appraisal.	
Outcomes	• Overall survival • Progression-free survival • Objective response rate • Complete remission • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Objective response rate • Complete remission • Partial remission • Adverse effects of treatment • Health-related quality of life • Stem Cell Transplant (SCT) rate	The manufacturer will also present data on the partial remission rate and stem cell transplant rate.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The analysis performed is in line with the NICE reference case, and Guide to the Methods of Technology Appraisal (2013). 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. Social care has been included within the end of life costs; no other PSS costs have been considered.

B.1.2 Description of the technology being appraised

In appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

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 Hodgkin lymphoma.

Brentuximab vedotin has been designated an orphan medicine in the EU for Hodgkin lymphoma, systemic anaplastic large cell lymphoma and primary cutaneous T-cell lymphoma. Details of the licensed indication are presented in Table 2.

Table 2: Technology being appraised: Brentuximab vedotin for relapsed or refractory CD30-positive Hodgkin's lymphoma (CDF review of TA446) [ID1366]

UK approved name and brand name	Brentuximab vedotin (Adcetris®)
Mechanism of action	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.
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 EMA/CHMP/471107/2012.[1] 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 Hodgkin lymphoma (HL) (EU/3/08/596) and Treatment of Anaplastic Large Cell Lymphoma (sALCL) (EU/3/08/595). In September 2012, the Committee for Orphan Medicinal Products (COMP) reviewed brentuximab vedotin's orphan designation and recommended that it be maintained for both HL and sALCL.[2]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Adcetris® is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): • following autologous stem-cell transplant (ASCT) or; • 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 systemic anaplastic large-cell lymphoma (sALCL). Adcetris® is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).[3]
Method of administration and dosage	The recommended dose of brentuximab vedotin is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. 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.[3]
Additional tests or investigations	None other than standard clinical practice
List price and average cost of a course of treatment	The NHS list price of brentuximab vedotin is £2,500 per 50mg vial (ex VAT). Based on mean cycles of 4.1 for the population covered in this submission (i.e. Population 3 from TA446), derived from real-world use in England on the CDF, the mean cost per course for an average patient is estimated at approximately £31,000 per patient.
Patient access scheme (if applicable)	As per the agreement with the Department of Health, a patient access scheme (PAS) in the form of a simple discount applies for all licensed indications of brentuximab vedotin in the United Kingdom. Unless otherwise stated, the analyses in this resubmission reflect the 'with PAS' price of brentuximab vedotin. The current PAS for brentuximab vedotin is a straight discount of [redacted] bringing the NHS net acquisition price from £2,500 per vial to [redacted] per vial.
*A conditional marketing authorisation represents an accelerated approval process and is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required.	

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

Classical Hodgkin lymphoma (HL) is a rare cancer of the immune system affecting 2.5 new patients per 100,000 of the population in the UK each year, [4] (directly standardised incidence rate of 4.0 and 2.7 per 100,000 population in males and females, respectively).[5] It typically affects people aged between 20-34 years of age, followed by another peak in adults aged >70 years.[6] Data from the Office for National Statistics shows that there were around 1,800 new cases of HL diagnosed in 2015 in England.[5] Hodgkin lymphoma accounts for 13% of all lymphomas diagnosed in 2015 and 0.6% of all cancers diagnosed, with 1-year survival being 91% in males and 93% in females and 5-year survival being 85% in males and 86% in females.[7] The majority of people with HL can achieve long term survival with standard frontline chemotherapy ± radiotherapy, or subsequently with the use of autologous stem cell transplantation (ASCT) in those eligible to receive this. However, there remains a small number of people with relapsed or refractory r/r HL following ASCT, or who are ineligible for ASCT or multi-agent chemotherapy, who have a very poor prognosis with currently available treatment options (other than brentuximab vedotin).

A summary of the treatment pathway for r/r HL and where brentuximab vedotin fits into this is shown in Figure 1 and Figure 2 below. During the previous NICE technology appraisal of brentuximab vedotin for the treatment of Lymphoma (Hodgkin's, CD30-positive) [TA446], brentuximab vedotin was recommended routine use on the NHS for patients who relapse post ASCT (referred to as 'Population 1' within TA446). This guidance has since been implemented in NHS England. Brentuximab vedotin for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT ('Population 2' within TA446) was not recommended for use on the NHS. The third population within TA446 was recommended for use on the CDF and the current resubmission focuses on this indication, namely the treatment of r/r HL patients who have received at least two prior therapies but are ineligible for a SCT or multi-agent chemotherapy. The use of brentuximab vedotin for Population 3 patients is outlined below in the overall treatment pathway for HL.

The "Guidelines on the management of primary resistant and relapsed classical Hodgkin's lymphoma" which were published by the British Committee for Standards in Haematology (BCSH)[8] and the British Society of Blood and Marrow Transplantation (BSBMT) include brentuximab vedotin as an option for patients who have relapsed after ASCT, and also as an option pre-ASCT for patients who are either ineligible for ASCT or who are eligible for ASCT but have PET +ve disease. The positioning of brentuximab vedotin for use in Population 3 (the so called "two lines ineligible" population), as represented in Figure 1 and Figure 2 below, is in line with the aforementioned BCSH guidelines.

Figure 1: Simplified treatment pathway in HL showing where brentuximab vedotin is used for patients in Population 3 of TA446

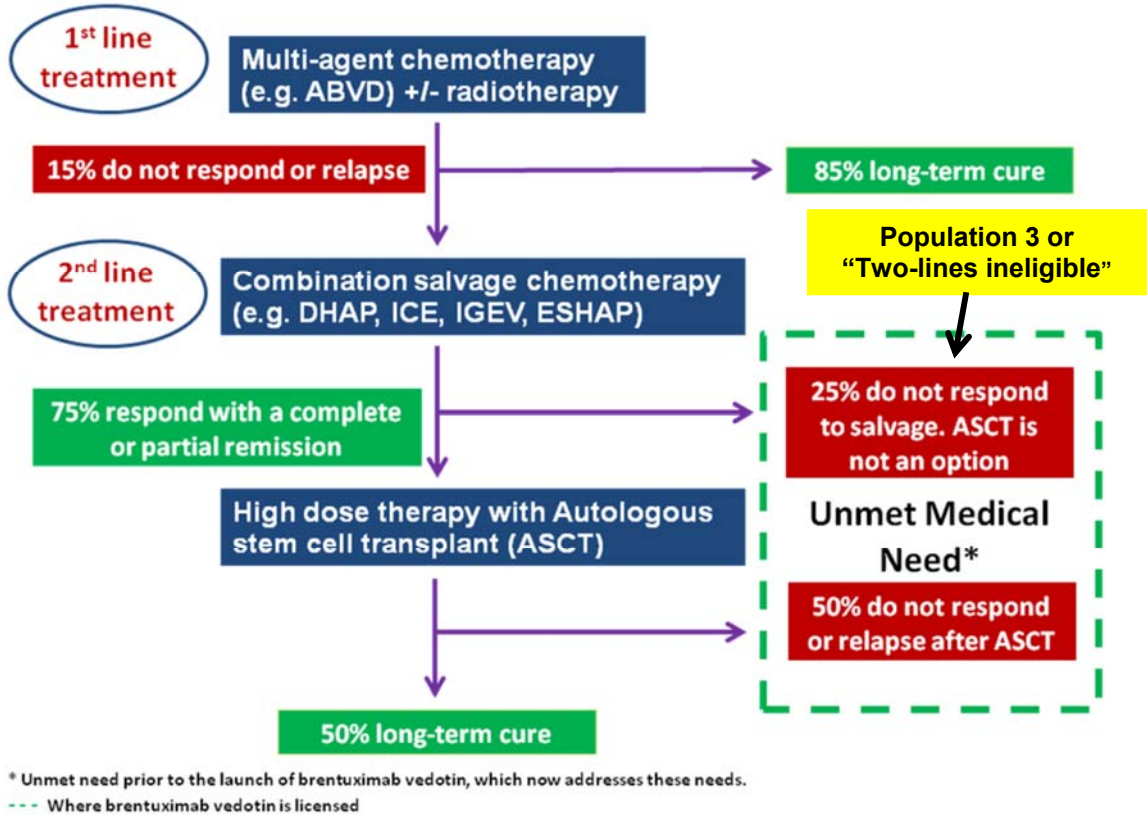
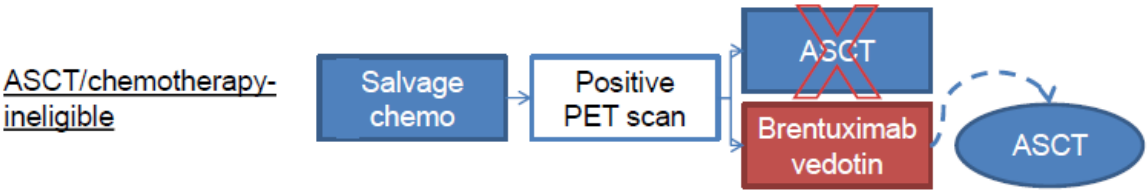


Figure 2: Simplified treatment pathway as included in the Chair's presentation at the second NICE Appraisal Committee Meeting during TA446



The benefits of brentuximab vedotin are that that it fills an unmet need for a group of heavily pre-treated patients with r/r HL who are:

- few in number – a total incidence of about 163 patients per year in England with r/r HL or which less than 100 would be eligible for Population 3;
- mostly young people of working age who are generally otherwise well. This has significant economic implications due to the impact of lost productivity; indeed, a US study showed that HL is the costliest cancer per death in men and women of working age 25;[9]
- at a stage of the disease where there are no proven treatment options, other than brentuximab vedotin;

- brentuximab vedotin provides the opportunity to bridge to a SCT in a proportion of patients who otherwise would not be eligible for this potentially curative intervention. Patients unsuitable for SCT can also benefit from treatment with brentuximab vedotin via significant and prolonged symptom reduction which often cannot be achieved with standard chemotherapy options.

B.1.4 Equality considerations

There are no additional equality issues concerning the use of brentuximab vedotin that have arisen since the initial NICE appraisal.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Not applicable.

The data presented in this resubmission document is a review of Technology Appraisal Guidance TA446 *'Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma'* [10] incorporating data collected through the Cancer Drugs Fund (CDF). Specifically, the review relates to the use of brentuximab vedotin for the treatment of patients with r/r HL following at least two prior therapies when SCT or multi-agent chemotherapy is not a treatment option (referred to as 'Population 3' within TA446), an indication that was the subject of a data collection via the CDF.

B.2.2 Summary of existing evidence

As part of the previous NICE appraisal of brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma (TA446), Takeda UK submitted evidence on the clinical and cost-effectiveness of brentuximab vedotin for treating patients with r/r HL following at least two prior therapies when SCT or multi-agent chemotherapy is not a treatment option. This section will summarise the clinical effectiveness evidence. A summary of the cost-effectiveness evidence, including a discussion of the original economic model can be found in Section B.3.1.

The original evidence presented by Takeda to NICE was the clinical data upon which EMA granted the marketing authorisation for brentuximab vedotin in this indication. The evidence came from 59 patients treated in Phase I/II studies, a Japanese-only study (TB-BC010088)[11] and a Named Patient Programme (NPP), [12] who had not undergone ASCT and had received one or more doses of brentuximab vedotin. Of these 59 patients, 41 had received the licensed dose of 1.8 mg/kg brentuximab vedotin every 3 weeks. The most significant finding from the original clinical evidence that was presented to EMA was that following treatment with brentuximab vedotin, about 1 in 5 (19%) patients that were previously unable to undergo SCT (because of chemo-refractory disease) became eligible for a SCT and thus potentially long-term cure of their disease. This, along with an objective response rate of 54% (22/41) and a complete response rate of 22% (9/41) in this highly chemo-refractory group of patients led to brentuximab vedotin being approved by EMA for this particular indication (the so-called "two lines ineligible patient population" or Population 3 within TA446).

For all prior evidence of the clinical effectiveness of brentuximab vedotin in this patient population, please refer to Section 4.11.10.4 (pages 105-106) of the original submission from Takeda submitted to NICE in late October 2015.

Since initial approval by EMA, there have been a number of publications consistent with, and further supporting the use brentuximab vedotin in this setting.[12-16] One of the largest of these, and that was presented previously to NICE, was a UK real-world observational study which collected data retrospectively on patients treated with brentuximab vedotin who were all previously ineligible for a SCT. The UK real-world observational study was co-ordinated by Dr Graham Collins of Oxford University Hospitals (and Chair of the NCRI Hodgkin

lymphoma subgroup), and collected data retrospectively on patients treated with brentuximab vedotin (mainly funded through the CDF) at 10 major centres in England. This observational dataset consisted of 78 patients who had received two prior lines of therapy and were all considered to be ineligible for SCT (due to insufficient remission) at the time when they received brentuximab vedotin. These data first became available to Takeda in late July 2016 and were incorporated into Takeda's response to NICE's first Appraisal Consultation Document (submitted to NICE in September 2016). At that time, the results from the UK observational dataset were pooled with the results of a recently completed Phase IV study of brentuximab vedotin (the C25007 study), and the pooled results were used to develop a health economic model to demonstrate the cost-effectiveness of brentuximab vedotin in this setting.

Subsequently, following review by the ERG and NICE committee, Takeda revised its approach to move away from using the pooled dataset in the model and instead used only the data that came directly from the UK observational dataset. This was based on the advice of the NICE committee as summarised in Section 4.16 of the second ACD where it states:

"the committee also agreed that the real-world UK dataset provided more relevant clinical data, compared with the pooled dataset, for the estimation of clinical effectiveness for brentuximab vedotin from a NHS perspective,"

The health economic model was therefore revised as part of Takeda's response to the second ACD to use only the clinical data from the UK observational study and these data continue to be used to inform many of the clinical inputs to the current health economic model (i.e. that which accompanies this resubmission).

A summary of the UK observational study and the key results derived from it are presented in Table 3 and Table 4, respectively.

Table 3: UK real-world observational study

Study	UK Observational study
Study design	Retrospective, real-world study
Population	Adult patients with relapsed or refractory Hodgkin lymphoma who have received two prior lines of therapy but are ineligible for stem cell transplant (due to insufficient remission).
Intervention(s)	Brentuximab vedotin
Comparator(s)	None
Reported outcomes specified in the decision problem	• Objective response rate (ORR) (%) • Progression-free survival (PFS) • Overall survival (OS)

All other reported outcomes	• Mean number of cycles brentuximab vedotin • Patient demographics (i.e. mean age, gender) • Post-brentuximab vedotin SCT rate (%) • Time to progression • Time to SCT • Time from progression to SCT

Table 4: Results from the UK real-world observational study.[17]

Outcome	Results (n=78)
ORR	51% (CR = 24%, PR = 27%)
Post BV SCT rate	58%
PFS	5.68 months (95%CI 4.21 - 17.05)
OS	37.2 months (95%CI 17.8 - not reached)
Mean No. of cycles of BV	4.1 (95% CI 3.7 - 4.6)
Abbreviations: ORR, overall response rate; BV, brentuximab vedotin; PFS, progression-free survival; OS, overall survival, SCT, stem cell transplant; CI, confidence interval; CR, complete response; PR, partial response.	

A more complete description of clinical effectiveness evidence from the UK real-world observational study can be found in *'Appendix to the ACD response, Part II'*, that was submitted by Takeda to NICE on the 17th October 2016.

At the end of TA446, the NICE committee concluded that although the results from the UK observational study supported the data on which brentuximab vedotin was initially approved by EMA and provided a highly relevant dataset from an NHS perspective, it was still associated with some degree of uncertainty. Specifically, the committee was concerned that the SCT rate seen in this study following treatment with brentuximab vedotin (58%) might not be generalisable beyond the 10 centres that contributed to this dataset.

To address this clinical uncertainty, the committee concluded that there would be merit in building on the valuable data already provided by the UK observational dataset by collecting additional data on the specific issue of the SCT rate following treatment with brentuximab vedotin in this setting. The committee acknowledged that this data would offer further insight on the clinical effectiveness of brentuximab vedotin, and provide a robust source of evidence for an influential factor in any further decisions about its cost effectiveness in this population. In order to do this, while maintaining patient access to brentuximab vedotin in the meantime, the committee recommended brentuximab vedotin for use within the CDF for this particular indication (i.e. Population 3 of TA446). A Data Collection Agreement was concluded between Takeda UK and NHS England, and Public Health England was asked to undertake a retrospective collection of the post-treatment SCT rate for all relevant patients (i.e. those who were SCT-naive) who had previously been treated with brentuximab vedotin for this indication through the original CDF.

A second area of clinical uncertainty identified by the committee related to what the SCT rate should be after single-agent chemotherapy which had been agreed during TA446 to be the

relevant comparator for brentuximab vedotin in this indication. Takeda had provided NICE with evidence from a literature review showing that the SCT rate after treatment with single-agent chemotherapy in this setting was very low (5.3%), but the committee was concerned that this may be an underestimate and wanted confirmation of this rate. It was not deemed feasible however to collect data on the post-treatment SCT rate for single-agent chemotherapy, because brentuximab vedotin had become the standard treatment used in this setting in the UK (via the original CDF). Hence, in the Data Collection Agreement, Takeda and NHS England agreed that this data point would instead be informed by a consensus of clinical expert opinion from the NCRI Hodgkin lymphoma subgroup.

The outcomes from the data collection during the CDF period, both for brentuximab vedotin and single-agent chemotherapy are described below in Section B.2.3.

B.2.3 Outcome of the CDF data collection

In June 2017, at the conclusion of NICE appraisal TA446 (*"Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma"*), the NICE committee recommended that brentuximab vedotin be included within the Cancer Drugs Fund (CDF) for the treatment of patients with r/r HL following at least two prior therapies when SCT or multi-agent chemotherapy is not a treatment option (referred to as 'Population 3' within TA446).

The rationale for inclusion within the CDF was to allow additional data to be collected retrospectively that would address two areas of clinical uncertainty that had been identified by the committee – namely, what is the post-treatment SCT rate in such patients after treatment with either brentuximab vedotin or single-agent chemotherapy (the agreed comparator for this population, as per the marketing authorisation for brentuximab vedotin). The post-treatment SCT rates are important factors in determining the cost-effectiveness of brentuximab vedotin in this setting.

Both data collection exercises have now been completed and the outcomes are available.

B.2.3.1 SCT rate following real world treatment with brentuximab vedotin

B.2.3.1.1 Background

Brentuximab vedotin has been available continuously in England since April 2013 through the CDF for this indication. During that time, it has become established across the country as the preferred treatment option for such patients and hence there is a large pool of patients that have received treatment with brentuximab vedotin in this setting. Data from some of these patients (sourced from 10 centres across England) was used by Takeda during TA446 as a source of initial evidence on the SCT rate after treatment with brentuximab vedotin. As part of the Data Collection Agreement between Takeda and NHS England for the CDF period, it was agreed to build on this initial evidence by undertaking a retrospective collection of SCT rates for all relevant patients at all centres who had received brentuximab vedotin for this indication through the original CDF, between April 2013 and March 2016. The data collection was to be lead and reported by the National Cancer Registration and Analysis Service (NCRAS) at Public Health England (PHE).

B.2.3.1.2 Method of Data Collection for brentuximab vedotin

A bespoke questionnaire was sent to 223 consultants across 106 trusts in England to request data on the treatment of 496 HL patients who had received CDF funding for brentuximab vedotin, from the 522 initial applications made to the CDF (see Figure 3).

The questionnaire was developed by NHS England (NHSE) and PHE, with input from NICE and two clinical experts, Dr Graham Collins, Consultant Haematologist, Oxford University Hospitals who had led the UK real-world observational study that provided the initial evidence provided by Takeda on the SCT rate after brentuximab vedotin (see Section B.2.2) and Professor John Radford, Consultant Medical Oncologist and Lead for the Lymphoma Service, The Christie NHS Foundation Trust. A copy of the questionnaire can be found in Appendix D.

The data collection period lasted for six weeks, and up to five reminders were sent to those consultants who had not returned the questionnaires.

The questionnaire was set to determine three main items of interest:

1. Whether or not the patients were SCT-naïve;
2. Whether or not the patients had been given brentuximab vedotin with the intention of bridging the patient to a SCT;
3. Whether the patients who received brentuximab vedotin actually had a SCT after receiving brentuximab vedotin (with or without subsequent salvage chemotherapy).

To ensure that estimates of the rates of SCT following brentuximab vedotin were available for all r/r HL patients who were SCT-naïve, three sensitivity analyses were undertaken:

1. **Sensitivity analysis 1:** Included 60 patients with no data (due to their consultant not returning the questionnaire). It was assumed (very conservatively and arbitrarily) that none of these patients received a SCT following brentuximab vedotin treatment;
2. **Sensitivity analysis 2:** Included 93 patients who received brentuximab vedotin but not with the intention of bridging the patient to a SCT;
3. **Sensitivity analysis 3:** Combination of sensitivity analyses 1 and 2 (a very conservative analysis).

The following two assumptions were made for these different scenarios:

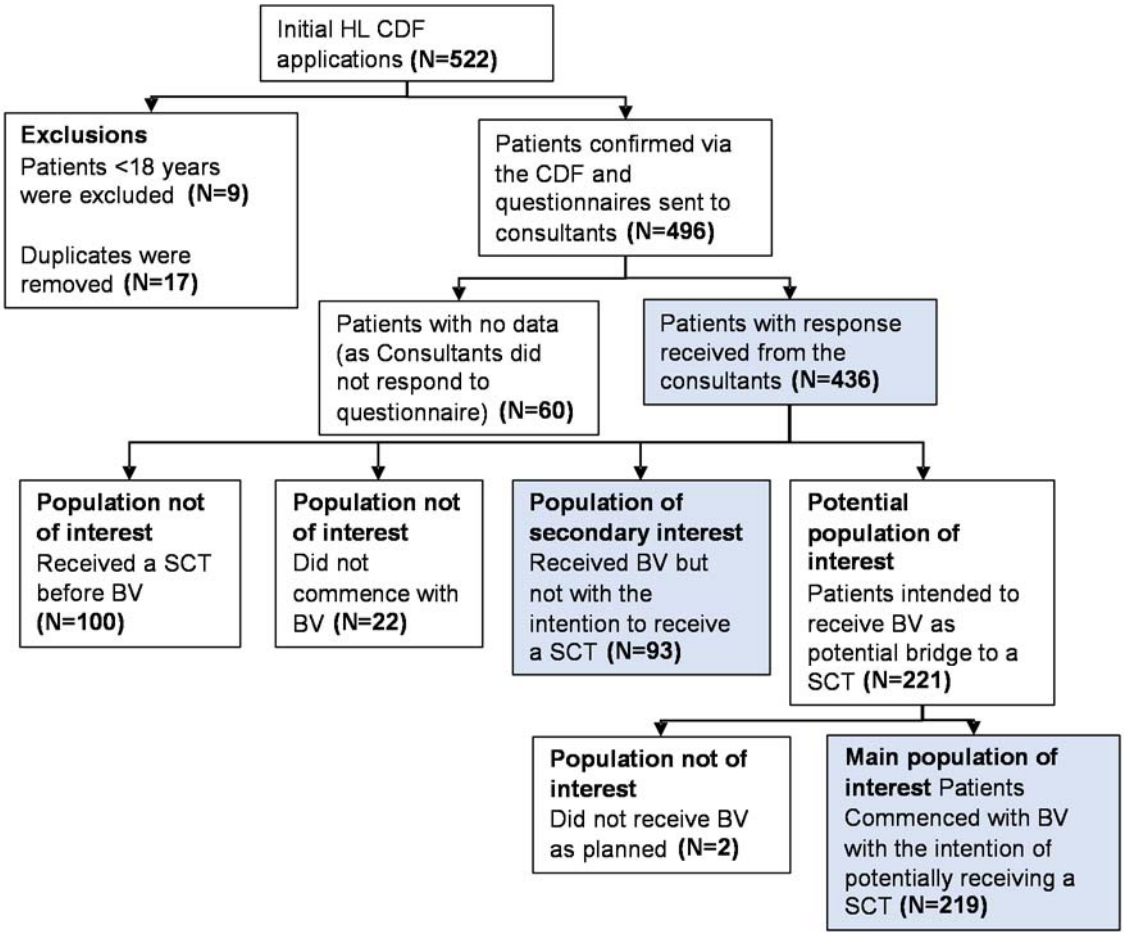
i. That all of the patients for whom there were no data were eligible, (i.e. assumed they had received brentuximab vedotin with the intention of bridging the patient to a SCT (and so included in the denominator), but that none of them received a SCT (and so not included in the numerator);

ii. The inclusion of the patients who had brentuximab vedotin with no intention of getting a subsequent SCT only increased the denominator in these sensitivity analyses and aligned with the wording in the relevant brentuximab vedotin marketing authorisation in Hodgkin lymphoma.

For the purpose of this resubmission and based on guidance received by Takeda from NHS England and the CDF team, the population chosen for the base case analysis is all SCT-naïve patients who received brentuximab vedotin and subsequently bridged to a SCT, regardless of whether or not the initial intention was to bridge to SCT (i.e. Sensitivity analysis 2). This is because NHS England and the CDF team feel it is important to ensure that the population included in the base case analysis is aligned with the marketing authorisation for brentuximab vedotin (this does not specify that brentuximab vedotin can only be prescribed in this setting for patients intended to be taken to SCT). If applied, such a restriction would prevent patients who can never receive a transplant (e.g. due to advanced age or co-morbidities) from availing of the disease control and other benefits offered by brentuximab vedotin. This would be unfair to what is already a highly disadvantaged group of patients.

This is different from the approach taken in the PHE report which identifies a *"Main Population of interest"* as those patients who received brentuximab vedotin with the intention of subsequently being bridged to a SCT.

Figure 3: Derivation of the population of interest from the initial CDF applications made for brentuximab vedotin for Hodgkin Lymphoma between April 2013 and March 2016



Abbreviations: HL, Hodgkin lymphoma; CDF, Cancer Drugs Fund; SCT, stem cell transplant; BV, brentuximab vedotin

Source: Public Health England Report.[18]

B.2.3.1.3 Results of Data Collection - SCT rate after brentuximab vedotin

There was an 88% (436/496) return rate of questionnaires from the 223 consultants who had applied for funding from the CDF between 01 April 2013 and 31 March 2016 to treat patients with r/r HL with brentuximab vedotin. The data were separated out into the two main indication groups: (i) brentuximab vedotin given to patients after a SCT (population not of interest for this resubmission) and (ii) brentuximab vedotin given in patients following two prior therapies when SCT or multi-agent chemotherapy was not a treatment option (SCT-naïve). Only the patients in the latter group were considered further. Those patients who did not have brentuximab vedotin at all were also excluded completely.[18]

The patients who were treated with brentuximab vedotin and subsequently underwent SCT were further split into two groups:

a. those patients who had brentuximab vedotin and then a SCT (with no other treatment before the SCT);

b. those patients who had brentuximab vedotin and then had salvage chemotherapy before the SCT.

B.2.3.1.4 Sensitivity analyses

The three sensitivity analyses described above in Section B.2.3.1.2 provided three sets of estimates of the rate of SCT following brentuximab vedotin in order to determine conservative estimates compared with what the PHE Report calls the *"Main Population of interest"* or the *"Main Cohort"* (where the denominator = 219 patients) (Table 5). The denominators for the three sensitivity analyses used are as follows:

i. **Sensitivity scenario 1:** includes patients who commenced brentuximab vedotin with the intention of receiving a SCT (n=219) and the 60 patients for whom there were no data (denominator = 279);

ii. **Sensitivity scenario 2:** includes patients who commenced brentuximab vedotin with the intention of receiving a SCT (n=219), plus the 93 patients who received brentuximab vedotin but with no intention that they would receive a SCT. This group reflects the known SCT rate in the CDF population in the relevant Hodgkin lymphoma indication as defined in the marketing authorisation (denominator = 312);

iii. **Sensitivity scenario 3:** includes patients who commenced brentuximab vedotin with the intention of receiving a SCT (n=219), plus the 93 patients who received brentuximab vedotin but with no intention that they would receive a SCT, plus the 60 patients for whom there were no data (denominator = 372).

Table 5: Number and percentage of patients having a SCT for the different sensitivity scenarios, including a breakdown into the type of SCT and whether or not the patients required salvage chemotherapy after the brentuximab vedotin before the SCT

Number and percentage of patients having a SCT for the different scenarios				
	Main cohort: BV with intention of getting a SCT	Main cohort plus patients with no data (i)	**Main cohort plus those given BV with no intention of a SCT (ii)**	Main cohort plus combination of (i) and (ii)
Denominator for each cohort	**219**	279	**312**	372
Underwent an allogeneic SCT	45 (21%)	45 (16%)	**45 (14%)**	45 (12%)
Underwent an autologous SCT	33 (15%)	33 (12%)	**33 (11%)**	33 (9%)
Had salvage CT after BV before SCT	50 (23%)	50 (18%)	**50 (15%)**	50 (13%)
Underwent SCT after BV[a]	**78 (36%)**	**78 (28%)**	**78 (25%)**	**78 (21%)**
Underwent SCT after BV +/- salvage[b]	**128 (58%)**	**128 (46%)**	**128 (41%)**	**128 (34%)**

[a] Patients who had BV and then a SCT straight afterwards

[b] Patients who had BV then a SCT or BV then salvage chemotherapy and then a SCT

The results for the PHE defined *"Main Cohort"* (patients receiving BV with the intent of getting to a SCT) are highlighted in grey in Table 5, and show a SCT rate of 36% and 58%, without and with salvage chemotherapy, respectively. The latter rate of 58% of r/r HL patients who were formerly deemed ineligible for a SCT being able to successfully bridge to a SCT following treatment with brentuximab vedotin is exactly aligned with the SCT rate seen in the UK real-word observational dataset (based on 78 patients from 10 English centres) which was used to inform the original economic analysis presented by Takeda as a part of its response to the first ACD.[17]

As described above (see Section B.2.3.1.2), based on guidance received by Takeda from NHS England and the CDF team, the population chosen for the base case analysis is all SCT-naïve patients who received brentuximab vedotin and subsequently bridged to a SCT, regardless of whether or not the initial intention was to bridge to SCT (i.e. Sensitivity analysis 2 as highlighted in blue in Table 5) The corresponding SCT rates are 25% and 41%, without and with salvage chemotherapy, respectively. In order to keep the analysis clean and focused on the effectiveness of brentuximab vedotin alone, the SCT rate of 25% (red text in Table 5) was selected as the input for the base case in the revised health economic model (see Section B.3). This avoids any confounding effect of salvage chemotherapy on the base case economic analysis, although a scenario analysis is also provided using the SCT rate of 41% and including the cost of salvage chemotherapy.

B.2.3.1.5 Comparison of results from CDF Data Collection with data appraised previously by NICE

As mentioned above, the results for the PHE defined '*Main Cohort*' (patients receiving brentuximab vedotin with the intent of getting to a SCT; 58% SCT rate) are exactly aligned with the SCT rate seen in the UK real-word observational dataset (based on 78 patients from 10 English centres) which was used to inform the original economic analysis presented by Takeda as a part of its response to the first ACD.[17] Hence, the results derived from the retrospective CDF data collection exercise for all relevant patients who received brentuximab vedotin in England validate the initial results based on a sample of these patients that were provided by Takeda to NICE previously during TA446, and which were used to generate the initial cost effectiveness estimates.

There is however greater granularity in the expanded dataset and this allows additional analyses to be undertaken, including whether patients were bridged to SCT directly from brentuximab vedotin alone (25% among all patients who received brentuximab vedotin, whether or not it was intended as a bridge to SCT) or whether they also received salvage chemotherapy prior to SCT (an additional 16%, giving a total SCT rate of 41%).

B.2.3.1.6 Conclusions

The retrospective CDF data collection for brentuximab vedotin was undertaken successfully and provided outcomes that validated the initial evidence on the post-treatment SCT rate that was presented by Takeda to NICE during the initial appraisal (TA446). As the data collection is now based on a much-expanded patient pool, it provides more robust evidence on the real world SCT rate that is achievable after treatment with brentuximab vedotin in patients who were previously unable to undergo SCT (mainly due to chemo-refractory disease).

B.2.3.2 SCT rate following treatment with single-agent chemotherapy

B.2.3.2.1 Background

As explained above, a second area of clinical uncertainty to be addressed during the CDF data collection period was the expected post-treatment SCT rate in this setting among patients treated with single-agent chemotherapy (the appropriate comparator for brentuximab vedotin in Population 3 as agreed during TA446).

Takeda had previously provided NICE with evidence from a literature review showing that the SCT rate after treatment with single-agent chemotherapy in this setting was very low (5.3%). However, the committee was concerned that this may be an underestimate and wanted confirmation of this rate.

B.2.3.2.2 Method of Data Collection for single-agent chemotherapy

However, it was not deemed feasible by NHS England to collect data on the post-treatment SCT rate for single-agent chemotherapy, because brentuximab vedotin has for many years been the standard treatment used in this setting in the UK (via the original CDF). Hence, there would not be data in NHSE's Systemic Anti-Cancer Therapy (SACT) database to

provide a real world SCT rate for single-agent chemotherapy in such patients. To overcome this data gap, the Data Collection Agreement between Takeda and NHSE agreed that this datapoint would instead be informed by a consensus of clinical expert opinion from the National Cancer Research Institute (NCRI) Hodgkin lymphoma clinical study group. This was deemed by NHS England to be the best data source to supplement and/or validate that already provided by Takeda during TA446.

Hence, NHSE and Takeda UK approached the Chair of the HL study group (Dr Graham Collins, Oxford University Hospitals) and requested that he discuss with the group and form an opinion on what the SCT rate would be for r/r HL patients treated with single-agent chemotherapy (excluding brentuximab vedotin and bendamustine which is not commissioned in this setting). This exercise was completed by Dr Collins and he provided Takeda and NHSE with a letter (dated 24th November 2017) summarising the group's view.[19]

B.2.3.2.3 Outcome of Data Collection - SCT rate after single-agent chemotherapy

The letter stated that none of the NCRI HL clinical study group have any experience of using single-agent chemotherapy in the SCT-naïve setting with the intention to bridging a patient to a SCT. This is because combination chemotherapy regimens would routinely be used. Before brentuximab vedotin was available, if combination chemotherapy was not a treatment option (as is the case in Population 3, based on brentuximab vedotin's marketing authorisation) then single-agent chemotherapy would be used in the palliative setting but with no intention to bridge to a potentially curative transplant.[19]

Therefore, the group felt it would not be helpful to decide arbitrarily on a best-guess number for what the SCT rate would be. They decided instead to review the available literature reporting on the use of non-brentuximab vedotin, non-bendamustine single-agent chemotherapy in the r/r HL SCT-naïve setting. The group identified the same four published papers[21-24] that were previously summarised by Takeda and provided to NICE as part of Takeda's response to the first ACD. The group felt that the quality of the evidence was low, with only a total of 3 out of 57 patients reported to have subsequently received a SCT following single-agent chemotherapy.

The group was aware that, as per the FAD for TA446,[10] the ERG and NICE Committee had previously favoured the SCT rate of 14.3% (2 out of 14 patients) derived from the Zinzani et al. (2000) paper[24] (along with a SCT rate of 53% after brentuximab vedotin – see Section 4.33 of the FAD).[10] However, the group stated that it *"would strongly caution against taking the Zinzani et al. paper as somehow more representative than the others……..there is no scientific basis for doing this."* Indeed, the group also stated that *"there is an argument for saying that the Zinzani et al. paper is unrepresentative of the transplantation rate we might see today with this agent"* (gemcitabine).[19]

The NCRI group concludes by stating that:[19]

> *"The group feels therefore that the overall stem cell transplant rate of 3 out of a total 57 (5.3%) is more representative than taking the Zinzani et al. paper alone. It is also the sort of transplant rate the group would expect using a single agent chemotherapy, apart from brentuximab vedotin, in this setting. We would encourage*

NICE to use the 5% value as the comparator single agent chemotherapy stem cell transplant rate."

B.2.3.2.4 Conclusions

A consensus opinion from clinical experts at the NCRI HL study group provided an estimate for the SCT rate (5.3%) after single-agent chemotherapy that is consistent with that provided previously to NICE by Takeda during TA446. The NCRI group recommends that this rate should be used for the comparator to brentuximab vedotin in the health economic modelling.

B.2.4 Survival outcomes from SCT

The model used to calculate the cost effectiveness of brentuximab vedotin for this indication is driven largely by 1). the percentage of patients that can be successfully bridged to SCT with either brentuximab vedotin or single-agent chemotherapy, and 2). the long-term outcomes achieved by such patients following SCT. Hence, in order to accurately estimate the cost effectiveness of brentuximab vedotin it is essential that appropriate and up to date evidence is used to measure the outcomes that are achieved after SCT.

B.2.4.1 ASCT outcomes data from Thomson et al. (2013)[19]

The original model used data from the Sureda et al. (2001)[20] publication for outcomes after ASCT. This was a dataset reporting the outcomes of 494 patients with r/r HL who received an ASCT between 1984-1998 at one of 46 Spanish centres, collected by the GEL/TAMO (Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea) Spanish Cooperative Group.

In the third NICE appraisal committee meeting held on 15 February 2017 (and subsequently in discussions with a number of UK lymphoma transplant experts), it has been highlighted that this dataset does not represent current UK, or indeed international, transplant practice and the patient outcomes that are now routinely achieved following an ASCT. This largely reflects a shift towards using PET-based response adjusted strategies, and reserving ASCT for patients achieving metabolic complete response (see below). Hence, using this more historical data significantly underestimates the actual benefits of ASCT in the patient population included in the health economic model.

In order to include more representative outcome data for ASCT, Takeda has been advised by clinical experts to use alternative published data from Thomson et al. (2013).[19] This includes data from 28 patients with r/r HL treated at University College London with an ASCT and followed up over 5 years, and which aligns with the outcomes published from Memorial Sloan Kettering Cancer Centre in larger but equivalent patient groups.[16,41,42] This data has now been used in preference to the Sureda et al. (2001)[20] data in the revised health economic model because it reflects the PET-response-adjusted transplantation strategy that is now routinely used across the UK in all transplant centres. Moreover, this approach is aligned with the current BCSH guidelines[8] for the management of r/r HL in the UK.

It is now an accepted fact that patients who are PET negative (achieve metabolic complete response) prior to ASCT have much more favourable outcomes post-ASCT than patients who have residual PET-avid disease before ASCT. According to modern, response-adjusted

transplantation strategy the latter patients would not be taken to an ASCT. Notably, this PET-response-adjusted transplantation strategy was not followed in the Sureda et al. (2001)[20] dataset, meaning that only 41% of patients in that dataset were in complete remission (CR) prior to their ASCT while a number (15%) actually had resistant disease prior to ASCT. To reiterate, this latter group would not nowadays proceed to ASCT in the UK, as reflected in the data gathered from UK experience of brentuximab vedotin in this setting. Multivariate analysis of the Sureda et al. (2001)[20] dataset demonstrated that the presence of active disease at transplantation (including both the group with resistant disease and those with less than complete response i.e. 59% of the cohort) was an adverse prognostic factor for outcomes. These considerations explain why the outcome results in the Sureda et al. (2001)[20] series are both significantly inferior to those we have now included in the health economic model, and are not reflective of the patients in the model.

In short, the Thomson et al. (2013)[19] publication provides outcome data for ASCT that is much more representative of current transplant practice and outcomes in the UK and therefore we have used this in preference to the now outdated Sureda et al. (2001)[20] data within the health economic modelling. This is a change that is unanimously supported by all UK based clinical experts we have consulted.

B.2.4.2 Allo-SCT outcomes data from Reyal et al. (2016)[21]

During the third NICE committee meeting held on 15 February 2017 it was highlighted by the transplant clinical expert present that there were issues in relation to the appropriateness of using data on allo-SCT outcomes from Sureda et al. (2012).[22] This publication reports outcomes from 78 patients with r/r HL who received an allo-SCT at 10 European centres (8 in Spain, 1 in Switzerland and 1 in Sweden) between the years 2000 and 2007.

The main issue identified with the Sureda et al. (2012)[22] dataset is that 86% of the patients included in it had failed a previous ASCT prior to receiving allo-SCT. By definition, the indication being considered in this re-appraisal is for patients receiving their first transplant (ASCT or allo-SCT) after treatment with either brentuximab vedotin or the comparator of single-agent chemotherapy. Hence, in addition to the fact that it represents a historical and non-UK dataset, the Sureda et al. (2012)[22] publication fundamentally does not provide the outcomes data that is needed for patients undergoing their first transplant. This is a major limitation of this dataset.

In discussions with a leading UK lymphoma transplant expert (Prof. Karl Peggs, University College London) it has been highlighted to Takeda that a more relevant and appropriate dataset to use for allo-SCT outcomes is that of Reyal et al. 2016.[21] This publication provides outcomes data for 116 patients with r/r HL undergoing allo-SCT at 4 UK transplant centres between 2005 and 2014 (63% of the allo-SCTs were carried out between 2010-2014). In addition, one of the study co-authors (Prof. Karl Peggs) was able to provide Takeda with outcomes data specifically for the 86 patients (74% of the total cohort) who were receiving allo-SCT as their first stem cell transplant, thus matching the requirements of the indication being considered in this re-appraisal.[23] This is a significant benefit of the Reyal at al. (2016)[21] dataset compared with that of Sureda et al. (2012).[22]

Furthermore, the Reyal et al. (2016)[21] dataset is aligned with the PET-response-adjusted transplantation strategy that is now routinely used across the UK in all transplant centres, and is advocated in the current BCSH guidelines for the management of r/r HL in the UK.[8]

Differences in transplantation platforms are also likely to be important with respect to survival outcomes. Direct comparison of the approach used by the Spanish group in the Sureda et al. (2012)[22] trial with that used by UK physicians (which incorporates alemtuzumab), suggests a significantly improved progression free survival using the UK platform.[24] Hence, data on outcomes using an alemtuzumab-based platform as in the Reyal et al. (2016)[21] dataset is again more relevant to cost-effectiveness models of UK practice. Finally, Prof. Karl Peggs confirmed that a prospective multi-centre UK trial has been completed (PAIReD: NCT00908180), confirming the outcomes documented in the retrospective Reyal et al. (2016)[21] dataset. A manuscript of these data is currently in preparation.

In summary, the Reyal et al. (2016)[21] publication provides outcome data for allo-SCT that is much more relevant to current transplant practice in the UK and therefore we have used this in preference to the Sureda et al. (2012)[22] data within the health economic modelling. This is a change that is unanimously supported by all UK based clinical experts we have consulted.

B.2.5 Adverse reactions

Details of adverse reactions in all patients following treatment with brentuximab vedotin are presented in Section 4.12 (pages 113-123) of the original dossier submitted by Takeda to NICE on 28 October 2015 as part of TA446. These are not specific to the particular indication that is the subject of this re-appraisal. No further evidence on the safety profile of brentuximab vedotin was requested by the NICE committee at the end of TA446. Hence, no additional data was collected for this post-CDF review of brentuximab vedotin.

B.2.6 Ongoing studies

There are currently no-ongoing studies in adult patients with r/r HL after at least two previous therapies when ASCT or multiagent chemotherapy is not an option.

B.2.7 Innovation

Brentuximab vedotin is a targeted therapy with a mechanism of action that is unique within r/r HL. Based on the high response rates achieved and its ability to bridge a significant proportion of patients to a potentially curative stem cell transplant (SCT), brentuximab vedotin is viewed by physicians and patient interest groups as a real “step-change” in the management of r/r HL. This is recognised in the FAD for TA446 where the following statement is included in Section 4.3:

> *“Brentuximab vedotin offers the chance of a potentially curative stem cell transplant, which the clinical experts considered of great importance. The clinical experts also highlighted that brentuximab vedotin had served as a curative treatment without stem cell transplant.”*

Over the past 5 years (through its continuous availability on the CDF), it has become firmly established as the preferred treatment option for the indication under review here, that is the

treatment of patients with r/r HL following at least two prior therapies when SCT or multi-agent chemotherapy is not a treatment option (Population 3 within TA446). This represents a patient group that had a very high unmet need and limited survival outcomes in the pre-brentuximab vedotin era.

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

- a convenient administration schedule (one 30-minute infusion every 3 weeks) that means it can be administered on an out-patient basis. This allows patients to live a more normal life and spend less time in hospital during treatment.

- improved tolerability compared to traditional, non-targeted chemotherapy. As a result, many clinical experts have commented (including in written form to NICE during consultation on TA446) that brentuximab vedotin delivers patients to SCT in better condition that is the case after other bridging agents (less cumulative toxicity etc.).

- a potentially positive impact on the quality of life of caregivers and family members. Given the young age of patients with HL (and hence likely young age of partners / caregivers) this could be substantial in terms of its impact on activities such as work.

B.3 Cost effectiveness

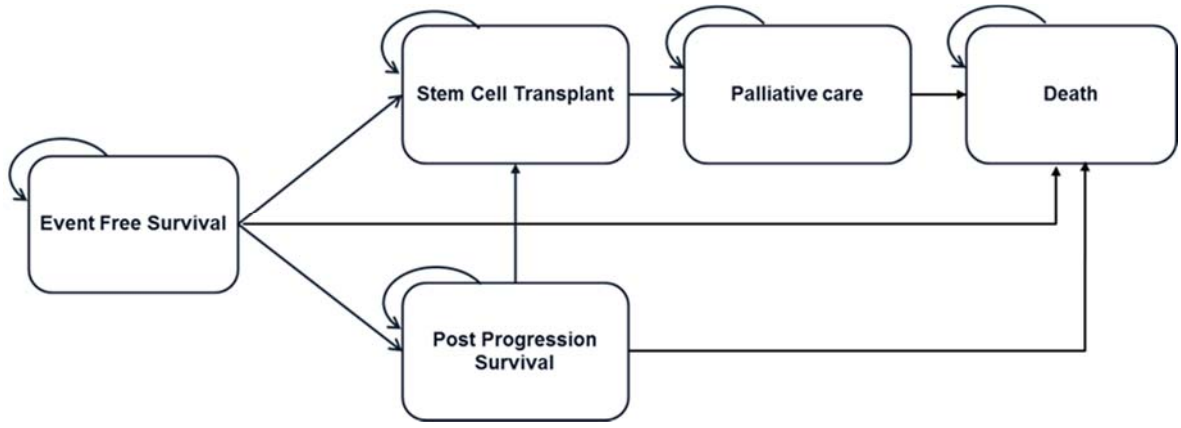
B.3.1 Original economic model

The model submitted as a part of TA446 was described at length in Takeda's response to the 1st Appraisal Consultation Document (ACD).[25] A brief summary is presented below.

A semi-Markov transition matrix model was developed to evaluate the outcomes in patients with Hodgkin lymphoma who are ineligible to receive multi-agent chemotherapy or SCT. The model was built in Microsoft Excel® according to NICE guidelines,[26] and describes the pathway of patients as they undergo treatment with either brentuximab vedotin or single-agent chemotherapy (the relevant comparator in this indication). Patients remained in the event-free survival (EFS) health state until they moved to either the SCT, disease progression (moving to post-progression survival) or death health state. Once their disease has progressed, patients remain in the post-progression survival health state until death.

Although SCTs are curative for at least 50% of patients, many will experience disease progression before dying from relapsed disease. This was modelled through a palliative care health state for the last 12 months of life in SCT, during which patients experience a lower quality of life (Figure 4). Due to the long survival seen with SCT, the time horizon of the model was set to 70 years, using a 1-week model cycle.

Figure 4: Model diagram



To calculate transitions between health states for brentuximab vedotin treated patients, parametric curve fitting was performed on data from usage of the product within the CDF.[17] Parametric survival curves were fitted for time from: (i) EFS to SCT; (ii) EFS to disease progression; and (iii) EFS to death. To select the appropriate parametric curve the method of Latimer et al. was used.[27]

There are two types of SCT available as treatment options for Hodgkin lymphoma, either autologous SCT (ASCT) or allogeneic SCT (allo-SCT). In ASCT (sometimes also called "high-dose therapy and stem cell support") the patient's own stem cells are first collected and stored and then, following high-dose chemotherapy, these stem cells are given back to the patient to rescue the bone marrow. Allo-SCT (sometimes also called an "allograft") is a different procedure which uses stem cells from a donor. The new blood cells derived from these donor stem cells can recognise the lymphoma cells as foreign and can help to eradicate them (this is known as the graft-versus-lymphoma effect and it is fundamental to how an allo-SCT works to combat the disease).

Survival outcomes for ASCT and allo-SCT patients was modelled from published literature [20, 22] by digitising published survival curves using the algorithm from Guyot et al. (2012)[28] and then fitting parametric curves to the digitised data for each type of SCT. This approach was taken as the data on survival post-SCT was extremely immature for brentuximab vedotin. Background mortality was implemented for all health states based on UK Life tables.[29]

To obtain outcomes for the comparator of best supportive care (i.e. single-agent chemotherapy as defined by the marketing authorisation for brentuximab vedotin), a systematic literature review was conducted which identified four papers detailing outcomes for relevant patients treated with such single-agent chemotherapy. The papers varied in their age and number of patients and treatments given, with one study of vinblastine, one of etoposide, one of gemcitabine, and one detailing multiple treatments[30-33]. One paper[31] had incomplete reporting (only outcomes for responders were given), leaving three papers. Of the three remaining papers, only one reported a Kaplan-Meier curve, thus preventing direct extrapolation, while all had incomplete reporting of patient characteristics, thus preventing the use of methods such as Matching Adjusted Indirect Comparison (MAIC). To model the outcomes of single-agent chemotherapy, a surrogate outcomes approach was taken. The probability of achieving a response or SCT was taken from the pooled literature studies, with conditional survival for each outcome then assumed to be the same as in the brentuximab

vedotin data (i.e. patients had the same survival for a given level of response and the same survival once they had received SCT). Differences in outcomes between treatments were therefore driven by the differential rates of response and SCT.

Utility data was taken from published sources including brentuximab vedotin clinical studies,[34] and a published study of utility post SCT.[35]

B.3.2 Changes to the health economic model

Subsequent to the original submission, further data has been collected retrospectively during the CDF period and the major issues identified by the NICE committee have been addressed. The changes made to the health economic model are discussed below, with the justification for the changes explained and details provided on the implementation of these changes

B.3.2.1 Correction of errors identified in the health economic model

In the process of updating the model for this post-CDF re-appraisal submission, an error was found in the model implementation. This error was first corrected before any subsequent analyses were performed.

The error related to the way in which transitions from health states were calculated. In the original model these were determined by curves that started in the first model cycle; however, this did not take into account that the risks changed over time, depending on when a patient moved into a health state. The model has now been corrected through the use of 'tunnel states' which account for how long a patient has been in a health state, and calculate the probability of transition appropriately.

Due to the length of the model time horizon, the number of health states, and thus permutations of risks that patients can be facing, the model coding has now increased substantially in complexity. As such, the decision was taken to extend the cycle length to 28 days (from 7 days) in order to minimise the number of tunnel states required. One consequence of this increased complexity (even with the cycle length increased) is that to generate results using the model now takes approximately 90 minutes – this limits the number of scenario and sensitivity analyses that can be performed. Furthermore, due to the time taken to run a simulation, probabilistic sensitivity analysis (PSA) is no longer feasible to perform because a run of ~1,000 simulations (as is commonly used) would take approximately 2 months.

B.3.2.2 Addition of a new health state - progression post-SCT

During the NICE committee meeting after which the decision was made to recommend brentuximab vedotin for use in the CDF for this indication, the committee discussed at length a perceived structural flaw in the model – namely that patients could not experience disease progression following SCT (see Section 4.31 (page 21) of the FAD)[36] where it states that:

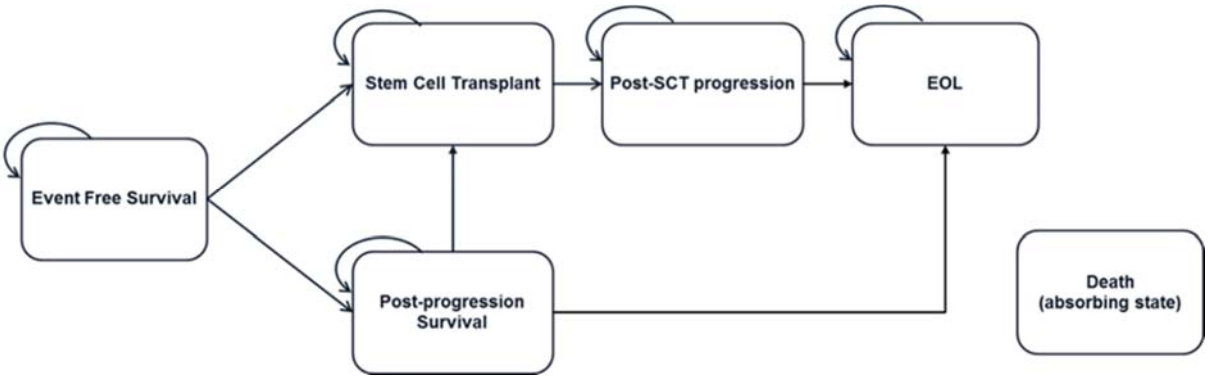
> *"The committee agreed with the ERG that there was a structural flaw in the company's original economic model"*

At that time, this issue was addressed in two ways – by Takeda through the use of a palliative care health state (which lasted for the final 12 months of life); and by the ERG through an assumption that all patients post-SCT had a utility of 0.5. The committee expressed their dissatisfaction with both of these approaches and this is reflected on page 22 of the FAD where it states:

> *"The committee further concluded that the company's updated model was overly optimistic and that the ERG's adjustments were overly pessimistic, and agreed that its preferred cost-effectiveness analysis would lie between the two approaches"*

In order to address the committee's concerns as summarised in the FAD, an extra health state of post-SCT progression has been added into the model, with higher resource use (same monitoring, but additional drug treatment) and lower quality of life compared to the pre-progression state. The revised model structure is now shown in Figure 5. The duration of time spent in this health state is determined from the extrapolated OS and PFS outcomes following ASCT and allo-SCT. The proportion of time spent alive but also progressed was calculated by comparing the total time spent alive (area under the OS curve) with the total time spent progression-free (area under the PFS curve), with the difference being the total time spent in this new post-SCT progression state.

Figure 5: Revised model diagram incorporating a post-SCT progression health state



The revised model structure also now includes an End of Life (EOL) health state. It is worth noting that the costs applied in this EOL health state are sourced from Round et al. (2015);[37] a peer reviewed study investigating the cost of care for oncology patients at the end of life in England and Wales. Given these costs were collected over a nine-month time period (the mean across the included cancers), the duration spent in this EOL health state was also fixed at 9 months.

Health Related Quality of Life (HRQoL) in the post-SCT progression state

A utility value of 0.38 has been used for the post-SCT progression state in the base case. This approach has been adopted because it might be expected that these patients would have a similar HRQL to those in the post-progression survival (PPS) state and 0.38 was the value used for the PPS state in the original model[34] (the default approach wherever possible is to maintain consistency with the original approach adopted). It should however be noted that this utility value is lower than might be expected and is derived from a vignette study. As

such, a scenario analysis reported in Section B.3.4.2 of this document explores the use of utilities derived from a study of nivolumab (the Checkmate 205 study)[38] which was conducted in a similar population of patients with r/r Hodgkin lymphoma.

Costs and Resource Use in the post-SCT progression health state

The medical and administration costs applied in the post-SCT progression state were informed by the advice of a clinical expert. Table 6 below reports the treatment regimens reported as being commonly administered, along with the estimated proportion of patients who receive each treatment following disease progression after either an ASCT or allo-SCT.

Table 6: Breakdown of treatments administered following progression after ASCT or allo-SCT

Regimen	ASCT	Allo-SCT
GEM-P (gemcitabine, cisplatin methylprednisolone)	1/3 (33.3%)	
Gemcitabine + methylprednisolone		25%
IVE (ifosfamide, epirubicin, etoposide)	1/3 (33.3%)	
Bendamustine + steroids	1/3 (33.3%)	25%
Donor lymphocyte infusion (DLI)		50%

The clinical expert indicated that such treatment would typically be administered for a mean duration of two months. Appendix E contains full details of the unit medical and administrative costs included in the model.

For ASCT, the per treatment cycle cost of GEM-P was £119, IVE was £1,659 and bendamustine + steroids was £6,240. The per cycle admin costs were assumed to be the same as those of salvage chemotherapy (£322 per model cycle) regardless of the treatment administered. Total cost of post-ASCT progression treatment was then adjusted for the proportion of patients that progress 5.2% (Appendix B) and the duration of treatment (2 cycles), resulting in a total cost of post-ASCT progression of £608.

For allo-SCT the per treatment cycle cost of gemcitabine + methylprednisolone was £101 and bendamustine + steroids was £6,240. The per cycle admin costs were assumed to be the same as those of salvage chemotherapy (£322 per model cycle) regardless of the treatment administered. For 50% of patients, it was assumed that they would receive donor lymphocyte infusions (DLI), at a cost of £7,100. It was assumed that those patients that received DLI did not receive further chemotherapy.

Total cost of post-allo-SCT progression treatment was then adjusted for the proportion of patients that progress 10.2% (Appendix A) and the duration of treatment (2 cycles), resulting in a total cost of post-ASCT progression of £364.

B.3.2.3 Allo-SCT outcomes data from Reyal et al. (2016)[21]

During the third NICE committee meeting held on 15 February 2017, it was highlighted by the transplant clinical expert present that there were issues in relation to the appropriateness

of using data on allo-SCT outcomes from Sureda et al. (2012).[22] This publication reports outcomes from 78 patients with r/r HL who received an allo-SCT at 10 European centres (8 in Spain, 1 in Switzerland and 1 in Sweden) between the years 2000 and 2007.

The main issue identified with the Sureda et al. (2012)[22] dataset is that 86% of the patients included in it had failed a previous ASCT prior to receiving allo-SCT. By definition, the indication being considered in this re-appraisal is for patients receiving their first transplant (ASCT or allo-SCT) after treatment with either brentuximab vedotin or the comparator of single-agent chemotherapy. Hence, in addition to the fact that it represents a historical and non-UK dataset, the Sureda et al. (2012)[22] publication fundamentally does not provide the outcomes data that is needed for patients undergoing their first transplant. This is a major limitation of this dataset.

In discussions with a leading UK lymphoma transplant expert (Prof. Karl Peggs, University College London) it has been highlighted to Takeda that a more relevant and appropriate dataset to use for allo-SCT outcomes is that of Reyal et al. (2016).[21] This publication provides outcomes data for 116 patients with r/r HL undergoing allo-SCT at 4 UK transplant centres between 2005 and 2014 (63% of the allo-SCTs were carried out between 2010-2014). In addition, one of the study co-authors (Prof. Karl Peggs) was able to provide Takeda with outcomes data specifically for the 86 patients (74% of the total cohort) who were receiving allo-SCT as their first stem cell transplant, thus matching the requirements of the indication being considered in this re-appraisal.[23] This is a significant benefit of the Reyal at al. (2016)[21] dataset compared with that of Sureda et al. (2012).[22]

Furthermore, the Reyal et al. (2016)[21] dataset is aligned with the PET-response-adjusted transplantation strategy that is now routinely used across the UK in all transplant centres, and is advocated in the current BCSH guidelines for the management of r/r HL in the UK.[8]

Differences in transplantation platforms are also likely to be important with respect to survival outcomes.[24] Direct comparison of the approach used by the Spanish group in the Sureda et al. (2012)[22] trial with that used by UK physicians (which incorporates alemtuzumab), suggests a significantly improved progression free survival using the UK platform. Hence, data on outcomes using an alemtuzumab-based platform as in the Reyal et al. (2016)[21] dataset is again more relevant to cost-effectiveness models of UK practice. Finally, Prof. Karl Peggs confirmed that a prospective multi-centre UK trial has been completed (PAIReD: NCT00908180), confirming the outcomes documented in the retrospective Reyal et al. (2016)[21] dataset. A manuscript of these data is currently in preparation.

In summary, the Reyal et al (2016)[21] publication provides outcome data for allo-SCT that is much more relevant to current transplant practice in the UK and therefore we have used this in preference to the Sureda et al. (2012)[22] data within the health economic modelling. This is a change that is unanimously supported by all UK based clinical experts we have consulted.

Extrapolation of data

To implement the change, each graph was first digitised and pseudo patient-level data was then obtained using the algorithm published by Guyot et al. (2012).[28] After obtaining pseudo patient-level data, parametric curve fitting was performed as detailed in the NICE Decision Support Unit document 14.[39] Extrapolations were capped such that the risk of death would

always be equal to or greater than background mortality. Clinical consultation was undertaken to ensure clinical plausibility of all extrapolated curves, with the Gompertz chosen for PFS and the Weibull curve for OS. Full details of the extrapolation and curve fitting are provided in Appendix A.

Estimating the proportion of time in the "post-SCT progression" and EOL states

The time spent in the "post-SCT progression" state was calculated by subtracting each of the following from the mean time alive following allo-SCT: (i) the mean time spent progression-free following allo-SCT; and (ii) the mean time in the EOL state (i.e. 9 months based on the publication on end of life costs by Round et al. (2015).[37] In order to avoid the further multiplication of tunnel states, post-SCT progression was calculated and applied as a proportion of the time spent in the SCT state. The costs and outcomes associated with treatment following progression after allo-SCT were weighted by the estimated proportion of time spent in this state). For a comprehensive description of curve fit statistics and calculations undertaken please see Appendix A.

B.3.2.4 ASCT outcomes data from Thomson et al. (2013)[19]

The original model used data from the Sureda et al. (2001)[20] publication for outcomes after ASCT. This was a dataset reporting the outcomes of 494 patients with r/r HL who received an ASCT between 1984-1998 at one of 46 Spanish centres, collected by the GEL/TAMO (Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea) Spanish Cooperative Group.

In the third NICE committee meeting held on 15 February 2017 (and subsequently in discussions with a number of UK lymphoma transplant experts) it has been highlighted that this dataset does not represent current UK, or indeed international, transplant practice and the patient outcomes that are now routinely achieved following an ASCT. This largely reflects a shift towards using PET-based response adjusted strategies, and reserving ASCT for patients achieving metabolic complete response (see below). Hence, using this more historical data significantly underestimates the actual benefits of ASCT in the patient population included in the health economic model.

In order to include more representative outcome data for ASCT, Takeda has been advised by clinical experts to use alternative published data from Thomson et al. (2013).[19] This includes data from 28 patients with r/r HL treated at University College London with an ASCT and followed up over 5 years, and which aligns with the outcomes published from Memorial Sloan Kettering Cancer Centre in larger but equivalent patient groups.[16, 40, 41] This data has now been used in preference to the Sureda et al. (2001)[20] data in the revised health economic model because it reflects the PET-response-adjusted transplantation strategy that is now routinely used across the UK in all transplant centres. Moreover, this approach is aligned with the current BCSH guidelines for the management of r/r HL in the UK.[8]

It is now an accepted fact that patients who are PET negative (achieve metabolic complete response) prior to ASCT have much more favourable outcomes post-ASCT than patients who have residual PET-avid disease before ASCT. According to modern, response-adjusted transplantation strategy the latter patients would not be taken to an ASCT. Notably, this

PET-response-adjusted transplantation strategy was not followed in the Sureda et al. (2001)[20] dataset, meaning that only 41% of patients in that dataset were in CR prior to their ASCT while a number (15%) had resistant disease prior to ASCT. To reiterate, this latter group would not nowadays proceed to ASCT in the UK, as reflected in the data gathered from UK experience of brentuximab vedotin in this setting.[18] Multivariate analysis of the Sureda et al. (2001)[20] dataset demonstrated that the presence of active disease at transplantation (including both the group with resistant disease and those with less than complete response i.e. 59% of the cohort) was an adverse prognostic factor for outcomes. These considerations explain why the outcome results in the Sureda et al. (2001)[20] series are both significantly inferior to those we have now included in the health economic model, and are not reflective of the patients in the model.

In short, the Thomson et al. (2013)[19] publication provides outcome data for ASCT that is much more representative of current transplant practice and outcomes in the UK and therefore we have used this in preference to the now outdated Sureda et al. (2001)[20] data within the health economic modelling. This is a change that is unanimously supported by all UK based clinical experts we have consulted.

Extrapolation of data

To implement the change, each graph was first digitised and pseudo patient-level data was then obtained using the algorithm published by Guyot et al.[28] After obtaining pseudo patient-level data, parametric curve fitting was performed as detailed in the NICE Decision Support Unit document 14.[39] Extrapolations were capped such that the risk of death would always be equal to or greater than background mortality. Clinical consultation was undertaken to ensure clinical plausibility of all extrapolated curves, with the Gompertz chosen for both OS and PFS. Full details of the extrapolation and curve fitting are provided in Appendix B.

Estimating the proportion of time in the "post-SCT progression" and EOL states

The time spent in the "post-SCT progression" state was calculated by subtracting each of the following from the mean time alive following ASCT: (i) the mean time spent progression-free following ASCT; and (ii) the mean time in the EOL state (i.e. 9 months based on the publication on end of life costs by Round et al. (2015).[37] In order to avoid the further multiplication of tunnel states, post-SCT progression was calculated and applied as a proportion of the time spent in the SCT state. The costs and outcomes associated with treatment following progression after SCT were weighted by the estimated proportion of time spent in this state). For a comprehensive description of curve fit statistics and calculations undertaken please see Appendix B.

B.3.2.5 SCT rate following treatment with brentuximab vedotin based on the Public Health England (PHE)/NHS England report.[18]

NICE guidance in TA446 recommended that brentuximab vedotin be included within the CDF for the indication being considered here (i.e. the treatment of r/r CD30-positive Hodgkin lymphoma after at least 2 prior therapies when SCT or multi-agent chemotherapy is not a treatment option). As specified in Section 4.1 of the Data Collection Agreement that formed

part of the Managed Access Agreement between Takeda UK and NHS England, the area of clinical uncertainty to be resolved during the CDF period was:[42]

> *"the proportion of patients treated with brentuximab vedotin or single agent chemotherapy that subsequently become eligible to receive a stem cell transplant (ASCT or allo-SCT)."*

As per Section 5.1 of the Data Collection Agreement, it was agreed that the main source of data collection would be:

> *"a retrospective analysis led by Public Health England of patients treated with brentuximab vedotin via the CDF in the NHS (approximately for those who initiated treatment between April 2013 and April 2016 in England identified via Blueteq). This data will be further supported by the detailed dataset already collected on some of these patients by Dr Graham Collins as part of a retrospective non-interventional trial."*

As stated in Section 6.1 of the Data Collection Agreement, the outcome data to be collected for brentuximab vedotin during the managed access agreement period was:

- *"Proportion of patients who receive an ASCT after treatment with brentuximab vedotin"*
- *"Proportion of patients who receive an allo-SCT after treatment with brentuximab vedotin"*

It was further agreed that for the single-agent chemotherapy comparator, Takeda would collaborate with the NCRI lymphoma trials group to request that they obtain expert opinion about the expected SCT rate and that this information would be used to inform assumptions within the resubmission following the period of the managed access agreement (see Section 6.2 of the Data Collection Agreement).

This data collection exercise was undertaken by PHE during the Summer of 2017 and the results were written up in a detailed report that was provided to both Takeda and NHS England in October 2017.[18]

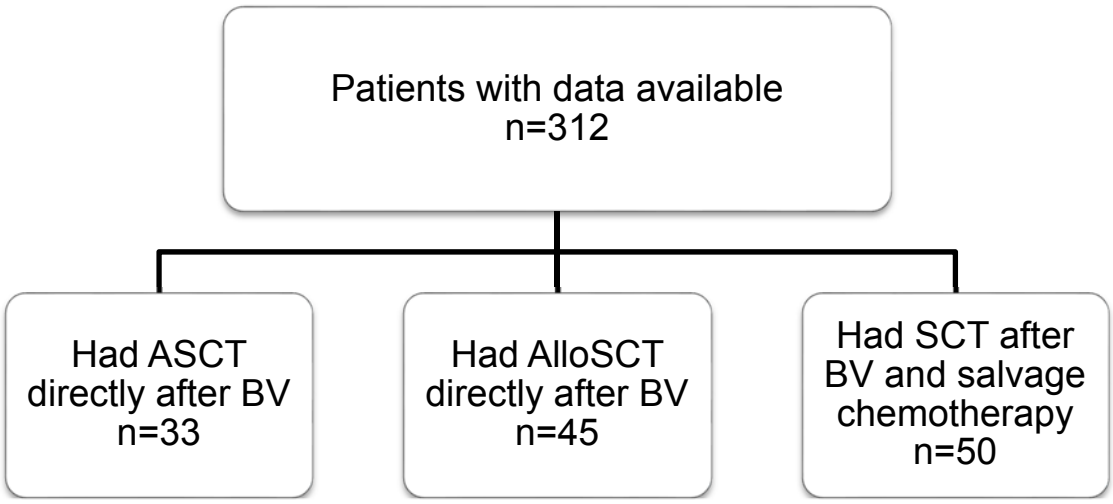
A bespoke questionnaire (see Appendix D) was sent to a total of 223 consultants across 106 trusts in England to ask about the treatment of 496 patients for whom brentuximab vedotin had been funded by the CDF for the treatment of Hodgkin lymphoma. The number of questionnaires returned was 436 (a response rate of 88%). One hundred patients who had received an SCT before brentuximab vedotin were excluded from the analysis (i.e. because this is not the relevant population), as were 22 patients who did not commence treatment with brentuximab vedotin at all. A further two patients were also excluded as they did not receive brentuximab vedotin as planned.

This left a core group of 312 patients who meet the particular requirements of the marketing authorisation for brentuximab vedotin in this setting and for whom data are available from the questionnaires. It is worth noting that of these 312 patients, 219 were patients who commenced brentuximab vedotin treatment with the intention of bridging to a subsequent

SCT (i.e. if a sufficient response was achieved) while 93 patients received brentuximab vedotin without the intention of bridging to an SCT.

The number of patients who received a subsequent SCT is summarised in Figure 6, which is derived from that data in Table 1 (page 15) of the PHE report.[18]

Figure 6: Derivation of SCT rates for brentuximab vedotin (BV) based on CDF data collection



From the data it can be seen that 78/312 (25%) patients had SCT directly after treatment with brentuximab vedotin while a further 50/312 (16%) proceeded to SCT after being treated with brentuximab vedotin and then receiving some additional salvage chemotherapy. This leads to an overall SCT rate of 128/312 (41%) among patients who received treatment with brentuximab vedotin. If the analysis is restricted to only the 219 patients who commenced brentuximab vedotin with the upfront intention of bridging to SCT (what the PHE report describes as the "*main cohort of interest*"), then the corresponding SCT rates are 78/219 (36%) and 128/219 (58%). However, we would note that the marketing authorisation for brentuximab vedotin in this setting (and also the funding provided by the CDF/NHS England) does not specify that it must be used with the intention of bridging to SCT.

Hence, arising from the data in the PHE report, there are four different SCT rates that could reasonably be used for brentuximab vedotin. In the base case of the health economic model we have taken a very conservative approach by using the lowest SCT rate of 25%, reflecting patients bridged to SCT directly from brentuximab vedotin and for the full marketing authorisation based cohort of 312 patients. However, we have also undertaken a sensitivity analysis using the SCT rate of 41% which reflects the overall transplantation rate that can be achieved in clinical practice if salvage chemotherapy is given after brentuximab vedotin. In the case of this sensitivity analysis we have also included the cost of the additional salvage chemotherapy that was administered to 16% of the patients. Ultimately, it is for the NICE committee to determine which approach they would consider the most reasonable, but we would emphasise that our chosen base case takes the most conservative option among those available.

As no data was collected on time to SCT in the CDF data (only SCT rates), model parameters have been derived from data collected from the UK observational study[17] as was

used in the previous appraisal. Hazard ratios are calculated between the rate applied and the original rate in the UK observational study data (Table 7).

Table 7: Hazard ratios applied to time to SCT (when changing SCT rate)

SCT rate applied	Calculation of hazard ratio	Hazard ratio applied
57.7% (FAD BV SCT rate)	57.7/57.7 = 1.00	1.00
41.0% (PHE BV SCT rate)	41.0/57.7 = 0.71	0.71
25.0% (alternative PHE BV SCT rate)	25.0/57.7 = 0.43	0.43
5.3% (SC SCT rate)	5.3/57.7 = 0.09	0.09

B.3.2.6 Comparator SCT rate from NCRI Consensus Statement

As discussed above, a further area of clinical uncertainty to be addressed during the CDF period was the proportion of patients treated with single-agent chemotherapy in this setting that become eligible for SCT.

As per the Data Collection Agreement, in order to address this uncertainty Takeda UK and NHS England approached the Chair of the UK NCRI Hodgkin study group (Dr Graham Collins, Oxford University Hospitals NHS Trust) seeking the group's opinion on what the SCT rate would likely be for patients with r/r Hodgkin lymphoma treated with single-agent chemotherapy (but not brentuximab vedotin or bendamustine) in this clinical setting. In response, Takeda UK and NHS England were provided with a letter signed by the Chair of the group (with 14 members of the group acting as co-signatories) which provides their consensus opinion on this matter.[43] The consensus view of the group was that none of the 4 papers[30-33] identified through the literature review is any more representative than the others, and that therefore the outcomes from the studies should be pooled. In conclusion, the letter states that:

> *"The group feels therefore that the overall stem cell transplant rate of 3 out of a total 57 (5.3%) is more representative than taking the Zinzani paper alone. It is also the sort of transplant rate the group would expect using a single agent chemotherapy, apart from Brentuximab vedotin, in this setting. We would encourage NICE to use the 5% value as the comparator single agent chemotherapy stem cell transplant rate."*

For this reason, a SCT rate of 5.3% for the comparator (single-agent chemotherapy) has been used within the revised health economic model.

B.3.3 Summary of the updated economic model

Results are presented below for the revised economic model, including the changes described above. For clarity, a table is provided showing the effect on the ICER of individual changes that are made to the model in order to construct the new base case. A complete list of inputs is given in Appendix E.

B.3.3.1 Table of ICERs for incremental update of the economic model

The changes to the model and their impact on the Incremental Cost Effectiveness Ratio (ICER) are shown in Table 8. ICERs are given including the impact of the confidential patient access scheme (PAS) – a [redacted]. This is because the PAS is agreed, and has been in place for a substantial period.

Table 8: Results of economic modelling including stepwise changes to the updated base case

	Scenario	ICER (with PAS)	ICER (no PAS)
	Original model used to prepare the FAD	£26,165	[redacted]
	FAD model with transition probability error corrected	£24,368	[redacted]
Individual changes to error corrected model	*Updating the corrected model with newly collected SCT rate data*		
	1. Brentuximab vedotin SCT rate of 25% from the CDF data	£32,749	[redacted]
	Addressing issues from the FAD		
	2. Allo-SCT outcomes data from Reyal et al. (2016)[21]	£14,033	[redacted]
	3. ASCT outcomes data from Thomson et al. (2013)[19]	£15,985	[redacted]
	4. Post-SCT progression health state added (including changes 2 & 3)	£10,235	[redacted]
			[redacted]
All changes made (new base case)		£14,101	[redacted]

B.3.3.2 Base case economic model results

Table 9 below details the base case pairwise results. The base case ICER has improved from the original submission. As can be seen in Table 8, this is primarily due to the updated SCT survival data, which shows better survival than the papers by Sureda et al.[26,28] The fall in the SCT rate does increase the ICER, however as patients also do not incur the cost of SCT, this rise is only modest with the base case being under £20,000 per QALY.

Table 9: Base case pairwise results including the PAS

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.48					
Brentuximab vedotin	[redacted]	[redacted]	12.39	[redacted]	[redacted]	7.91	£5,026	£14,101

For completeness, results are also provided here without the impact of the PAS, where the ICER rises to [redacted] (Table 10).

Table 10: Base case pairwise results using the list price of brentuximab (no PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.48					
Brentuximab vedotin	[redacted]	[redacted]	12.39	[redacted]	[redacted]	7.91	£5,971	£16,753

Table 11 details the cost breakdown. Of the incremental cost, the majority is either due to the use of brentuximab vedotin, or the costs of SCT.

Table 11: Cost breakdown

	Undiscounted			Discounted		
	Brentuximab vedotin	Standard care	Incremental	Brentuximab vedotin	Standard care	Incremental
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Of the additional QALYS, the major gains are in the allo-SCT and ASCT states. This is in keeping with the higher SCT rate observed with brentuximab vedotin, in allowing more patients to undergo potentially curative therapy (Table 12).

Table 12: QALY breakdown

	Undiscounted			Discounted		
	Brentuximab vedotin	Standard care	Incremental	Brentuximab vedotin	Standard care	Incremental
EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASCT PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

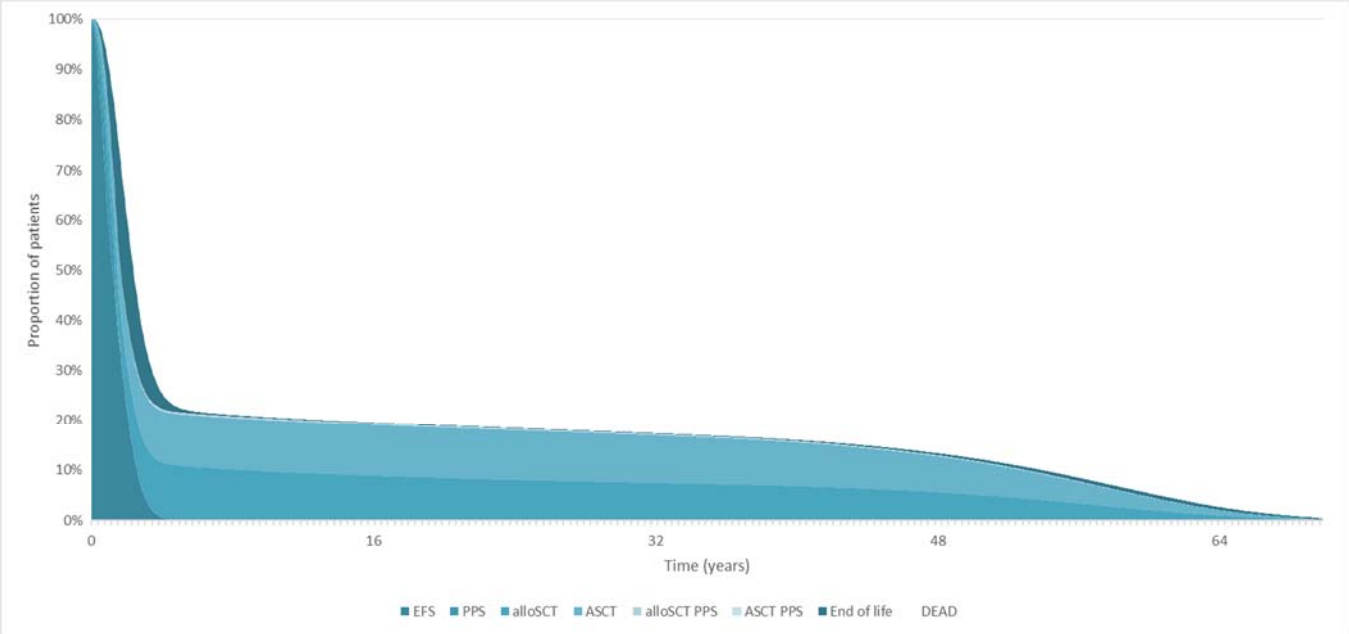
This additional time in allo-SCT and ASCT is illustrated in the undiscounted life years from the model. Whilst brentuximab vedotin has slightly fewer years spent pre-SCT, that is as patients progress to SCT at a much greater rate, then exhibiting longer survival, with an overall survival gain of approximately 8 years (12.39 vs. 4.48; Table 13).

Table 13: LY breakdown

	Undiscounted		
	Brentuximab vedotin	Standard care	Incremental
EFS	1.34	1.37	-0.02
PPS	0.09	0.11	-0.02
Allo-SCT	4.35	1.03	3.31
ASCT	5.18	1.23	3.95
Allo-SCT PPS	0.49	0.12	0.37
ASCT PPS	0.28	0.07	0.22
End of life	0.65	0.55	0.11
Total	**12.39**	**4.48**	**7.91**

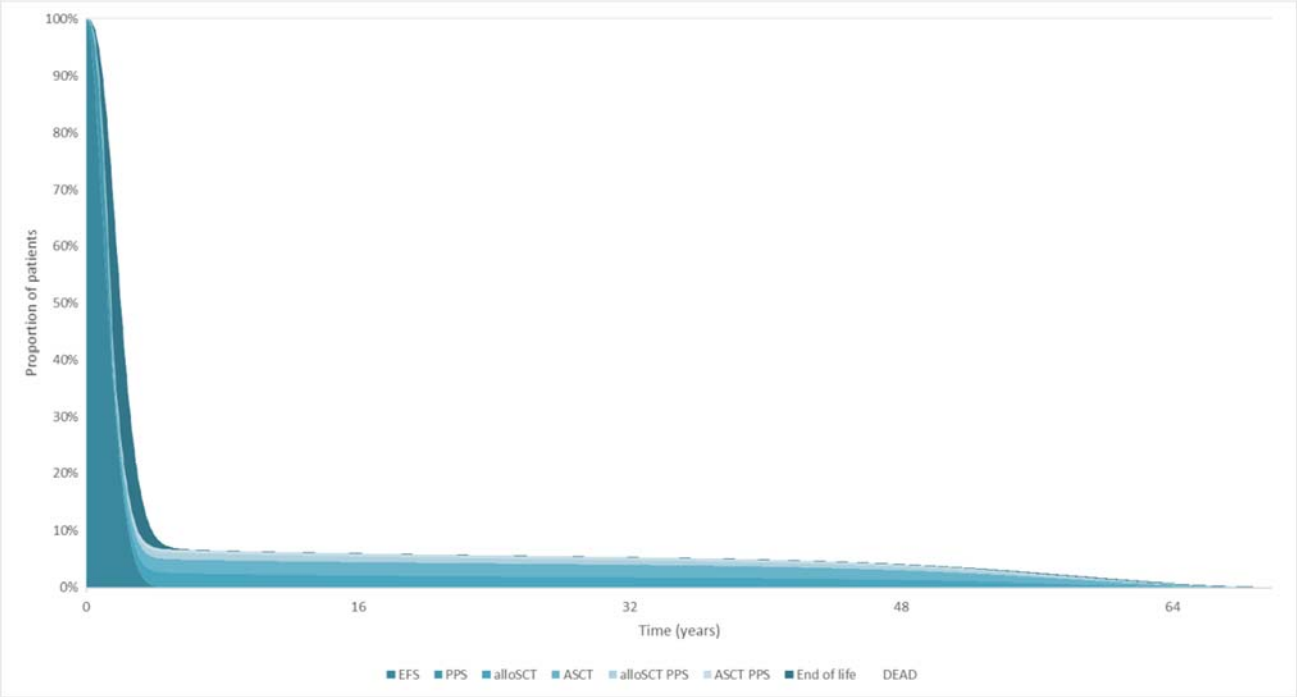
The results for brentuximab vedotin are shown graphically in Figure 7. As can be seen, the proportion of patients alive falls over the first few years before stabilising as only patients who have undergone SCT exhibit long term survival.

Figure 7: Markov trace – Brentuximab vedotin



A similar pattern is seen with standard care (Figure 8). The long-term survival however is at a lower level as fewer patients receive SCT.

Figure 8: Markov trace – Standard care



B.3.4 Scenario analyses

Scenario analyses around the main model parameters are presented below.

B.3.4.1 Use of alternative SCT rate for brentuximab vedotin from the Public Health England report

As discussed in Section B.3.2.2 Addition of a new health state - progression post-SCT, some patients proceeded to SCT having received additional salvage chemotherapy after their initial treatment with brentuximab vedotin. The inclusion of this additional salvage chemotherapy (which is costed in the model) increased the SCT rate in the brentuximab vedotin arm to 41% (compared with 25% in the base case which includes only patients bridged directly from brentuximab vedotin to SCT). Table 14 below details the pairwise results of this scenario, where the ICER falls to £11,638/QALY from £14,101/QALY in the base case.

The fall in the ICER is caused by the incremental QALY gain with brentuximab vedotin increasing by 1.68 QALYs (from 2.82 in the base case to 4.50), an increase which more than offsets the associated increase in incremental costs of £12,557 ([redacted] vs. [redacted]). In other words, the cost of the additional salvage chemotherapy is more than offset by the additional health gain that arises from bridging an extra 16% of patients to a potentially curative SCT (note the incremental LY gain increases by 4.76, from 7.91 in the base case to 12.67 in this scenario).

Table 14: Pairwise results – inclusion of higher SCT rate by the use of further salvage chemotherapy

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.48					
Brentuximab vedotin	[redacted]	[redacted]	17.15	[redacted]	[redacted]	12.67	£4,128	£11,638

B.3.4.2 Use of alternative utility data

As noted in Section B.3.4.1 above, the utility data included in the original submission relies heavily on the publication by Swinburn et al. (2015).[34] As mentioned previously, this is a vignette study and therefore is not based on the EQ-5D-3L responses as preferred according to the NICE methods guide.[26]

In this scenario analysis, we replace the values derived the vignette study with those derived from EQ-5D data collected in a study (the Checkmate 205 study)[38] in which nivolumab was administered to patients with relapsed or refractory classical Hodgkin lymphoma after ASCT

and in whom the majority (74%) had received prior treatment with brentuximab vedotin, in addition all patients had had prior ASCT.

Table 15: Utility values in the base case and scenario analysis

Health state		Base Case Utility Value (Source)	Scenario analysis (Source)
Event Free Survival		0.82 (Swinburn et al. 2015)[34]	0.84 (Checkmate 205)[38]
Stem Cell Transplant	Up to 14 days	0.42 (Van agthoven 2001)[35]	0.42 (Van agthoven 2001)[35]
	14 days to 3 months	0.60 (Van agthoven 2001)[35]	0.60 (Van agthoven 2001)[35]
	After 3 months	0.77 (Van agthoven 2001)[35]	0.77 (Van agthoven 2001)[35]
Post Progression Survival		0.38 (Swinburn et al. 2015)[34]	0.715 (Checkmate 205)[38]
Post SCT relapse		0.38 (Swinburn et al. 2015)[34]	0.715 (Checkmate 205)[38]
End of Life		0.38 (Swinburn et al. 2015)[34]	0.50 (Park et al. 2006)[44]

The utility value from the Checkmate 205 study[38] for the post-progression health state (0.715) is considerably higher than that from the vignette study (0.38). In addition, and despite the higher value, it could be argued that the utility values derived from the Checkmate 205 study may actually underestimate the true values likely in this setting because this study was undertaken in a group of patients where the majority had received prior brentuximab vedotin (i.e. most patients in Checkmate 205 are at a later line of therapy). Table 16 details the pairwise results of this scenario, showing that the ICER remains essentially the same as in the base case (£13,709/QALY vs. £14,101/QALY). This is because the change in utilities for the post-progression health state affects both arms (the incremental QALY gain in this scenario is [redacted] vs. [redacted] in the base case) whilst the impact is also mitigated by discounting (as first a patient must have had an SCT, and then progressed).

Table 16: Pairwise results – scenario analysis using post-progression utilities from the Checkmate 205 study.[38]

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.48					
Brentuximab vedotin	[redacted]	[redacted]	12.39	[redacted]	[redacted]	7.91	£5,026	£13,709

B.3.4.3 Use of alternative discounting rates for technologies with a long time horizon

The NICE methods guide (Section 6.2.19) states:

> *"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."*[26]

We believe brentuximab vedotin could be deemed eligible for the lower discount rates that can be considered for such technologies. Based on our modelling, after 30 years approximately 20% of patients treated with brentuximab vedotin are projected to still be alive. This is because brentuximab vedotin has been shown in multiple datasets to allow large numbers of patients to achieve disease remission and thus be able to be bridged to a potentially curative SCT. Table 17 details the pairwise results of applying a lower discount rate of 1.5%, and this shows a further decrease in the ICER to below £10,000 per QALY.

Table 17: Pairwise results – lower discount rate of 1.5% applied for costs and QALYs

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.48					
Brentuximab vedotin	[redacted]	[redacted]	12.39	[redacted]	[redacted]	7.91	£5,136	£9,327

B.3.4.4 Use of the original model from the FAD

We are confident that the changes we have made to the health economic model (in particular, the addition of a post-SCT progression state and the use of more appropriate data sources for the outcomes from ASCT and allo-SCT) lead to ICERs that are more robust, reliable and reflective of the true cost effectiveness of brentuximab vedotin than those derived from the original model used to develop the FAD in TA446.

Nevertheless, in the interests of transparency and in the spirit of changing as little as possible from the original submission, we also include two scenarios here in which the corrected version of the original model is merely updated with the new SCT rates for brentuximab vedotin derived from the Public Health England report.[18] Hence, in this scenario, the SCT rates are set to 3/57 (5.3%) for the comparator of single-agent

chemotherapy (as discussed in Section B.3.2.3) and either 25% (base case, bridging directly from brentuximab vedotin) or 41% (includes the option to receive additional salvage chemotherapy) for brentuximab vedotin.

The results for these two scenarios are shown in below. The results show that with a SCT rate of 25% in the error corrected model, the ICER is £32,749 per QALY (Table 18). Using an SCT rate of 41% this falls to £27,803 (Table 19).

Table 18: Pairwise results – corrected model used for the FAD with SCT rates of 5.3% for standard care and 25% for brentuximab vedotin

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	2.88					
Brentuximab vedotin	[redacted]	[redacted]	5.68	[redacted]	[redacted]	2.80	£14,451	£32,749

Table 19: Pairwise results – corrected model used for the FAD with SCT rates of 5.3% for standard care and 41% for brentuximab vedotin

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	2.88					
Brentuximab vedotin	[redacted]	[redacted]	7.29	[redacted]	[redacted]	4.42	£12,147	£27,803

Despite the use of data which has been highlighted to be inappropriate for the indication under consideration, the ICERs remain around the threshold.

B.3.5 Validation

To establish the validity of the model, an independent experienced modeler carried out a quality check of the model at each major stage of completion. Clinical consultation was undertaken in order to validate the OS and PFS outcomes with the expert on the previous NICE committee, Prof Karl Peggs.[23] Prof. Peggs reviewed the outcomes that were modelled for both ASCT and allo-SCT, along with the associated costs within the model to ensure their clinical validity.

B.3.6 Interpretation and conclusions of economic evidence

The base case results (ICER of £14,101/QALY) demonstrate that brentuximab vedotin is clearly cost-effective at the standard cost-effectiveness threshold of £20,000-£30,000 per QALY. Whilst not based on randomised controlled trial data, the expanded evidence base used to support the modelling is now more robust than previously. In particular, the real world SCT rate with brentuximab vedotin derived from the extensive data collection that was

undertaken during the CDF period are very consistent with, and thereby validate, the original data that was based on a much smaller group of patients.

The results of scenario analyses show that for many uncertainties in the model, the ICER either does not change (utilities) or it decreases. Most notably, the inclusion of patients who received additional salvage chemotherapy after brentuximab vedotin but before SCT reduces the ICER to below £12,000/QALY. The use of a lower discount rate which we believe can be justified, also reduces the ICER to below £10,000 per QALY. For completeness we also provide scenarios showing the ICER using the corrected model on which the FAD for TA446 was developed, but updated with the new SCT rates for brentuximab vedotin from the CDF data collection. At the SCT rate of 25% for brentuximab vedotin it is slightly above the standard cost effectiveness threshold, while at the 41% rate it is below the threshold.

Whilst some uncertainties inevitably remain around the clinical data and economic model, we believe these are unlikely to result in an ICER that is above the standard cost-effectiveness threshold.

B.3.7 End of life criteria

It is unclear whether or not brentuximab vedotin meets the NICE 'End of Life' criteria, which are given in Section 6.2.10 of the NICE methods guide as:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- 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.[26]

In the revised model base case, the median survival for standard care (single-agent chemotherapy) patients is 2.04 years, with a mean of 4.48 years. Brentuximab vedotin is expected to provide substantial gains to life (an incremental 7.91 life years; 12.39 vs. 4.48), primarily through the increase in patients achieving SCT – an approximately threefold extension to life expectancy.

Table 20: End of life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Three publications of historical data,[30, 32, 33] modelled outcomes.	B.2.3.2 B.3.3.2
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	Observational data collection, CSF data collection, modelled outcomes	B.2.2 B.3.3.2

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Brentuximab Vedotin Re-Appraisal

Public Health England Report Commissioned by NHS England

Reporting on brentuximab vedotin used as a potential bridge to stem cell transplantation in adults with relapsed or refractory CD30-positive Hodgkin lymphoma

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Contents

Executive Summary

This report was commissioned by NHS England to assist NICE in their re-appraisal of the use of brentuximab vedotin within its marketing authorisation. This covers the treatment of patients with relapsed or refractory CD30-positive Hodgkin lymphoma following at least two prior therapies when stem cell transplantation or multi-agent chemotherapy is not a treatment option. This report focusses on the use of brentuximab vedotin within this population defined by the marketing authorisation as a potential bridge to receiving a subsequent stem cell transplant (SCT).

Introduction

In April 2017, the NICE Appraisal Committee reviewed the clinical and cost effectiveness of brentuximab vedotin in CD30-positive confirmed relapsed or refractory Hodgkin lymphoma following at least two prior therapies when stem cell transplantation or multi-agent chemotherapy is not a treatment option, and requested further evidence be obtained before a decision could be made around the use of this drug in such SCT-naïve patients (TA446). The NICE appraisal highlighted clinical uncertainty around the estimate of the proportion of patients who were able to proceed to have a SCT following treatment with brentuximab vedotin in this indication. They recommended that the drug remain temporarily in the Cancer Drugs Fund (CDF), so as to allow patients to continue to get the treatment, if approved, while the information on the clinical uncertainty was collected and assimilated.

To obtain an estimate of effectiveness in the ‘real world’, i.e. outside of a randomised controlled trial, NHS England commissioned Public Health England to examine how many SCT-naïve patients, who received brentuximab vedotin via CDF funding between April 2013 and March 2016, subsequently went on to receive a SCT. The CDF provided access to patients with relapsed or refractory CD30-positive Hodgkin lymphoma for two populations: either after SCT or following at least two prior therapies where SCT or multi-agent chemotherapy was not a treatment option. This second population was therefore the same population as in the marketing authorisation and thus the same population appraised by NICE and recommended to remain in the CDF until re-appraisal.

Methods

The NHS England CDF database was designed to capture the information from the application forms submitted by clinicians requesting funding for patients meeting the clinical criteria for drugs within the CDF. For this NICE re-appraisal the details of all Hodgkin lymphoma patients who were approved for use of brentuximab vedotin were extracted, including details about the consultant who made the application. To be able to determine the SCT-naïve patients from those who had a SCT prior to receiving brentuximab vedotin, a bespoke questionnaire was designed and sent to 223 consultants across 106 trusts in England to ask for data about the treatment of 496 patients for whom brentuximab vedotin had been funded by the CDF for the treatment of Hodgkin lymphoma.

Analysis of the data returned on the questionnaire detailed whether or not the patients were SCT-naïve; whether they had been given brentuximab vedotin with the intention of bridging the patient to having a SCT; and whether the patients who were given the drug with the intention of a SCT actually had a SCT after brentuximab vedotin (with or without subsequent salvage chemotherapy). The main cohort of interest is those patients who were SCT-naïve and were given brentuximab vedotin with the intention of bridging the patient to be able to have a SCT. The clinical uncertainty is the rate of patients in this cohort of interest actually getting a SCT.

Three sensitivity analyses were undertaken to ensure that estimates of the rates having a SCT following brentuximab vedotin were available for all of the patients included in the population defined by the relevant indication in the marketing authorisation. Additionally, the effect of the 60 patients (12%) for whom there were no data (because their consultants did not return the questionnaire) was examined. The first analysis included these 60 patients with missing data, and it was assumed that none of them received a SCT following brentuximab vedotin. The second analysis included the 93 patients who received brentuximab vedotin but the treating consultant clearly indicated that there had not been any intention of having a SCT afterwards. The third sensitivity analysis was the combination of both of these scenarios.

Results

Of the 496 questionnaires sent to consultants who had applied for CDF funding between 01 April 2013 and 31 March 2016, 436 (88%) were returned. Of these, 219 patients were recorded as SCT-naïve and were treated with brentuximab vedotin with the intention of bridging the patient to be able to have a SCT. This is the main cohort of interest.

There were 78 patients (36%) who had a SCT immediately after brentuximab vedotin (without the use of subsequent salvage chemotherapy); this is the main result. When the 50 patients who had brentuximab vedotin then received salvage chemotherapy before a SCT were also included, this figure rose to 58%.

The sensitivity analyses provided three sets of estimates of the rate of SCT following brentuximab vedotin to determine conservative estimates.

(I) The first sensitivity analysis, i.e. the inclusion of the 60 patients with the 219 patients in the main cohort, gave an estimate of the rate of SCT following brentuximab vedotin (without any salvage chemotherapy being required) of 28%. This figure was 46% if the 50 patients having salvage chemotherapy before the SCT were also included.

(II) For the second sensitivity analysis, the inclusion of the 93 patients, who were SCT-naive but who received brentuximab vedotin with no intention to use as a bridge to a SCT, with the main cohort gave a SCT rate of 25% with no salvage chemotherapy (41% with salvage chemotherapy as well).

(III) The corresponding estimates of the SCT rates following brentuximab vedotin for the combination of both of these with the main cohort, giving a denominator of 372, were 21% and 34%, respectively.

Conclusion

This report provides estimates of the proportion of SCT-naïve relapsed or refractory CD30-positive Hodgkin lymphoma patients who had a SCT following treatment with brentuximab vedotin, either with or without salvage chemotherapy. These patients had not been suitable candidates for a stem cell transplant with conventional treatments.

The main result was that 36% of the SCT-naïve patients who had the intention of getting brentuximab vedotin to bridge them to a SCT went on to have a SCT following the use of brentuximab vedotin without any salvage chemotherapy; or 58% when patients who had the drug then salvage chemotherapy before the SCT were also included.

Sensitivity analyses showed that at least 21% (the lowest proportion) of the SCT-naïve patients who were given the drug within the relevant indication contained in the brentuximab vedotin marketing authorisation then had a SCT.

Introduction

Hodgkin lymphoma is a relatively uncommon cancer of the immune system and mainly affects people in their early 20's and adults over the age of 70. Data from the Office for National Statistics shows that there were around 1,800 new cases of Hodgkin lymphoma diagnosed in 2015 in England, with a directly standardised incidence rate of 4.0 per 100,000 population in males and 2.7 per 100,000 populations in females.[1] Hodgkin lymphoma accounts for 13% of all lymphomas diagnosed in 2015 and 0.6% of all cancers diagnosed, with 1 year survival being 91% in males and 93% in females and 5 year survival being 85% in males and 86% in females.[2]

Standard treatment for more advanced stages of Hodgkin lymphoma is usually chemotherapy ± radiotherapy and will cure around 65-80% of patients.[3] A modest proportion of Hodgkin lymphoma patients will develop refractory or relapsed disease after their initial treatment. If the Hodgkin lymphoma returns after previous chemotherapy, the usual treatment (known as salvage therapy) for fit patients is intensive chemotherapy followed by high dose chemotherapy and an autologous or allogeneic stem cell transplant (SCT).[3,4] Patients with relapsed or refractory Hodgkin lymphoma who are unfit for, or fail to respond sufficiently to, such treatment receive palliative chemotherapy.

Patients can relapse several months to years after the initial treatment, although the majority of patients experience a relapse within two years of the initial treatment.[5] The aim of salvage therapy is to achieve a negative positron emission tomography (PET) scan that shows no sign of active disease before an autologous or allogeneic SCT can be considered as SCTs reduce the risk of subsequent relapse.

Most Hodgkin lymphomas contain a surface protein marker called CD30.[6] This can be targeted by some drugs as part of treatment; one such drug is brentuximab vedotin, which is an antibody - drug conjugate.

Background to this report

Brentuximab vedotin has been available in England via the Cancer Drugs Fund (CDF) since early 2013. It was approved for funding for several indications in lymphoma. Two of these were in direct accordance with the marketing authorisation of brentuximab vedotin in adults (aged 18 and over) with confirmed CD30-positive relapsed or refractory Hodgkin lymphoma who either (i) had received an autologous stem cell transplant (SCT) before they were considered for brentuximab vedotin, or (ii) had received at least two prior therapies and where SCT or multi-agent chemotherapy was not a treatment option and thus were SCT-naïve.[4]

As with all drugs which entered the CDF prior to 31 March 2016, the clinical and cost effectiveness of brentuximab vedotin is being reviewed by NICE. This is to determine if the drugs provide sufficient value for money and can be recommended for routine funding. NICE completed the appraisal for brentuximab vedotin in this indication in June 2017 and recommended:

a) the use of brentuximab vedotin for routine commissioning in patients who had relapsed or refractory disease after autologous SCT;

b) the use of brentuximab vedotin via the CDF for patients with relapsed or refractory Hodgkin lymphoma after at least two prior therapies who were unable to proceed to combination chemotherapy or autologous SCT.[3]

Part of the reasoning behind the recommendation by NICE that brentuximab vedotin continues to be funded temporarily through the CDF in this second group of patients was to allow further evidence to be assimilated on a key clinical uncertainty. This uncertainty was the proportion of SCT-naïve patients with relapsed or refractory Hodgkin lymphoma, previously treated with at least two prior therapies and in whom SCT or multi-agent chemotherapy was not a treatment option, were then treated with brentuximab vedotin, subsequently having a SCT. Understanding what this rate is will be important in determining the potential clinical and cost effectiveness of brentuximab vedotin for this group of patients.

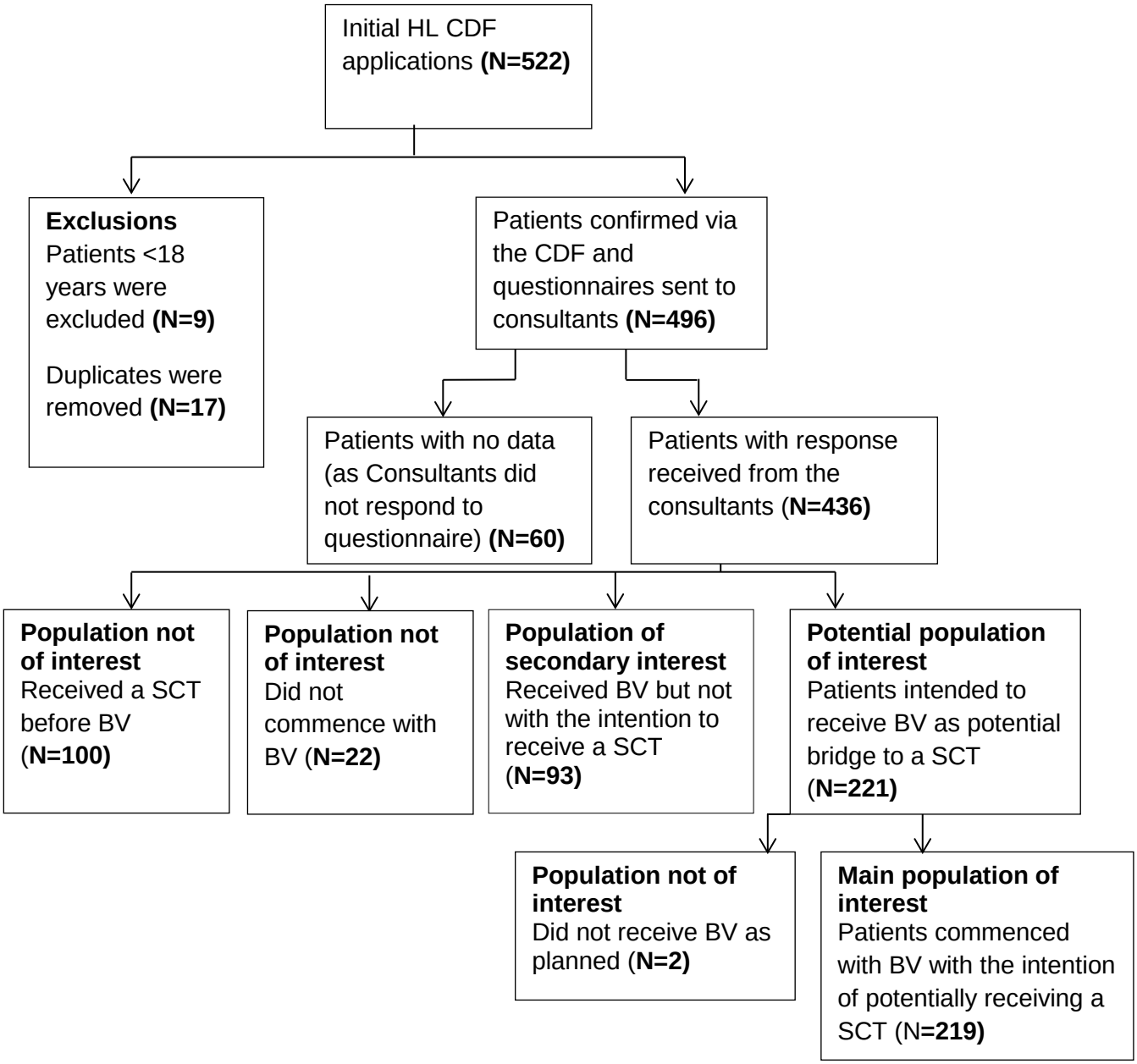
To address this uncertainty, Hodgkin lymphoma patients who had previously received brentuximab vedotin via the CDF were identified as the cohort to be used to determine the SCT rate achieved with the use of brentuximab vedotin for CD30-positive SCT-naïve Hodgkin lymphoma patients. NHS England commissioned the National Cancer Registration and Analysis Service (NCRAS) at Public Health England (PHE) to support the collection and reporting of this information in the form of a questionnaire for those Hodgkin lymphoma patients treated with brentuximab vedotin since 2013 via CDF funding.

This report will support the NICE re-appraisal of brentuximab vedotin in this indication. It will be used as part of the evidence considered when NICE develops its recommendations as to whether or not the drug should be routinely commissioned.

Methods

The cohorts of interest were identified from the 522 initial applications made to the Cancer Drugs Fund (CDF) for brentuximab vedotin for CD30-positive confirmed refractory or relapsed Hodgkin lymphoma on the CDF between April 2013 and March 2016 (**Figure 1**).

Figure 1: Derivation of the population of interest from the initial CDF applications made for brentuximab vedotin for Hodgkin Lymphoma between April 2013 and March 2016



Abbreviations: HL, Hodgkin lymphoma; CDF, Cancer Drugs Fund; SCT, stem cell transplant; BV, brentuximab vedotin.

Identification of the cohorts of interest

The cohort of interest comprised stem cell transplant (SCT)-naïve patients who were treated with brentuximab vedotin. Of these, some patients received brentuximab vedotin with the intention of receiving a subsequent SCT, should they demonstrate a good response to treatment. Another group of patients received brentuximab vedotin without any such intent. Of greatest importance is the rate of SCT in the group of patients given brentuximab vedotin for whom there was the intention of proceeding to a SCT if there was sufficient response to treatment.

As mentioned above, brentuximab vedotin was approved for two indications for Hodgkin lymphoma patients within the CDF. However, as the NHS England CDF database was designed to capture the information from the application forms submitted by clinicians requesting funding for patients meeting the clinical criteria for drugs within the CDF, there was no reason for the database to hold details of possible clinical subgroups. To obtain this detailed clinical information requested by NICE required a bespoke data collection and analysis. The information required was something that enabled differentiation of the pre-SCT and post-SCT population from the group who received brentuximab vedotin following at least two prior therapies where SCT or multi-agent chemotherapy was not a treatment option; and for this latter group to identify whether there was an intention to proceed to a SCT or not. To do this, NHSE and PHE (with input from NICE and two clinical experts, Dr Graham Collins, Consultant Haematologist, Oxford University Hospitals NHS Foundation Trust and Professor John Radford, Consultant Medical Oncologist and Lead for the Lymphoma Service, The Christie NHS Foundation Trust) developed a Hodgkin lymphoma questionnaire regarding the treatment of all of the relevant patients. A copy of the questionnaire can be found in **Appendix 1**.

This bespoke questionnaire was sent to 223 consultants across 106 trusts in England to ask for data about the treatment of the 496 patients for whom brentuximab vedotin had been funded by the CDF for the treatment of Hodgkin lymphoma.

Data extraction and use of the questionnaire

Data were extracted from the NHS England CDF database for patients aged 18 or over who had a diagnosis of Hodgkin lymphoma and had an approved application on the CDF for the treatment of brentuximab vedotin between 1 April 2013 and 31 March 2016. Questionnaires for these patients were sent to the consultants named on the original CDF application form with the intention of being able to isolate the populations into those of interest and those not of interest. **Figure 1** presents a flowchart detailing the original numbers of applications on the CDF, and the various exclusions applied. In total, questionnaires were posted out to 223 consultants relating to 496 patients.

During a six-week data collection period, up to five reminders were sent to those consultants who had not returned the questionnaires. A range of media was used - post, phone and email - to ensure the highest number of forms were completed. If a consultant had left the organisation after the patient had been treated, the Trust was asked to pass the questionnaire on to the consultant who was subsequently responsible for that patient's care. At the end of the data collection period, questionnaires for 436 (88%) patients had been returned. The responses from the completed questionnaires were entered into an Excel spreadsheet and subsequently analysed in Stata version 13. A sample of 152 (35%) were manually checked for data entry accuracy; and two mistakes were found. These were corrected before the analyses were undertaken.

Isolating the population of interest and the numbers having a SCT subsequent to brentuximab vedotin

The data were separated out into the two main indication groups, i.e. (i) brentuximab vedotin given after a SCT (population not of interest) and (ii) brentuximab vedotin given in patients following two prior therapies when SCT or multi-agent chemotherapy was not a treatment option. Only the patients in the latter group were considered further.

Those patients who did not have brentuximab vedotin at all were also excluded completely.

Patients who had brentuximab vedotin but not with the intention of proceeding to a SCT were excluded from the main analyses. They were, however, included in the supplementary sensitivity analyses and as such, were a population of secondary interest.

Thus, the final population of interest used to address the area of clinical uncertainty from the NICE appraisal for the main analyses was those who had brentuximab vedotin with the intention of bridging the patient to having a SCT.

There were two possible groups of patients who were viewed as being a ‘success’ in terms of having a SCT following brentuximab vedotin. These groups were:

a) those patients who had brentuximab vedotin and then a SCT (with no other treatment before the SCT);

b) those patients who had brentuximab vedotin and then had salvage chemotherapy before the SCT (**Figures 2 and 3**).

Sensitivity analyses

Additionally, three separate sensitivity analyses were undertaken to assess how the proportion getting a SCT changed in certain scenarios:

(I) the influence of the missing questionnaires;

(II) the decision to exclude from the final cohort those patients who were given brentuximab vedotin but not with the intention of bridging the patient to a SCT. This was to align the additional analysis with the relevant brentuximab vedotin indication in Hodgkin lymphoma for those patients following at least two prior therapies where SCT or multi-agent chemotherapy was not a treatment option;

(III) the combination of both of these scenarios.

The following assumptions were made for these different scenarios:

(I) that all of the patients for whom there were no data were eligible, i.e. assumed they had received brentuximab vedotin with the intention of bridging the patient to a SCT (and so included in the denominator), but that none of them received a SCT (and so not included in the numerator);

(II) The inclusion of the patients who had brentuximab vedotin with no intention of getting a subsequent SCT only increased the denominator in these sensitivity analyses and aligned with the wording in the relevant brentuximab vedotin marketing authorisation in Hodgkin lymphoma.

Results

Of the initial 522 applications for Cancer Drugs Fund (CDF) funding for brentuximab vedotin for CD30-positive Hodgkin lymphoma disease, 496 were included in the study after duplicates and children had been removed. Questionnaires were sent to 223 consultants across 106 trusts in England relating to these 496 patients. The number of questionnaires returned was 436, resulting in there being data for 88% of the patients.

The 100 patients who received a stem cell transplant (SCT) before brentuximab vedotin were excluded, as were the 22 patients who did not commence with brentuximab vedotin at all. The 93 patients who received brentuximab vedotin without the intention of having a subsequent SCT were separated from the main analyses (**Figure 1**).

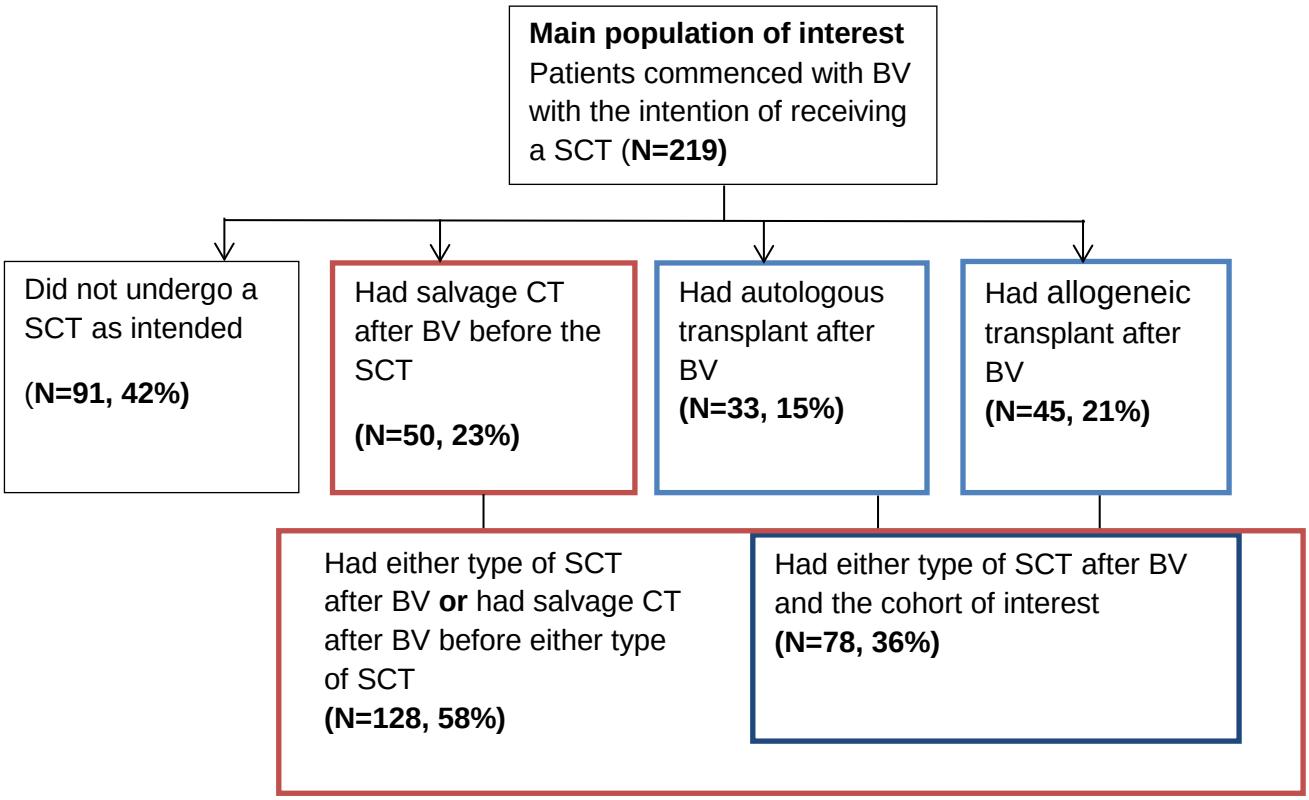
Main analyses

The cohort of interest for the main analyses contained 219 patients. All of these were SCT-naïve when they received brentuximab vedotin, though they had all had at least two prior therapies. These patients started brentuximab vedotin treatment because a SCT or multi-agent chemotherapy was not a treatment option at the time. These patients were given the drug with the intention that they would be able to receive a SCT should a sufficient response occur. Two patients were excluded because they did not receive brentuximab vedotin after all, even though it had been intended that brentuximab vedotin would help bridge these patients to getting a SCT.

Of the 219 patients in the main population of interest, 78 (36%) patients subsequently were treated with a SCT without the use of salvage chemotherapy after the brentuximab vedotin before the transplant. A further 50 (23%) patients underwent a SCT but these patients required further salvage chemotherapy following treatment with brentuximab vedotin (**Figures 2 and 3**).

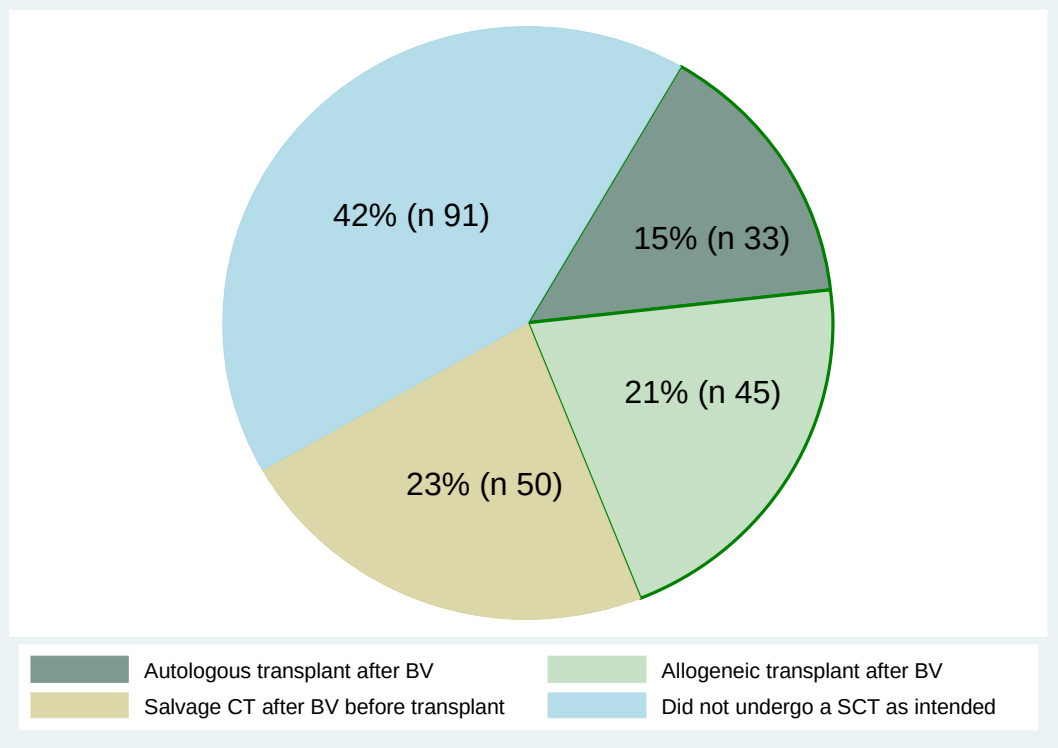
There were 91 (42% of the 219 patients who received brentuximab vedotin with the intention to bridge the patient to SCT) patients who did not actually undergo a SCT; of these, their consultants had provided comments in 43 questionnaires. Some of the reasons why patients did not go on to receive a SCT as planned were because patients had died, had developed progressive disease, were not fit enough to receive a SCT, did not respond to the brentuximab vedotin treatment or the patient declined a SCT.

Figure 2: Flowchart showing process and responses for eligible patients.



Abbreviations: HL, Hodgkin lymphoma; CDF, Cancer Drugs Fund; SCT, stem cell transplant; BV, brentuximab vedotin.
Note: percentages do not add up to 100% due to rounding errors.

Figure 3: Summary of whether or not patients had brentuximab vedotin as planned



Sensitivity analyses

Table 1 shows the results for each of the three sensitivity analyses compared with the results for the patients in the main analyses (**denominator = 219**). The denominators for the three sensitivity analyses used are as follows:

(I) **Sensitivity scenario 1:** includes patients who commenced with brentuximab vedotin with the intention of receiving a SCT (219) and the 60 patients for whom there were no data (**denominator = 279**);

(II) **Sensitivity scenario 2:** includes patients who commenced with brentuximab vedotin with the intention of receiving a SCT (219), plus the 93 patients who received brentuximab vedotin but with no intention that they would receive a SCT. This group reflects the known SCT rate in the CDF population in the relevant Hodgkin lymphoma indication as defined in the marketing authorisation (**denominator = 312**);

(III) **Sensitivity scenario 3:** includes patients who commenced with brentuximab vedotin with the intention of receiving a SCT (219), plus the 93 patients who received brentuximab vedotin but with no intention that they would receive a SCT, plus the 60 patients for whom there were no data (**denominator = 372**).

Table 1: Number and percentage of patients having a SCT for the different sensitivity scenarios, including a breakdown into the type of SCT and whether or not the patients required salvage chemotherapy after the brentuximab vedotin before the SCT

Number and percentage of patients having a SCT for the different scenarios				
	Main cohort: BV with intention of getting a SCT	Main cohort plus patients with no data (I)	Main cohort plus those given BV with no intention of a SCT (II)	Main cohort plus combination of (I) and (II)
Denominator for each cohort	***219***	***279***	***312***	***372***
Underwent an allogeneic SCT	*45 (21%)*	*45 (16%)*	*45 (14%)*	*45 (12%)*
Underwent an autologous SCT	*33 (15%)*	*33 (12%)*	*33 (11%)*	*33 (9%)*
Had salvage CT after BV before SCT	*50 (23%)*	*50 (18%)*	*50 (15%)*	*50 (13%)*
Underwent SCT after BV[a]	**78 (36%)**	**78 (28%)**	**78 (25%)**	**78 (21%)**
Underwent SCT after BV +/- salvage[b]	**128 (58%)**	**128 (46%)**	**128 (41%)**	**128 (34%)**

a Patients who had BV and then a SCT straight afterwards
b Patients who had BV then a SCT or BV then salvage chemotherapy and then a SCT

For the patients within the relevant part of the brentuximab vedotin marketing authorisation in Hodgkin lymphoma and assuming all of the patients with missing data were eligible but did not have a SCT (scenario III), the lowest possible proportion of patients in the CDF proceeding directly to SCT after brentuximab vedotin could be 21%.

Similarly for these patients in scenario (III), the lowest possible proportion of patients in the CDF treated with brentuximab vedotin and then with salvage chemotherapy and SCT could be 34%.

Conclusion

This report shows that some patients with relapsed or refractory CD30-positive Hodgkin lymphoma following at least two prior therapies when stem cell transplant (SCT) or multi-agent chemotherapy was not a treatment option were, with the help of brentuximab vedotin, able to go on to receive a SCT.

The main finding was that 36% (78 out of 219) of the SCT-naïve patients who had the intention of getting brentuximab vedotin to bridge them to a SCT had a SCT following the use of brentuximab vedotin without any salvage chemotherapy. This proportion rose to 58% (128 out of 219) when patients who had brentuximab vedotin then salvage chemotherapy before the SCT were also included with those who did not require salvage chemotherapy.

The sensitivity analyses showed that the proportion of patients having a SCT directly following brentuximab vedotin within the marketing authorisation of brentuximab vedotin in Hodgkin lymphoma (following at least two prior therapies when SCT or multi-agent chemotherapy was not a treatment option) was a minimum of 21% when the patients with no data were included but all were assumed not to proceed to SCT. Of the known responses in the relevant indication in the brentuximab vedotin Hodgkin lymphoma marketing authorisation, 25% of patients proceeded directly after brentuximab vedotin to SCT.

References

1. Office for National Statistics. Cancer Registration Statistics, England: 2015. 2017.

2. Office for National Statistics. Cancer Survival in England: 2010 and 2014 and followed up to 2015. 2017.

3. National Institute for Health and Care Excellence. Brentuximab Vedotin for treating CD30-positive Hodgkin lymphoma [ID722]: 2016. 2016.

4. Rancea M, Monsef I, Von Tresckow B, Engert A, Skoetz N (2013) High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma (review). *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.:CD009411. DOI:10.1002/14651858.CD009411.pub.2

5. Lymphoma.org. About lymphoma [Internet]. Lymphoma association: 2015 [cited 2017 Sep]. Available from: https://www.lymphomas.org.uk/about-lymphoma/treatment-lymphoma/follow-appointments

6. National Institute for Health and Care Excellence. Brentuximab Vedotin for treating CD30-positive Hodgkin lymphoma-STA: 2016. 2016.

Appendix 1 - Questionnaire

1. Did this patient have an autologous stem cell transplant prior to brentuximab vedotin therapy?	YES / NO If yes, then no further information is required
2. Did this patient have an allogeneic stem cell transplant prior to brentuximab vedotin therapy?	YES / NO If yes, then no further information is required
3. Was brentuximab vedotin given with the intention to bridge the patient to stem cell transplantation?	YES / NO
4. Did this patient commence Brentuximab vedotin as planned? If not, please state reason(s).	YES / NO If no, please state reason and no further information is required.
5. Did this patient have an autologous stem cell transplant directly following the Brentuximab vedotin therapy?	YES / NO If yes, no further information is required
6. Did this patient have an allogeneic stem cell transplant directly following the Brentuximab vedotin therapy?	YES / NO If yes, no further information is required
7. Did this patient require further salvage chemotherapy following treatment with brentuximab vedotin and then have an autologous transplant?	YES / NO If yes, no further information is required
8. Did this patient require further salvage chemotherapy following treatment with brentuximab vedotin and then have an allogeneic transplant?	YES / NO

Addendum

Subsequent to provision of the initial draft of this report to NHSE, NICE and the pharmaceutical company, PHE were requested to supply some additional information relating to the detailed breakdowns for two groups of patients defined in these two questions:

1. *Of the 50 patients who received BV followed by salvage chemotherapy and then a transplant, what proportion received an autologous stem cell transplant vs.an allogeneic stem cell transplant?*

Number of patients who underwent a SCT following salvage chemotherapy after brentuximab vedotin

	Number of patients
Had salvage chemotherapy following treatment with brentuximab vedotin and then underwent an autologous transplant	19
Had salvage chemotherapy following treatment with brentuximab vedotin and then underwent an allogeneic transplant	32
Total	**50**

Note: the numbers in the different SCT types do not add up to the number of distinct patients, 50, because there was 1 patient where the questionnaire stated that the patient had had both an autologous SCT and an allogeneic SCT. Despite attempts to clarify this, it proved not possible for the actual stem cell transplant type to be identified for this patient.

2. *For the 100 patients who received a stem cell transplant prior to BV, what proportion received an allogeneic SCT vs. an autologous SCT?*

Number of patients who underwent a SCT prior to brentuximab vedotin

	Number of patients
Underwent autologous stem cell transplant prior to brentuximab vedotin	87
Underwent an allogeneic stem cell transplant prior to brentuximab vedotin	17
Total	**100**

Note: the numbers in the different SCT types do not add up to the number of distinct patients, 100, because there were 4 patients where the questionnaire stated that the patients had undergone both an autologous SCT and an allogeneic SCT prior to brentuximab vedotin. Despite attempts to clarify this, it proved not possible for the actual stem cell transplant type to be identified for these 4 patients.

Added November 2017

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Single technology appraisal

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma (CDF review of TA446) [ID1366]

Dear Takeda,

The Evidence Review Group, BMJ evidence, and the technical team at NICE have looked at the submission received on 22 January 2018 from Takeda. 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 **5 February 2018.** 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 commercial in confidence in turquoise, and all information submitted as academic in confidence 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 Victoria Kelly, Technical Lead (victoria.kelly@nice.org.uk). Any procedural questions should be addressed to Stephanie Callaghan, Project Manager (stephanie.callaghan@nice.org.uk).

Yours sincerely

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Section A: Clarification on effectiveness data

A1. Please provide baseline characteristics for patients in the four cohorts listed in Table 5, page 24 of the company submission (the main cohort, main cohort plus patients with no data, main cohort plus those given BV with no intention of a SCT and main cohort plus combination of the previous two). Please include but don't limit to:

- Age at diagnosis (median)
- Age at start of BV therapy (median)
- Gender
- Number of prior therapies (median and range)
- PET response-adjusted SCT (y/n)
- Conditioning
- Stage or performance status

A2. Please provide additional information about the "One hundred patients who had received an SCT before brentuximab vedotin were excluded from the analysis (i.e. because this is not the relevant population)". Please confirm how many of these patients are from populations 1, 2 or 3 (as referred to in TA446, section 4.3)?

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please unlock all cells in the company models.

B2. **Priority question:** Please provide additional sensitivity analyses using the estimates for the "main cohort plus combination of (i) and (ii)" from Table 5, page 24 of the company submission. That is:

a. patients that underwent SCT after BV (21%) and
b. patients that underwent SCT after BV +/- salvage chemotherapy (34%).

Please provide the results of these analyses in both the original model (with appraisal committee preferred options) and the company's revised model.

B3. **Priority question:** Please provide one-way sensitivity analyses on all new parameter estimates included in the submission. Please conduct these analyses in both the new and original economic models and display the results in tornado diagrams.

B4. **Priority question:** In the economic model, the ERG is unable to run the macro 'tunnel_insert'. Please clarify if this macro is needed to apply changes to cells shaded yellow. Please correct this in the model.

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B5. **Priority question:** Please undertake a formal assessment of the existence (or not) of proportional hazards for PFS and OS following allo-SCT, and PFS and OS following SCT, such as using log-log plots and Schoenfeld residuals assessing the clinical plausibility of the assumption.

B6. **Priority question:** Please update columns C, G and I in the company's economic model for the 'Survival and Progression' tab to reflect the updated submission as the ERG is unable to validate the survival data in the submission with the current labels and distributions in the economic model. Also:

a. Please ensure all survival models assessed for goodness of fit are available in the dropdown lists.
b. Please ensure survival data from Sureda *et al.* is available as an option in the model.

B7. Please provide further justification for the change in the health economic model to account for changes in risk over time (company submission section B.3.2.1, page 32), given its negative impact on the functionality of the model. In addition, please can the company illustrate the impact of not making this amendment on the model results.

B8. Please confirm if an adjustment was made to the original model (corrected with the committee's preferred options) to account for the committee's concerns around utilities accrued post-SCT? As quoted by the company from the FAD:

> "The committee further concluded that the company's updated model was overly optimistic and that the ERG's adjustments were overly pessimistic, and agreed that its preferred cost-effectiveness analysis would lie between the two approaches"

If the original model has not be amended to address this concern, please make the required amendment in order to present an appropriate scenario with minimal changes from the original submission (as opposed to within the new model).

B9. Age-related utility decrements are not applied in the base case analysis, although they are included as model inputs in Appendix E. Please revise the base case analysis to include the adjustment. If the company decides not to use age-related utility decrements, please justify why this was considered unnecessary.

B10. Please explain why ASCT mobilisation, ablation and post-transplant costs are set to zero in the submission and economic model (company model; "Costs" tab, cells F354:359) as the uncertainty in Appendix E and references in the economic model infer costs will be incurred for those resources.

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B11. Please explain why the risk ratios presented in Table 7, page 40 of the company submission are described as hazard ratios?

B12. Please clarify if the hazard ratios in the economic model should equal 1 in the base case analysis for TTP relative to SC and PPS relative to SC (company model; "Survival and Progression" tab, cells I40 and I42).

B13. Please clarify which figures (and subfigures) were digitised from Reyal *et al.* 2016 to obtain allo-SCT PFS and OS data.

B14. In the economic model, the ERG is unable to run the macro "scenario analyses" and "Prob_Scenarios" and cannot find worksheets titled "Scenario Analysis" and "Scenarios breakdown". Please correct this in the model.

B15. Please explain the rationale for the difference in cost and duration between the palliative care health state in the original model and EOL health state in the revised submission.

B16. Please explain the rationale for including an EOL health state when a one-off cost could be applied to all patients who die.

B17. Please clarify how Round *et al.* 2015 was identified and chosen to inform the model.

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Yours sincerely

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Section A: Clarification on effectiveness data

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- Age at diagnosis (median)
- Age at start of BV therapy (median)
- Gender
- Number of prior therapies (median and range)
- PET response-adjusted SCT (y/n)
- Conditioning
- Stage or performance status

As stated in Takeda's resubmission of evidence for this appraisal (see Section B.3.2.5 of Document B submitted to NICE in mid-January 2018), the areas of clinical uncertainty to be resolved during the CDF period were specified in the Data Collection Agreement (DCA) between Takeda UK and NHS England, as follows:

> *"the proportion of patients treated with brentuximab vedotin or single agent chemotherapy that subsequently become eligible to receive a stem cell transplant (ASCT or allo-SCT)."*

Section 6.1 of the DCA specifies the outcome data to be collected retrospectively for brentuximab vedotin during the CDF period, which was:

- *"Proportion of patients who receive an ASCT after treatment with brentuximab vedotin"*
- *"Proportion of patients who receive an allo-SCT after treatment with brentuximab vedotin"*

Hence, the data collection exercise undertaken (as agreed with NHSE and NICE) was focused on the rate of successful bridging to SCT that can be achieved with brentuximab vedotin in a real world setting. The questionnaire that was used during the CDF data collection exercise is attached to Takeda's resubmission of evidence for this appraisal (see Appendix D of Document B, submitted to NICE in mid-January 2018).

Data was not collected on any of the baseline characteristics listed above, as this information was not considered necessary to address the committee's uncertainty in relation to the rate of bridging to SCT with brentuximab vedotin in real world UK clinical practice. All data available from the data collection exercise is included within the Public Heath England report which was included as Reference No. 18 in our resubmission of evidence (Document

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B) – we should also note that Takeda do not have access to the individual questionnaires, and only the summary data presented in this report.

A2. Please provide additional information about the "One hundred patients who had received an SCT before brentuximab vedotin were excluded from the analysis (i.e. because this is not the relevant population)". Please confirm how many of these patients are from populations 1, 2 or 3 (as referred to in TA446, section 4.3)?

As explained below, we can conclude with confidence that all 100 patients who had received an SCT before brentuximab vedotin (and were therefore excluded from the analysis) came from Population 1 within TA446.

The retrospective data collection agreed between Takeda and NHSE covered the period between April 2013 and March 2016, and was based on applications made to the old CDF for brentuximab vedotin. During this time, brentuximab vedotin was on the CDF for only two indications within r/ r Hodgkin lymphoma:

- Population 1 from TA446 (post-ASCT patients)
- Population 3 (following at least two prior therapies when SCT or multi-agent chemotherapy is not a treatment option; in other words SCT-naive patients).

Patients within Population 2 from TA446 (consolidation in patients at high risk of relapse or progression after ASCT) were never included in the CDF, and indeed this indication was only approved by EMA in July 2016. Hence, there could not be any patients from Population 2 of TA446 within the 100 patients with a prior SCT.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please unlock all cells in the company models.

As discussed on the clarification call with NICE and the ERG on 1st February 2018, there are no locked cells within the model. Given the number of calculations required to populate the model with tunnel states, many of the patient transitions are now undertaken in visual basic. In order to update the analyses, please re-run the relevant visual basic macro (by pressing the button labelled "Recalculate tunnel states" on the sheet TunnelCalcs – BV).

B2. **Priority question:** Please provide additional sensitivity analyses using the estimates for the "main cohort plus combination of (i) and (ii)" from Table 5, page 24 of the company submission. That is:

a. patients that underwent SCT after BV (21%) and

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The sensitivity analyses requested in Questions B.2a and B.2b represent very conservative (and we would argue unfair) analyses as these assume that none of the 60 patients for whom there were missing data (12% of the total cohort) received a SCT following treatment with brentuximab vedotin. Whilst such assumptions (negative outcomes for patients for whom there is no data) are common in trials with control arms; in this case, the reason data is missing is not due to the patients themselves but because their consultants failed to return the questionnaire.

We are not aware of any clinical rationale that would justify such an assumption, and its only effect is to increase the denominator and thereby reduce the SCT rate for brentuximab vedotin arbitrarily. While we accept that there is a rationale for the "main cohort plus (ii)" analysis (i.e. to align with the Marketing Authorisation for brentuximab vedotin), and which we use as our base case, we can see no similar rationale or justification for the "main cohort plus combination of (i) and (ii)" (i.e. marketing authorisation plus assuming missing data means no SCT) analyses requested here.

Despite these major caveats, we have nevertheless provided this sensitivity analysis (21% SCT rate after brentuximab vedotin) as requested. The results, using the company's revised model, are presented below and the ICER ("with PAS") still remains under £20,000/QALY. The "without PAS" ICER is [redacted] /QALY.

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	10.88	[redacted]	[redacted]	6.46	£5,740	£18,850

b. patients that underwent SCT after BV +/- salvage chemotherapy (34%).

The concerns raised in our response above to Question B.2a also apply equally well here. However, despite these caveats, we have as requested provided this sensitivity analysis (34% SCT rate after brentuximab vedotin +/- salvage chemotherapy) and the ICER ("with PAS") remains well below £20,000/QALY. The "without PAS" ICER is [redacted] /QALY.

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	15.23	[redacted]	[redacted]	10.80	£4,414	£14,457

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Please provide the results of these analyses in both the original model (with appraisal committee preferred options) and the company's revised model.

The results, using the company's revised model, are provided above in the answers to B.2a and B.2b.

In relation to the results of an analysis using the original model (with appraisal committee preferred options) there are multiple issues in presenting such analysis. Firstly, it is not clear from the FAD for TA446 exactly what the "committee preferred options" were. There were a number of analyses proposed by the ERG but not all of these were accepted as reasonable by the committee. In the FAD, the committee were equally critical of both the company and the ERG approaches, with a figure in between the two used as an assumption to overcome the limitations of each of the approaches (particularly around the lack of a post-SCT state). In order to undertake such an analysis, Takeda would require further guidance from NICE regarding what the "committee preferred options" are within the original model.

Secondly, we would caution strongly against using any cost effectiveness results derived from the original model for decision-making purposes regarding brentuximab vedotin in this indication, for two major reasons:

1. The original model contains a "structural flaw" as first identified by the ERG and accepted by the NICE committee (see Section 4.31 of the FAD for details). This flaw is described in the FAD for TA446 as limiting *"the model's ability to accurately capture the costs and benefits associated with stem cell transplant"* and this is described as being *"particularly problematic in a model in which a change in stem cell transplant eligibility was the key effect of brentuximab vedotin"*.

   It is clear that this structural flaw was regarded as a major limitation by the committee and it is mentioned on numerous occasions within the FAD for TA446. Hence, our rationale for addressing this concern in the new model submitted with our resubmission of evidence, and our caution about using any results derived from the original model for decision-making purposes regarding brentuximab vedotin.

2. The original model uses outdated SCT outcomes data (for both ASCT and allo-SCT) that do not reflect current UK or international transplant practice, and the corresponding outcomes now being achieved following SCTs. In the third NICE Appraisal Committee meeting held on 15 February 2017, it was highlighted by the clinical experts present that the SCT outcomes data used in the original model (i.e. Sureda *et al.* 2001 for ASCT and Sureda *et al.* 2012 for allo-SCT) significantly underestimated the survival outcomes that are now being achieved after both ASCT and allo-SCT. This data also did not allow for the derivation of the progression after

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SCT health state needed to address the issues raised in Point 1 above (i.e. the structural flaw).

The inappropriateness of the SCT outcomes data used in the original model has been confirmed in subsequent follow-up interactions we have had with a number of UK lymphoma transplant experts. For this reason, as discussed in detail in Section B.2.4 of our evidence resubmission (Document B), the new model uses SCT outcomes data that are more relevant and up to date than those in the original model.

We would further caution against using the original model with the ERG's proposed adjustments to post-SCT survival rates and SCT utilities as these were considered overly pessimistic by the committee. In this regard, we would note the comment in Section 4.31 of the FAD for TA446 that *"the committee further concluded……that the ERG's adjustments were overly pessimistic"*. There are essentially two aspects to this:

Firstly, against the backdrop of a model that already underestimated survival outcomes after SCT, we would argue (as did the clinical experts present at the third committee meeting) that it is unreasonable to then apply a further arbitrary 20% decrement on survival rates, as was proposed by the ERG to address the structural flaw in the model (see Section 4.31 of the FAD for TA446). In support of this, we would highlight the comment in the same section of the FAD that *"the committee noted comments from the clinical experts who disagreed with the ERG's adjustments to account for the model flaw, stating that fewer patients would progress than the ERG had assumed"*. As stated above, subsequent follow-up interactions with a number of UK lymphoma transplant experts have confirmed that the original model significantly underestimated the survival outcomes that are now being achieved after both ASCT and allo-SCT.

Secondly, there are also issues with the SCT utilities adjustment (reduced to 0.5) that was proposed by the ERG. This was acknowledged by the committee, as reported in Section 4.31 of the FAD where it states: *"the committee noted comments from the clinical experts who disagreed with the ERG's adjustments to account for the model flaw, stating that fewer patients would progress than the ERG had assumed when generating an average utility of 0.5. The committee agreed that the ERG utility adjustments were overly pessimistic".* Moreover, we would note that few advanced cancer submissions contain utilities as low as 0.5 for end stage disease, and thus to have patients alive for a substantial period of time with a utility this low does not have face validity.

B3. **Priority question:** Please provide one-way sensitivity analyses on all new parameter estimates included in the submission. Please conduct these analyses in both the new and original economic models and display the results in tornado diagrams.

Takeda will comply with this request. The one-way sensitivity analyses will be provided by 6th February 2018. Takeda apologise for the slight delay from the requested timelines.

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B4. **Priority question:** In the economic model, the ERG is unable to run the macro 'tunnel_insert'. Please clarify if this macro is needed to apply changes to cells shaded yellow. Please correct this in the model.

As discussed on the clarification call with NICE and the ERG on 1st February 2018, there is no error with this macro. The ERG agreed on the call that the relevant macro works. To run the macro press the button labelled "Recalculate tunnel states" on the sheet TunnelCalcs – BV.

B5. **Priority question:** Please undertake a formal assessment of the existence (or not) of proportional hazards for PFS and OS following allo-SCT, and PFS and OS following SCT, such as using log-log plots and Schoenfeld residuals assessing the clinical plausibility of the assumption.

The ERG confirmed on the clarification call on 1st February 2018 that this question was one included on their provisional list and is no longer considered to be relevant. As such, Takeda have not addressed it.

B6. **Priority question:** Please update columns C, G and I in the company's economic model for the 'Survival and Progression' tab to reflect the updated submission as the ERG is unable to validate the survival data in the submission with the current labels and distributions in the economic model. Also:

a. Please ensure all survival models assessed for goodness of fit are available in the dropdown lists.

All labels have been updated in the model that is re-submitted along with Takeda's response to these clarification questions in order to ensure that it is easy to follow. The functionality has also been added to test all curves used for survival modelling following SCT.

b. Please ensure survival data from Sureda *et al.* is available as an option in the model.

In the revised model structure the sources originally used for estimating SCT outcomes (i.e. Sureda *et al.* 2001 for ASCT and Sureda *et al.* 2012 for allo-SCT) have not been applied. The first reason for this is that it is not feasible to robustly incorporate these data sources into the new model structure. In order to implement the Sureda datasets into the updated model structure, Kaplan Meier (KM) data is required for both PFS and OS following SCT. KMs of PFS following allo-SCT are reported in Sureda *et al.* 2012, but the same level of data is not reported for ASCT in Sureda *et al.* 2001, with only a median time to relapse of 12 months reported. To implement progression using Sureda *et al.* 2001 data, an exponential curve would have to be applied to ASCT, which would assume constant hazards. However,

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it has been shown in the data from Thomson *et al.* (2012) that it is invalid to assume that hazards of progression following ASCT are constant.

A second reason for not implementing the original sources of SCT outcomes in the revised model structure is they are now known to significantly underestimate survival outcomes after transplant. As discussed in greater detail in Section B.2.4 of our evidence resubmission (Document B), during the third NICE appraisal committee meeting held on 15 February 2017 (and subsequently in discussions with a number of UK lymphoma transplant experts), it has been highlighted that the Sureda datasets do not represent current UK transplant practice and the patient outcomes that are now routinely achieved following either ASCT or allo-SCT. As summarised in Section B.2.4 of our evidence resubmission (Document B, submitted January 2018):

- The Sureda *et al.* (2001) post-ASCT outcomes data from Spain does not reflect the modern PET-response-adjusted transplantation strategy that is current UK clinical practice. In the Sureda *et al.* publication a response-adjusted strategy was not followed, meaning that only 41% of patients in that dataset were in CR prior to their ASCT while a number (15%) actually had resistant disease prior to ASCT. In line with UK guidelines, this latter group would not nowadays proceed to ASCT in the UK; this is because it is well documented that patients who are PET-negative prior to ASCT have much more favourable outcomes post-ASCT than patients who have residual PET-avid disease before ASCT. The UK specific data, presented by Thompson *et al.* (2012), provides outcomes data for ASCT that is much more representative of current transplant practice and outcomes in the UK and has therefore replaced the Sureda *et al.* data in the updated economic model submitted in January 2018. This approach has been supported by all UK based clinical experts we have consulted.

- The Sureda *et al.* (2012) post-alloSCT outcomes data does not reflect the indication being considered in this re-appraisal, which is for patients receiving their first transplant (ASCT or allo-SCT) after treatment with either brentuximab vedotin or the comparator of single-agent chemotherapy. The Sureda *et al.* 2012 data (from non-UK centres) included 86% of patients who had failed a previous ASCT prior to receiving allo-SCT. Thus, for the majority of patients in the Sureda *et al.* 2012 dataset, allo-SCT was not their first transplant; this is a major limitation of that data. The new outcomes data, which has now been used in preference to the Sureda *et al.* 2012 data, comes from 4 UK transplant centres and includes 86 patients who received allo-SCT as their first stem cell transplant, in line with the indication being considered for brentuximab vedotin. This data also reflects the UK PET-response-adjusted transplantation strategy and a pre-transplant conditioning regimen with alemtuzumab which is now routinely used across the UK. Finally, Professor Karl Peggs of UCL has confirmed to us that a prospective multi-centre UK trial has been completed (PAIReD: NCT00908180), confirming the outcomes documented in the updated

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dataset. A manuscript of these data is currently in preparation. Again, the update to the allo-SCT outcomes data used in the model has been unanimously supported by all UK based clinical experts we have consulted.

This is also discussed in our response to Question B2 above.

B7. Please provide further justification for the change in the health economic model to account for changes in risk over time (company submission section B.3.2.1, page 32), given its negative impact on the functionality of the model. In addition, please can the company illustrate the impact of not making this amendment on the model results.

It was necessary to change the model to account for changes in risk over time in order for the estimated HRQL and cost outcomes to be correct. For example, the hazard of dying after SCT is clearly not constant (the KM curves plateau). The risk of death post-SCT is therefore conditional on the duration of time that has elapsed since the patient has had an SCT. If this correction had not been implemented, the model estimation process would have been incorrect with a direction of bias that is difficult to predict and which could change depending on model settings.

As outlined in Table 8 within Section B.3.3.1 of Takeda's evidence resubmission (Document B), the effect of correcting the amendment was relatively small in terms of its impact on the ICER. The first two rows of Table 8 in the evidence resubmission illustrate the small size of the change. The error was noticed when efforts were being made to incorporate a new post-SCT progression health state within the cost-effectiveness model (a change that was undertaken to address a structural flaw in the model that was identified previously by both the ERG and the NICE committee).

The fix was implemented prior to adding the additional health state. Given the small impact on the ICER when using the original model structure it seems reasonable to infer that had the fix not been implemented, and the revised structure adopted, the resulting ICER would have been similar to the current base case; although we cannot be certain in which direction the error would have been. However, as this hypothetical model does not exist, we cannot provide the ICER that would empirically demonstrate this.

B8. Please confirm if an adjustment was made to the original model (corrected with the committee's preferred options) to account for the committee's concerns around utilities accrued post-SCT? As quoted by the company from the FAD:

> "The committee further concluded that the company's updated model was overly optimistic and that the ERG's adjustments were overly pessimistic, and agreed that its preferred cost-effectiveness analysis would lie between the two approaches"

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If the original model has not be amended to address this concern, please make the required amendment in order to present an appropriate scenario with minimal changes from the original submission (as opposed to within the new model).

As stated in Section 4.31of the FAD for TA446, the concern of the committee was that patients who progressed to SCT in the original model could not then move back to the event-free or post-progression survival states (this was described by the ERG and the committee as a structural flaw). In the response to the second ACD for TA446, Takeda attempted to address this concern by amending the original model structure to include a palliative care state. While this was regarded as better than the original model, the ERG did not consider that this structural change corrected the underlying flaw because including a palliative state was not equivalent to including a post-progression survival state. The ERG was still concerned that the model locked in an overly optimistic prognosis for people having SCT.

To address this structural flaw, the ERG proposed adjusting the average utility value for patients who remain in the SCT state to 0.5 (rather than 0.77 as in Takeda's model). The clinical experts at the third Appraisal Committee meeting disagreed with the utility adjustment to 0.5 because they believed fewer patients would progress than the ERG had assumed when calculating an average utility of 0.5. The committee agreed that the ERG utility adjustments were overly pessimistic. Hence, given that the committee has previously rejected such utility adjustments to the original model, we see no merit in repeating this adjustment.

Rather, the revised model structure we have now submitted (mid-January 2018) appropriately addresses the committee's underlying concern by including a post-SCT progression health state. The revised model uses data on progression post-SCT to accurately model the amount of time where patients would experience a low utility. As such, the revised model not only addresses the criticism of the original model but it is also more methodologically appropriate. The revised model now assumes that patients have a utility of 0.77 when progression-free following SCT, which falls to 0.38 on disease progression.

As discussed in our answer to Question B6b above, it was not possible to add this new health state using the original model due to limitations in the reporting of ASCT outcomes data from Sureda *et al.* 2001.

B9. Age-related utility decrements are not applied in the base case analysis, although they are included as model inputs in Appendix E. Please revise the base case analysis to include the adjustment. If the company decides not to use age-related utility decrements, please justify why this was considered unnecessary.

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The ERG is correct that this is an error - this control was incorrectly set in the base case. Re-running the model with this adjustment included, along with the correction in response to Question B11 gives the results presented in Table 1.

Table 1: Base case pairwise results including the PAS

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	£5,041	£16,535

All the cost-effectiveness results reported in this response are produced with both corrections applied.

As these errors also affected the results scenarios in the re-submission, Appendix F reports corrected results for all analyses with both corrections applied (the results in appendix F will be provided to NICE by 6th February 2018; Takeda apologise for the slight delay from the requested timelines).

B10. Please explain why ASCT mobilisation, ablation and post-transplant costs are set to zero in the submission and economic model (company model; "Costs" tab, cells F354:359) as the uncertainty in Appendix E and references in the economic model infer costs will be incurred for those resources.

The cost of ASCT included in the economic model is a total cost, incorporating all of the different aspects of the procedure. As explained in Takeda's response to the first ACD published during TA446, this cost was derived from clinical expert input received from 5 expert clinicians based in English centres that undertake ASCTs. All 5 clinicians placed the total cost of ASCT in the region of £25,000 per transplant. Clinical expert input was sought because the NHS Reference Cost of ASCT (~ £10,000) was acknowledged by clinicians as lacking credibility. The cost of ASCT included in the revised model is the same as that in the original model (£25,000) and it is worth noting that this cost was not challenged previously by either the ERG or the committee during TA446.

B11. Please explain why the risk ratios presented in Table 7, page 40 of the company submission are described as hazard ratios?

The ERG is correct that these cells are incorrectly named and applied as hazard ratios. This has been corrected in the updated model with the values now applied as relative risks.

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Please note, that results presented in our responses to Question B2 and Question B9 include this correction, along with the correction stated in response to Question B9. Appendix F gives corrected model results for all analyses in the evidence resubmission (the results in appendix F will be provided to NICE by 6th February 2018; Takeda apologise for the slight delay from the requested timelines).

B12. Please clarify if the hazard ratios in the economic model should equal 1 in the base case analysis for TTP relative to SC and PPS relative to SC (company model; "Survival and Progression" tab, cells I40 and I42).

These hazard ratios are not used to predict outcomes and represent functionality used in the original submission. The base case approach is to predict outcomes using a surrogate approach (based upon response), which has not changed since the model used for the FAD from TA446.

All hazard ratios were set to 1.00 to ensure that they have no effect on results; however, to avoid confusion these have now been removed from the model.

B13. Please clarify which figures (and subfigures) were digitised from Reyal *et al.* 2016 to obtain allo-SCT PFS and OS data.

The allo-SCT PFS and OS data were obtained from the study outlined in the publication by Reyal *et al.* 2016, however they were not taken directly from the manuscript itself. Professor Karl Peggs of UCL (London), a co-author of the Reyal *et al.* manuscript, indicated that the appropriate target population for this specific indication are those patients who have not received a previous ASCT (86 out of 116 patients as outlined in Table 1 of Reyal *et al.* 2016). This is consistent with the Marketing Authorisation for brentuximab vedotin which, for this specific indication, states that ASCT is "not a treatment option".

Professor Peggs provided figures illustrating the KM data for these specific patients. These KM figures were then digitised and analysed as per the description in Appendix A of the submission document.

B14. In the economic model, the ERG is unable to run the macro "scenario analyses" and "Prob_Scenarios" and cannot find worksheets titled "Scenario Analysis" and "Scenarios breakdown". Please correct this in the model.

The macro "Prob_Scenarios" should have been removed along with the worksheets titled "Scenario Analysis" and "Scenarios breakdown". Automatic scenario analysis was included within the model used for the FAD when computational burden was low (prior to inclusion of tunnel states) as the output of each scenario could be efficiently reported.

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Given the computational power required for the corrected model, automatic scenario analyses are no longer the most efficient way of producing results. The macro has been removed; should the user wish to run scenarios please change the relevant controls and re-run the "tunnel insert" macro.

On the clarification call held on 1st February 2018 the ERG confirmed that they understood the practical need to remove the functionality to automate the scenario analyses given the computational complexity of the updated model.

B15. Please explain the rationale for the difference in cost and duration between the palliative care health state in the original model and EOL health state in the revised submission.

Following a detailed review of ERG and Committee comments as summarised in the FAD for TA446, it became clear that the previous structure was seen to cause a degree of confusion. It seemed that this was not helped by the amalgamation within one health state of both palliative (i.e. non-curative) treatment and general end of life care. In order to reduce this confusion, increase the transparency of the model, and ensure costs and utilities were incurred at the appropriate point in time for patient tracking and discounting, separate health states were programmed for:

1. the costs associated with reducing disease burden following relapse after receiving SCT (the post-SCT progression health state), and
2. the costs associated with caring for oncology patients as they approach the end of life.

Round *et al.* 2015 is a well conducted study and published manuscript that is frequently used in NICE submissions for end of life costs in oncology. We therefore chose to use this source and modelled the duration of time spent in this state, such that it accorded with the time horizon over which these costs were accrued in Round *et al.* (2015).

B16. Please explain the rationale for including an EOL health state when a one-off cost could be applied to all patients who die.

A new health state was added in order to increase transparency as it made clear the separation of: (i) the costs associated with reducing disease burden following relapse after SCT; and (ii) the general costs associated with caring for oncology patients as they approach the end of life (see the response to Question B.15 above).

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An important advantage of using a separate health state is that it allows different HRQL values when in receipt of treatments to proactively reduce disease burden following relapse after SCT, than when in the final stages of life. This is consistent with clinical expert advice received by Takeda that following relapse after SCT it is unlikely that patients will have a very low HRQL for the entire period (particularly when on treatment). By having a different health state it is feasible to implement a scenario analysis whereby the HRQL value applied in these two different stages differ. This approach is outlined in Section B.3.4.2 of the evidence re-submission. Takeda consider this an important analysis, but we have kept this as a sensitivity analysis to retain consistency with the original submission wherever possible.

A further reason to not incur values as a 'lump sum' is that this is not good modelling practice. In incurring costs or utilities on an event, this reduces transparency, increases the risk of errors, and affects the accuracy of results due to discounting.

B17. Please clarify how Round *et al.* 2015 was identified and chosen to inform the model.

The source for End of Life costs was identified via a targeted review of recent submissions to NICE for oncology medicines. Two sources emerged as being the strongest candidates: (i) the study undertaken by Addicott and Dewer 2008 on behalf of the King's Fund; and (ii) Round *et al.* 2015. The advantages of Round *et al.* 2015 are that it has been published in a peer reviewed journal and was undertaken more recently.

Round *et al.* 2015 is a well conducted study and provides a robust source for End of Life costs. However, it should be noted that the ICER is likely to be relatively insensitive to the precise cost allocated while in the End of Life state because the same cost is applied to both treatment arms. This is illustrated by the fact that when the cost from Round *et al.* is varied between its upper and lower bound, the ICER only changes from £16,861 per QALY to £15,785 per QALY (these ICERs include the corrections described in our response to Questions B9 and B11).

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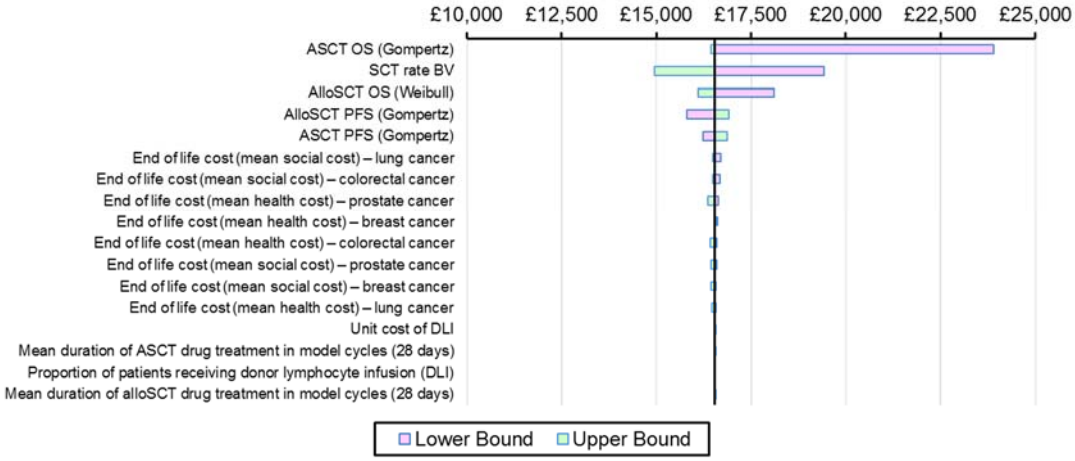
Addendum to the response to the ERG's Questions (06/2/2018)

Below is the response to Question B3. It was necessary for Takeda to respond to this question one day later than initially requested, apologies.

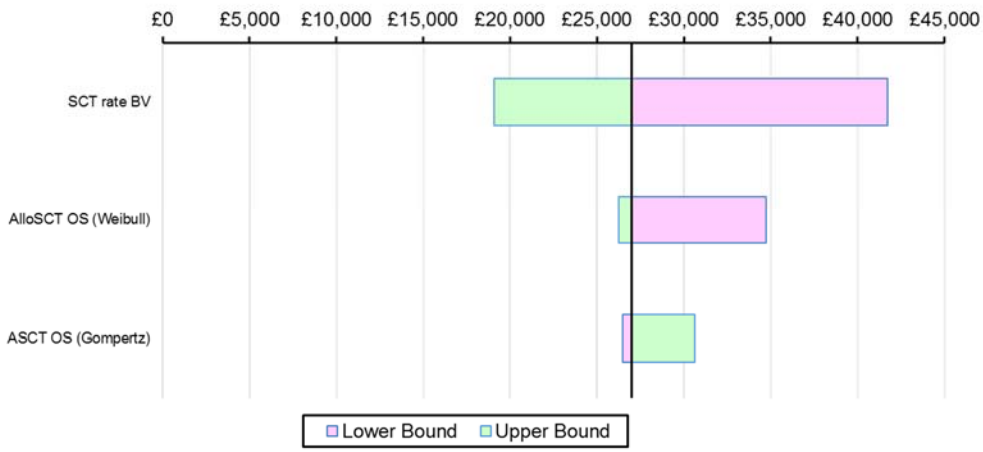
B3. **Priority question:** Please provide one-way sensitivity analyses on all new parameter estimates included in the submission. Please conduct these analyses in both the new and original economic models and display the results in tornado diagrams.

The upper and lower bounds for all of the parameters are derived from the 2.5th and 97.5th percentiles of each parameter's confidence interval. For a description of each of the parameters please see Appendix E of the original submission

One-way sensitivity analyses for parameters added to updated economic model



One-way sensitivity analyses for parameters added to original economic model



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Single technology appraisal

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma (CDF review of TA446) [ID1366]

Appendix F

Submitted by Takeda UK

6th February 2018

Appendix F: Summary of the updated economic model (following clarification questions)

Results are presented below for the revised economic model, these include all changes detailed in the resubmission, along with those requested by the ERG during clarification questions.

Table of ICERs for incremental update of the economic model

The changes to the model and their impact on the Incremental Cost Effectiveness Ratio (ICER) are shown in Table 1. ICERs are given including the impact of the confidential patient access scheme (PAS) – a discount of [redacted]. This is because the PAS is agreed, and has been in place for a substantial period of time (initially as a PAS, then as a CAA with NHS England, and again as a PAS currently).

Table 1: Results of economic modelling including stepwise changes to the updated base case

	Scenario	ICER (with PAS)	ICER (no PAS)
	Original model used to prepare the FAD	£26,165	[redacted]
	FAD model with transition probability error corrected	£26,976	[redacted]
Individual changes to error corrected model	*Updating the corrected model with newly collected SCT rate data*		
	1. Brentuximab vedotin SCT rate of 25% from the CDF data	£35,499	[redacted]
	Addressing issues from the FAD		[redacted]
	2. Allo-SCT outcomes data from Reyal et al. (2016)[21]	£18,002	[redacted]
	3. ASCT outcomes data from Thomson et al. (2013)[19]	£16,708	[redacted]
	4. Post-SCT progression health state added (including changes 2 & 3)	£11,798	[redacted]
			[redacted]
All changes made (new base case)		£16,535	[redacted]

Base case economic model results

Table 2 below details the base case pairwise results. The base case ICER has improved from the original submission. As can be seen in Table 1, this is primarily due to the updated SCT survival data, which shows better survival than the papers by Sureda et al.[26,28] The fall in the SCT rate does increase the ICER, however as patients also do not incur the cost of SCT, this rise is only modest with the base case being under £20,000 per QALY.

Table 2: Base case pairwise results including the PAS

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	£5,041	£16,535

For completeness, results are also provided here without the impact of the PAS, where the ICER rises to [redacted] (Table 3).

Table 3: Base case pairwise results using the list price of brentuximab (no PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	£5,993	[redacted]

Table 4 details the cost breakdown. Of the incremental cost, the majority is either due to the use of brentuximab vedotin, or the costs of SCT.

Table 4: Cost breakdown

	Undiscounted			Discounted		
	Brentuximab vedotin	Standard care	Incremental	Brentuximab vedotin	Standard care	[redacted]
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Of the additional QALYs, the major gains are in the allo-SCT and ASCT states. This is in keeping with the higher SCT rate observed with brentuximab vedotin, in allowing more patients to undergo potentially curative therapy (Table 5).

Table 5: QALY breakdown

	Undiscounted			Discounted		
	Brentuximab vedotin	Standard care	Incremental	Brentuximab vedotin	Standard care	Incremental
EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASCT PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

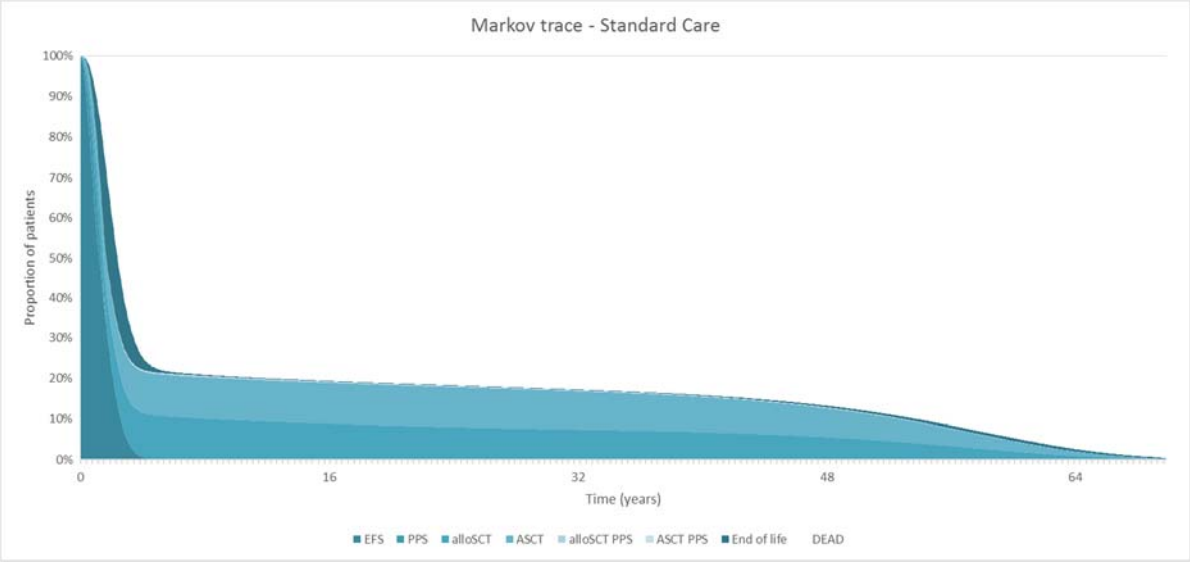
This additional time in allo-SCT and ASCT is illustrated in the undiscounted life years from the model. Whilst brentuximab vedotin has slightly fewer years spent pre-SCT, that is as patients progress to SCT at a much greater rate, then exhibiting longer survival, with an overall survival gain of approximately 8 years (12.28 vs. 4.43; Table 6).

Table 6: LY breakdown

	Undiscounted		
	Brentuximab vedotin	Standard care	Incremental
EFS	1.34	1.37	-0.02
PPS	0.09	0.11	-0.02
Allo-SCT	4.30	1.01	3.29
ASCT	5.12	1.21	3.92
Allo-SCT PPS	0.49	0.11	0.37
ASCT PPS	0.28	0.07	0.21
End of life	0.65	0.55	0.10
Total	12.28	4.43	7.85

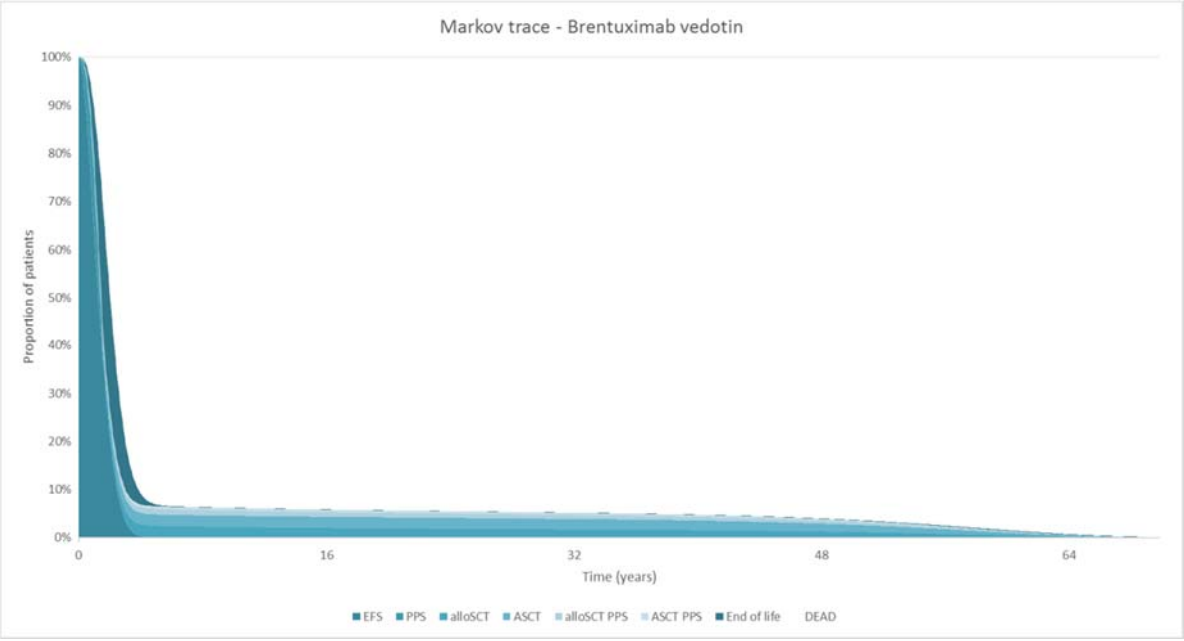
The results for brentuximab vedotin are shown graphically in Figure 1. As can be seen, the proportion of patients alive falls over the first few years before stabilising as only patients who have undergone SCT exhibit long term survival.

Figure 1: Markov trace – Brentuximab vedotin



A similar pattern is seen with standard care (Figure 2). The long-term survival however is at a lower level as fewer patients receive SCT.

Figure 2: Markov trace – Standard care



Scenario analyses

Scenario analyses around the main model parameters are presented below (all results are "with PAS").

Use of alternative SCT rate for brentuximab vedotin from the Public Health England report

Some patients proceeded to SCT having received additional salvage chemotherapy after their initial treatment with brentuximab vedotin. The inclusion of this additional salvage chemotherapy (which is costed in the model) increased the SCT rate in the brentuximab vedotin arm to 41% (compared with 25% in the base case which includes only patients bridged directly from brentuximab vedotin to SCT). Table 7 below details the pairwise results of this scenario, where the ICER falls to £13,503/QALY from £16,535/QALY in the base case.

The fall in the ICER is caused by the incremental QALY gain with brentuximab vedotin increasing by [redacted] QALYs (from [redacted] in the base case to [redacted]), an increase which more than offsets the associated increase in incremental costs of [redacted] ([redacted] vs. [redacted]). In other words, the cost of the additional salvage chemotherapy is more than offset by the additional health gain that arises from bridging an extra 16% of patients to a potentially curative SCT (note the incremental LY gain increases by 4.81, from 7.85 in the base case to 12.66 in this scenario).

Table 7: Pairwise results – inclusion of higher SCT rate by the use of further salvage chemotherapy (with PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	17.08	[redacted]	[redacted]	12.66	£4,127	£13,503

Use of alternative utility data

The utility data included in the original submission relies heavily on the publication by Swinburn et al. (2015).[34] As mentioned previously, this is a vignette study and therefore is not based on the EQ-5D-3L responses as preferred according to the NICE methods guide.[26]

In this scenario analysis, we replace the values derived from the vignette study with those derived from EQ-5D data collected in a study (the Checkmate 205 study)[38] in which nivolumab was administered to patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and in whom the majority (74%) had received prior treatment with brentuximab vedotin, in addition all patients had had prior ASCT.

Table 8: Utility values in the base case and scenario analysis

Health state		Base Case Utility Value (Source)	Scenario analysis (Source)
Event Free Survival		0.82 (Swinburn et al. 2015)[34]	0.84 (Checkmate 205)[38]
Stem Cell Transplant	Up to 14 days	0.42 (Van agthoven 2001)[35]	0.42 (Van agthoven 2001)[35]
	14 days to 3 months	0.60 (Van agthoven 2001)[35]	0.60 (Van agthoven 2001)[35]
	After 3 months	0.77 (Van agthoven 2001)[35]	0.77 (Van agthoven 2001)[35]
Post Progression Survival		0.38 (Swinburn et al. 2015)[34]	0.715 (Checkmate 205)[38]
Post SCT relapse		0.38 (Swinburn et al. 2015)[34]	0.715 (Checkmate 205)[38]
End of Life		0.38 (Swinburn et al. 2015)[34]	0.50 (Park et al. 2006)[44]

The utility value from the Checkmate 205 study[38] for the post-progression health state (0.715) is considerably higher than that from the vignette study (0.38). In addition, and despite the higher value, it could be argued that the utility values derived from the Checkmate 205 study may actually underestimate the true values likely in this setting because this study was undertaken in a group of patients where the majority had received prior brentuximab vedotin (i.e. most patients in Checkmate 205 are at a later line of therapy). Table 9 details the pairwise results of this scenario, showing that the ICER remains essentially the same as in the base case (£16,535/QALY vs. £16,584/QALY).

Table 9: Pairwise results – scenario analysis using post-progression utilities from the Checkmate 205 study[38] (with PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	£5,041	£16,584

B.3.4.3 Use of alternative discounting rates for technologies with a long time horizon

The NICE methods guide (Section 6.2.19) states:

> *"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."*[26]

We believe brentuximab vedotin could be deemed eligible for the lower discount rates that can be considered for such technologies. Based on our modelling, after 30 years approximately 20% of patients treated with brentuximab vedotin are projected to still be alive. This is because brentuximab vedotin has been shown in multiple datasets to allow large numbers of patients to achieve disease remission and thus be able to be bridged to a potentially curative SCT. Table 10 details the pairwise results of applying a lower discount rate of 1.5%, and this shows a further decrease in the ICER to approximately £11,000 per QALY.

Table 10: Pairwise results – lower discount rate of 1.5% applied for costs and QALYs (with PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	4.43					
Brentuximab vedotin	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	£5,150	£11,269

B.3.4.4 Use of the original model from the FAD

We are confident that the changes we have made to the health economic model (in particular, the addition of a post-SCT progression state and the use of more appropriate data sources for the outcomes from ASCT and allo-SCT) lead to ICERs that are more robust, reliable and reflective of the true cost effectiveness of brentuximab vedotin than those derived from the original model used to develop the FAD in TA446.

Nevertheless, in the interests of transparency and in the spirit of changing as little as possible from the original submission, we also include two scenarios here in which the corrected version of the original model is merely updated with the new SCT rates for brentuximab vedotin derived from the Public Health England report.[18] Hence, in this

scenario, the SCT rates are set to 3/57 (5.3%) for the comparator of single-agent chemotherapy (as discussed in Section B.3.2.3) and either 25% (base case, bridging directly from brentuximab vedotin) or 41% (includes the option to receive additional salvage chemotherapy) for brentuximab vedotin.

The results for these two scenarios are shown in below. The results show that with a SCT rate of 25% in the error corrected model, the ICER is £35,449 per QALY (Table 11). Using an SCT rate of 41% this falls to £29,825 (Table 12).

Table 11: Pairwise results – corrected model used for the FAD with SCT rates of 5.3% for standard care and 25% for brentuximab vedotin (with PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	2.86					
Brentuximab vedotin	[redacted]	[redacted]	5.64	[redacted]	[redacted]	2.78	£14,531	£35,449

Table 12: Pairwise results – corrected model used for the FAD with SCT rates of 5.3% for standard care and 41% for brentuximab vedotin (with PAS)

	Total			Incremental			Cost per LY	Cost per QALY
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Standard care	[redacted]	[redacted]	2.86					
Brentuximab vedotin	[redacted]	[redacted]	7.27	[redacted]	[redacted]	4.41	£11,939	£29,825

Despite the use of data which has been highlighted to be inappropriate for the indication under consideration, the ICERs remain around the threshold.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (CDF review of TA446) [ID1366]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Bloodwise
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Bloodwise's mission is to beat all blood cancers – stopping people from dying, improving the lives of everyone affected by blood cancer, and where possible preventing people getting blood cancer in the first place. We do this by funding world leading research, supporting all those affected by blood cancer, and campaigning for improvements in care and services. We are entirely funded by voluntary donations and have approximately 100 members of staff and 140 patient ambassadors plus many more volunteers and supporters.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We sent an email to our database of patient ambassadors asking them to contact us to share their experiences of Hodgkin lymphoma (HL) and brentuximab vedotin. Our submission is based on these responses and we have used direct quotes. We also consulted our medical advisory panel, an expert group of clinicians, to gain further insight into the condition and patients' experiences using this treatment from a clinical perspective. We also referred to the responses we received when preparing a previous submission to the Scottish Medicines Consortium for the Patient and Clinical Engagement Meeting to determine the added value of brentuximab in the treatment of both hodgkin lymphoma and anaplastic large cell lymphoma.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The most common symptom of HL is swollen lymph nodes often in the neck, armpit and groin. Other common symptoms are fever, weight loss, night sweats, fatigue and itching. It is most common in people aged 15-25 and over 50. Treatment for HL usually includes intensive chemotherapy with the considerable side effect profile that goes with this and in some cases radiotherapy and steroids. If patients do not respond well to treatment, the next step is usually more lines of toxic chemotherapy in attempts to become eligible for a stem cell transplant. The following accounts from HL patients who contacted us to share their experiences convey the difficulties faced in terms of symptoms experienced, delay in diagnosis and treatment: “Hodgkin's was in one word, exhausting! I went misdiagnosed for a year/ two years and had my symptoms before lumps appeared. These started in the early days with a rash, similar to eczema, I'd had eczema as a child so knew it didn't seem normal but repeatedly was told eczema was all it was, but eventually I was covered head to toe in bright red, cracked, intensely itchy skin. My legs were covered in large pus filled spots, my skin wept constantly to the point a towel could be soaked from it and my skin was in intense physical pain. Due to constant itching I had no sleep. As months went on I had continual throat infections, chest infections, ears felt blocked with a slight ringing but at each doctor’s visit I was told they were ok. My sinuses were completely compacted, I lost all sense of smell, the skin on my ears cracked completely. I had a large crack across my neck of infected skin. Closer to diagnosis I had pains in my arms, like a deep aching similar to flu aches and pains, heart palpitations, lumps showed around collar bone, veins on chest were pronounced. I went from a size 12 to a size 6 possibly 4 in around 3 months. My eyes were puffy every morning and red with large amount of green rubbish. I was asleep constantly, always tired, hot and pouring with sweat but at times freezing cold. [I suffered from] dizzy spells. The list goes on! In general it was totally exhausting and frustrating as my issues were classed as 'allergies' or a 'virus' so I was always put in with a nurse and nobody saw the huge deterioration. Everyday was a battle to carry on as the

	symptoms mounted up. When I was diagnosed the mass was enormous it filled the whole chest cavity and was only slightly off major blood vessels." "For me it was a long hard time of many different treatments and slowly worsening health due to the continued impact of harsh chemotherapy along with the increasing anxiety as I failed to achieve remission, whilst having a young family and being removed from the normal life of a should be healthy 30 + year old." "HL and its associated treatments are very hard on the body and mind. I lived with it for an unknown number of months before diagnosis as my symptoms were not tied together until very late…. Extreme fatigue, drench sweats, excruciating itching and crippling back pain made living everyday life miserable at times. For me, as my disease was refractory, not seeing the common treatment path working took a toll on all of my family's mental health." Patients also referred to the lives of the family members who cared for them being put on hold as they waited for a diagnosis and helped them through the gruelling chemotherapy treatment they received.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients described the use of multiple conventional chemotherapy regimes as long and gruelling especially where certain treatments failed after several months of enduring them. They listed significant side effects including fatigue, nausea, constipation, lack of taste and hair loss. One patient told us that while she was on a conventional chemotherapy treatment plan, she reached a stage where she was so exhausted she could barely cook for herself and relied on her mother coming to her home everyday to

	make her breakfast so that she had enough energy to face the day. Another patient described how she had been left with permanent symptoms of numbness, nerve damage and aches in her legs caused by chemotherapy In addition to the significant physical and emotional side effects of the conventional intravenous chemotherapy, patients also cited the practical difficulties associated with multiple hospital trips.
8. Is there an unmet need for patients with this condition?	There is a need for less aggressive treatments with reduced hospital admission. Where HL patients have not responded to traditional chemotherapy and are not able to have a stem cell transplant, brentuximab can offer them a chance to receive effective, less invasive treatment with minimal side effects which can then enable them to proceed to stem cell transplant where traditional chemotherapy has failed. Patients also described how receiving treatment for the condition can feel like they "gambling" beyond the standard paths and that there is a greater need for certainty.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Brentuximab is much less intensive and exhausting than conventional chemotherapy. Patients report a number of advantages to the treatment. The following patient quotes are typical of the feedback we received: "The most important thing about living with Hodgkin's lymphoma is achieving balance; balance between work, family and social life, fitness and treatment. The incredible thing about brentuximab is that it is much less intensive and exhausting than a conventional chemotherapy. This means that I have more time and energy to focus on living. In the last six months since I was put back on brentuximab, I have run the park run (regularly), climbed mountains, rambled through the South Downs, worked, cycled and sailed. I travel, visit friends and family,

	and try to make the very most of non-treatment time." "The clinical side effects of BV [brentuximab vedotin] were fairly minimal…. I was much more healthy and energised when compared to other treatments throughout the BV cycles." Patients also highlighted the ease of the treatment and need for less visits to hospital than with traditional chemotherapy: "Brentuximab compared to traditional chemo was a dream, quick infusions minimal side effects, my life returned to normal for the duration of my brentuximab treatment I was able to go into work and regain some form of normality." The high response rate and improved speed at which some patients reported improvements, and the simplicity of administration meant many patients spoke highly of the drug's ability to relieve the psychological distress they normally associated with their cancer treatment. In the context of the indication being appraised (treating HL in adults with relapsed or refractory disease after at least 2 previous therapies when they cannot have autologous stem cell transplant or multi-agent chemotherapy) both clinicians and patients describe brentuximab as hugely significant not only in its use in this context as an alternative treatment plan but also because it can be used as a bridge to potentially curative stem cell transplant in patients who are refractory to conventional chemotherapy combinations . One clinician we consulted explained how "this is the critical indication and is particularly relevant in young people who otherwise would have to be exposed to more and more lines of toxic chemotherapy in attempts to become transplant eligible….. the bridge to transplant – this is absolutely essential …and the main use of brentuximab vedotin in young people."

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The most common side effect reported was peripheral neuropathy, causing numbness in fingers and toes. Occasionally this would give patients difficulty in performing tasks such as opening jars, but this was relatively rare. Patients also reported tiredness and nausea as side effects but that this was not significant enough to deter from the benefits of the treatment. Overall, patients felt that side effects had much less impact than previous treatments they had taken.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	HL patients who fall within the specific category of the indication being appraised (relapsed or refractory disease after at least 2 previous therapies and they cannot have autologous stem cell transplant or multi-agent chemotherapy) benefit particularly from the use of brentuximab as they have no other treatment options available to them and the clinical trial results indicate that brentuximab is the only drug many of these patients respond to. A key point is that the treatment can enable these patients, who are mostly children and young adults to enter into remission and thus proceed to a stem cell transplant. A clinician we consulted who treats many young HL patients stated that “without access to brentuximab, there will undoubtedly be an increase in disease related deaths in young people with Hodgkin’s”.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and	Brentuximab is only administered once every 3 weeks meaning patients only need to be in hospital for 2 days in each 3-week cycle. This is beneficial for those with mobility or other issues which make it difficult to travel to hospital on a more regular basis.

the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Brentuximab vedotin is considered a step-change in the way HL is treated particularly in the indication being appraised by the committee as it gives those who have not responded to conventional treatment or are not suitable for a stem cell transplant a chance to receive curative treatment and can act as a bridge to transplant for those patients.
- Patients reported a rapid improvement in symptoms in between treatment cycles, enabling them to exercise, return to work and regain some form of normality in contrast to their experiences of traditional chemotherapy.
- Patients reported that treatment with brentuximab was much less intensive and exhausting than conventional chemotherapy with significantly less hospital visits required.
- Patients reported minimal side effects which had much less of an impact than previous treatments they had taken.
- It would be a huge step backwards if the treatment is not approved for routine commissioning following the recommendation for

use within the CDF particularly because it is funded in Scotland and Wales.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Lymphoma Association is a national charity registered in England and Wales and in Scotland. Our primary aim and objective is to provide information, advice, support and training to everyone affected by lymphoma. We work throughout the UK, publishing leading, quality-assured written information on lymphoma, operating a clinical trials information service (Lymphoma TrialsLink at www.lymphomas.org.uk/lymphoma-trialslink) and providing a national helpline, a network of support groups and a buddy scheme. We have also developed a survivorship and well-being programme specifically designed for those with lymphoma (*Live Your Life*). We also provide education and training courses for healthcare professionals, as part of their CPD. Our income (which has been of the order of £1.5m to £1.7m for each of the last three years) is predominantly generated by voluntary donations from the public and by grants from charitable trusts and foundations. These sources account for about 90% of our income in any given year. We also generate income from delegate fees for our education and training programme (which accounts for about 5% of our income in any given year) and from project-based grants or sponsorship from pharmaceutical companies (which, again, accounts for about 5% of our income each year).
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	We gather information from our network of patients and carers who are linked to us through our role as a national lymphoma information, support and training charity in the UK, as well as collaborating with partner lymphoma charities and not-for-profit organisations internationally. We have access to people affected by lymphoma via our national helpline, network of support groups, buddy schemes, our Live Your Life survivorship programme, our conferences and events, the readers of our "Lymphoma Matters" magazine, people who contribute to our online forums, and via the circulation of surveys/feedback forms.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients with relapsed or refractory Hodgkin lymphoma often have many symptoms, which can be debilitating and distressing. They also know that, despite all the treatment they have been through, their life-expectancy is severely limited. They are faced with a choice between: • treatments that they know have little chance of success (particularly in the long term) but risk them developing significant side effects and/or spending large parts of their remaining life away from family and friends in hospital, or • purely palliative care, which is likely to give them a life-expectancy of a few months only and potentially with a number of symptoms. Even those who are fit enough and have the possibility of a donor to enable them to undergo an allogeneic transplant may not be able to do so if their lymphoma cannot be controlled again with effective treatment first. Achieving a cure in these patients can allow them to return to work and make an active contribution to society as well as having a profound positive impact on physical and psychological health. Many patients with relapsed or refractory Hodgkin lymphoma are young with the potential for a long and active life if they can undergo transplant. Patients unsuitable for transplant can also benefit from palliative

	treatment giving significant and prolonged symptom reduction which cannot be achieved with standard chemotherapy options. Following transplant, patients, who are often in their prime childbearing and family years, can have a long and healthy life. The Patient Expert we have nominated for this appraisal/review points out that Hodgkin lymphoma has a peak of incidence in people under 30 and is the most common cancer in teenagers and young adults. As such and being a 30-year-old woman herself with Hodgkin lymphoma, she wants to live like a 30-year-old: *"I have aches and I get tired but, fundamentally, I try to live life to the full. I was, until very recently, teaching almost full-time in a boarding school. This proved not to be sustainable whilst undergoing treatment with Brentuximab and I am now looking for a part-time role. The most important thing about living with Hodgkin lymphoma is achieving balance; balance between work, family and social life, fitness and treatment. The incredible thing about Brentuximab is that it is much less intensive and exhausting than a conventional chemotherapy. This means that I have more time and energy to focus on living."*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients or carers would like to see a cure to their Hodgkin lymphoma or failing that a strong, durable remission, or for those in palliative care a life-extending treatment that keeps their lymphoma under control. In addition, whatever the outcome patients or carers would like treatments to have lower toxicity profiles and reduced or manageable side effects of after effects.

	Most patients in this situation know their life-expectancy is severely limited and that the current treatments offer little chance of success (particularly in the long term) but risk significant side effects and/or may require large amounts of time to be spent in hospital. The alternative is palliative care, which allows them to spend the time they have left with family and friends as much as possible. Patients want more effective therapy that still offers them a good chance of spending time at home. For relapsed/refractory disease, chemotherapy will be the usual treatment, with patients reporting experience of a number of different regimens, such as gemcitabine, vinblastine, vinorelbine, alone or in combination. Such treatments will carry a higher toxicity profile and significant side effects and after affects. Most of the standard and established treatments for relapsed/refractory disesase will carry a higher toxicity profile and significant side effects and after affects, although some, more recently treated, patients will have experience of brentuximab vedotin or nivolumab, both of which represent a step-change in the treatment and management of Hodgkin lymphoma, albeit for a small group of patients at a certain point in the treatment pathway. *"I chose to have an allogeneic stem cell transplant. For a while I wondered whether I had made the right decision. The transplant recovery was such hard work and I suffered with depression. I developed a rash that turned out to be graft-versus-host disease, but it wasn't too problematic. I also had problems with my heart and lungs …*

	"… I was told that after having the transplant my blood type would change to that of my donor. Up until 2.5 years after the transplant, however, my blood type was still not changing and I was having to have blood transfusions ever two weeks for over two years for anaemia … *"…. my blood type changed overnight [after 2.5 years]."* Female HL patient, diagnosed at age of 26 *"For me the worst part of having lymphoma has been the side effect that I am still experiencing. I find I can no longer concentrate or focus on things, something the doctor has told me is known as 'chemo brain'. "* *Male HL patient, diagnosed at age of 27* *"Someone recently asked me how I felt about being diagnosed with lymphoma. I told them it felt like I had been dropped in the middle of the sea with no lifejacket, no boat, no equipment to help me. I didn't have time to think about how I was going to get to the other side, I just had to deal with it. I knew that thinking "why me?" wouldn't help; I had to stay strong and focus on myself in order to get to the other side."* *Male HL patient, aged 28 at diagnosis* The patient expert we have nominated for this appraisal/review adds the following points:

	"If Brentuximab was not available to me, I would instead have to be on a conventional chemotherapy. I am currently caring for my partner (he recently had neck surgery) and this would certainly not be possible had I been on a conventional chemotherapy. While I was on a conventional chemotherapy (before Brentuximab) I reached a stage where I was so exhausted I could barely cook for myself. My Mum had to come to my home and make me breakfast to give me enough energy to face the day."
8. Is there an unmet need for patients with this condition?	Yes – please see above points.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	In short, greater effectiveness, ease of administration, fewer sides and less toxicity, with increased life expectancy. Some patients speak of this treatment being a life-saving treatment, where no other treatments work. From the feedback we have received, patients cited the following benefits: • Ease and speed of administration of the treatment, described in terms of "a simple 30-minute infusion with a flush and I was finished".

	• Limited side effects (although these included peripheral neuropathy that continued beyond the treatment but subsided after a year) that were manageable and described by one patient as an acceptable "trade off" for the benefits of the treatment. However, it is known that there can be serious side effects with the treatment and one patient reported being neutropenic during one cycle of the treatment, which ended up with hospitalisation due to a fever shortly after receiving the treatment. Another patient, who generally spoke very positively about the treatment, did also indicate that six cycles was about as much as she could bear owing to the neuropathy in her hands and feet. • The speed with which the treatment has a noticeable effect – one patient reported her previously visible lumps almost completely disappearing after the first cycle of treatment. • The overall impact and efficacy of the treatment, best summed up by one patient who described it so: "I was told I was in remission for the first time in seven years. It was overwhelming." The majority of patients achieve a response – often quite quickly. The treatment is then life-prolonging compared to existing treatment options in this group. In patients having this as a 'bridge' to allogeneic transplant, some may eventually be cured. The treatment can be delivered rapidly in a day care unit and side effects are usually manageable and familiar to anyone who has had previous treatment for lymphoma. Our patient expert for this appraisal/review adds:

	"In the last six months since I was put back on Brentuximab, I have run the park run (regularly), climbed mountains, rambled through the South Downs, worked, cycled and sailed. I travel, visit friends and family, and try to make the very most of non-treatment time. *"Immediately after a Brentuximab dose, for a few days, I am acutely tired. I am less ambitious with my activities for these days. Mercifully Brentuximab is administered in a three-week cycle so I still have two and half weeks in my cycle when I have good energy levels and this time is invaluable."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There are some side effects to the treatment, but they are generally seen as manageable and some of them (eg, fatigue and peripheral neuropathy) will already be known to most patients from their experience of harsher chemotherapy regimes. For some, there can be serious side-effects, as noted in an earlier answer. For those who are receiving the treatment as part of palliative care, the side effects will be seen as a reasonable trade-off for the benefit of extra time with family and loved ones.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The ease of administration and the three-weekly treatment cycle will benefit all patients, as will the lower toxicity levels. However, older or more vulnerable patients, or those with mobility issues may benefit more than others from these advantages, including fewer trips to hospital than with some other regimes.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Hodgkin lymphoma has twin peaks of incidence in those under 30 and those over 65 years old. If access to treatment is denied to these patients, then there is potentially an issue of age discrimination against both young and old people.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Brentuximab vedotin represents a step-change in treatment for this group of patients. • Efficacy of treatment means improved life-expectancy for many patients compared with the current alternatives. • Rapid relief of symptoms. • Ease and speed of treatment, meaning patients are able to spend time with their family and friends and not in hospital. • Fewer side effects than other chemotherapy that may be offered in this situation, which are manageable and usually familiar to patients who have had previous treatment for lymphoma.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (CDF review of TA446) [ID1366]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	This appraisal is confined to the indication 'relapsed after 2 prior lines of chemotherapy and not suitable for stem cell transplantation'. This indication covers 2 groups of people: 1. Those who are fit for a stem cell transplant but are not suitable, as they have not entered a deep enough remission. We know well from prior research that an autologous stem cell transplant (ASCT, which is standard of care for relapsed Hodgkin Lymphoma) only has a reasonable cure rate if patients are in a complete metabolic remission (CMR) as assessed by FDG-PET, immediately beforehand. If they are not, there is good evidence that alternative treatment to induce a CMR then results in a high cure rate from

disability.)	subsequent ASCT. It is therefore common practise for a fit patient who has relapsed after first line treatment, to receive 1st line salvage treatment in the form of combination chemotherapy. If their PET scan is positive after this, patients then often receive brentuximab vedotin with the aim of deepening their remission and going onto ASCT (or sometimes allogeneic SCT). When used in this setting, brentuximab vedotin is part of a curative strategy. 2. Those who are not fit for a stem cell transplant. These are elderly and / or co-morbid patients. In this setting, brentuximab vedotin is used palliatively to induce remissions and improve quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Again I will split this into the 2 groups of patients: 1. A deepening remission whether a partial remission (> 50% decrease in tumour volume) or complete remission. A complete response is much preferred as a bridge to ASCT. However a stable partial remission can be used as a bridge to allogeneic stem cell transplantation. 2. For unfit patients, any remission (partial or complete) is likely to lead to an improved quality of life, albeit temporarily.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely. For fit patients with relapsed disease it is imperative we induce deep remission prior to stem cell transplantation, to maximise the chance of cure. Both UK published data (Eyre *et al*, Brit J Haematol) and the national CDF data collection exercise show that BV is effective at doing this in a significant proportion of patients. For older patients, progressive Hodgkin lymphoma is associated with numerous symptoms of fatigure, drenching sweats, anorexia, severe pruritus etc. Alleviating these symptoms with effective, albeit palliative, treatment is a high priorty. Current single agent chemotherapy is not very effective in this setting and combination chemotherapy is not tolerated by most patients in this group.
What is the expected place of the technology in current practice?	
9. How is the condition	Brentuximab vedotin is currently the ‘go-to’ agent for both groups of patients in this setting as it has

currently treated in the NHS?	demonstrable efficacy and it is well tolerated. The major side effect is peripheral neuropathy which is manageable with dose reduction, cycle lengthening or on occasion, cessation of drug.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – although the BCSH guideline for relapsed / refractory Hodgkin lymphoma is a little out of date, brentuximab vedotin is discussed as an option.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	1st line salvage choice does vary across the country (ICE, ESHAP, GDP etc). However, brentuximab vedotin is used by the majority of centres (academic and district general) as 2nd line salvage in fit patients as a bridge to ASCT when they are not in a deep enough remission. Also for the unfit patient group, brentuximab is widely used as 3rd line treatment as there is little else available in this setting.
• What impact would the technology have on the current pathway of care?	Brentuximab is well embedded into current treatment pathways across the UK in the groups outlined above.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. It is being used widely in the above settings and will I'm sure continue to be used if reimbursement continues.
• How does healthcare resource use differ	Brentuximab is current care.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Brentuximab is not difficult to give. It can be used by any hospital which delivers outpatient based chemotherapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil – it is being used now.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	As stated above, it is current standard of care.
• Do you expect the technology to increase length of life more than current care?	In fit patients, brentuximab increases length of life as it is used as part of a curative strategy. In unfit patients the focus is more on quality of life.
• Do you expect the technology to increase health-related quality of	Although there are no comparative trials looking a QoL with brentuximab, it is a well tolerated agent and centres are very used to managing the well know side effect of peripheral neuropathy.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional	As stated – it is the current standard of care for these patient groups.

tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Most centres now would routinely perform a PET scan after 4 courses of treatment. If the PET shows a partial or complete remission, treatment continues. If it shows stable or progressive disease, treatment should stop.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The calculation would need to include its use as a bridge to potentially curative stem cell transplantation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	When first introduced, brentuximab was indeed innovative. It has now become standard of care however within its licensed indications.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – when it was first introduced. It was the drug with highest demonstrated single agent activity in Hodgkin lymphoma.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as outlined above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Peripheral neuropathy is a common side effect. This can be severe. However brentuximab has been used now for some years and centres are well used to monitoring for it. Sometimes dose reductions and delays are required. Sometimes treatment needs to be discontinued. Thankfully it is reversible on stopping treatment in the majority of patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The pivotal phase II trials did not reflect this indication well.

• If not, how could the results be extrapolated to the UK setting?	We have performed a UK retrospective data collection which is published (Eyre et al, Brit J Haematol). There has also been a national CDF data collection exercise.
• What, in your view, are the most important outcomes, and were they measured in the trials?	- efficacy of bridging to stem cell transplant - PFS in whole cohort.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The CDF data collection exercise.
20. Are you aware of any new evidence for the comparator	No. Although PD1 inhibitors have been introduced recently, their current indication is only after BV failure.

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
21. How do data on real-world experience compare with the trial data?	In pretty much any clinical trial, or real world data collection, BV in Hodgkin shows 60-70% overall response rate and 25-30% complete response rate. Irrespective of when the drug is used and what patient group.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Efficacy as bridge to transplant in fit patients
- Palliation in unfit patients
- Current standard of care in these settings
- Well known and manageable toxicity profile
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission into the NICE appraisal for the use of brentuximab in relapsed/refractory Hodgkin lymphoma following at least 2 prior therapies when stem cell transplantation or multi-agent chemotherapy is not an option

1. One of the key uncertainties in this appraisal identified in February 2017 was the rate of subsequent stem cell transplantation (SCT) following treatment with brentuximab (BV). As BV had been in the CDF for several years and NHS England was confident that it could obtain retrospective but reliable real world NHS data on this outcome, the NICE Technology Appraisal Committee recommended BV to the CDF (whilst this data was being collected) for the population of patients with relapsed/refractory Hodgkin lymphoma (HL) following treatment with at least 2 prior therapies when neither SCT nor multi-agent chemotherapy was an option.
2. Every patient accessing a CDF drug has to have a CDF application form completed by his/her clinician and thus a unique application number is generated. This therefore allows every patient who has had BV via the CDF to be identified and thus the clinician involved can be traced. The Systemic Anti-Cancer Therapy (SACT) team at Public Health England audited all the national CDF patients accessing BV between April 2013 and April 2016, this time frame being chosen to allow sufficiently mature follow-up so as to be sure of the SCT rate after treatment with BV. Patients having CDF BV in this period could be post-SCT (now a NICE recommended indication and thus irrelevant to this appraisal) or be fit for SCT but unable to proceed to SCT or be unfit for SCT.
3. 496 CDF patients were identified and detailed questionnaires sent to 223 consultants in 106 Trusts. There was an 88% response rate in terms of replies. NHS England regards this as being outstandingly high considering that this was a retrospective audit involving a very great number of clinicians and Trusts in a time frame in which consultant haematologist staff turnover in some DGH Trusts has been high. NHS England therefore rejects the ERG criticism that the proportion of missing data is large (n=60, 12%) given the size and type of this data collection in a real world NHS setting. NHS England is proud of the very high rate of return of the BV questionnaires by NHS consultants, one reason being the importance attached to the use of BV in HL by its prescribers. NHS England therefore regards the data generated as being robust and one that NICE can use in its decision making.
4. 219 patients were identified as being SCT naïve and having received BV as a potential bridge to SCT. 93 patients received BV with no intention of a subsequent SCT. 124 patients were treated with BV post-SCT. There were 60 nil returns, the majority of these coming from clinicians in small (DGH) Trusts. NHS England considers it likely that most of these 60 patients were either post-SCT (and had been referred back to the local Trust after failure of SCT) or were not candidates for SCT as they had received the BV at the DGH.
5. Of the 219 patients given BV with a view to a potential SCT and with known audit outcomes (n=219), 36% proceeded from treatment with BV directly to SCT. An additional 22% had BV followed by further chemotherapy and then SCT, making an overall SCT rate of 58%. These percentages directly accord with the figures found in a selected centre BV audit in the potential bridge to SCT group as previously reported by [redacted]. The [redacted] data was a centre-led audit and was based on less than half the patient numbers in this SACT audit. It is reassuring

for the NHS that these national figures are so aligned with a selected 10 centre audit.

6. If the 93 patients in whom there was no intent of subsequent SCT are included in the denominator (n=219+93=312), 25% proceeded from BV directly to SCT. When those who had BV followed by further chemotherapy and then SCT are included, the overall SCT rate was 41%.
7. If the 60 patients are included in whom there was no data but all assumed to be pre-SCT with no SCT performed (n=219+60=279), 28% proceeded from BV directly to SCT. When those who had BV followed by further chemotherapy and then SCT are included, the overall SCT rate was 46%.
8. If the 93 patients in whom there was no intent of subsequent SCT are included as well as the 60 patients in whom there was no data but all are assumed to be pre-SCT and no subsequent SCT (n=219+93+60=372), 21% proceeded from BV directly to SCT. When those who had BV followed by further chemotherapy and then SCT are included, the overall SCT rate was 34%.
9. One other major uncertainty in the February 2017 appraisal of BV in HL is the SCT rate following chemotherapy with a single agent in patients who have relapsed/refractory disease after at least 2 regimens and who cannot have multi-agent chemotherapy ie the comparator rate of SCT if BV was not available. 1st and 2nd line chemotherapy regimens for HL typically contain 4 and 3 drug combinations, respectively. Even if it is assumed that patients have just had 2 multi-agent combinations, this means that patients relevant to this appraisal have been exposed to 7 drugs yet have relapsed/refractory disease. Thus in relation to further chemotherapy, responses to single-agent treatment are modest and generally of short duration. It is certainly asking much of single-agent chemotherapy to induce a significant response in the wake of 4-drug 1st line chemotherapy and then 3-drug 2nd line chemotherapy in HL as well as a response that is durable enough to last the time frame required to schedule SCT. NHS England therefore agrees with a 5% figure for the SCT rate consequent to single agent chemotherapy.
10. NHS England notes the base case ICERs from the company and the ERG as both being less than £20K/QALY and the fact that few of the scenario analyses produce ICERs that are above £30K/QALY.
11. BV for this indication in patients with relapsed/refractory HL following at least 2 prior therapies and when SCT or multi-agent chemotherapy is not an option has been in the National CDF since April 2013 and was in the then regional CDFs since 2012. It has thus been in use in this setting in England for 6 years and as a consequence NHS England understands why it is regarded by patients and clinicians as being current standard of care.
12. NHS England is optimistic that NICE will be able to recommend BV in this indication for routine commissioning.
13. The license for brentuximab in this indication in HL is limited to adults. Relapsed/refractory HL 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 this setting would not be valid in paediatric and teenager populations. In this situation, NHS England would ensure the funding of brentuximab within routine commissioning to extend to relevant patients under the age of 18 years.
14. NHS England confirms the high degree of engagement shown by Takeda in the CDF data collection and commercial access discussions.

15. NHS England is grateful to Dr [redacted] for his leadership in the English HL community in promoting the return of the BV audit forms by his consultant peers.
16. NHS England acknowledges too the hard work and persistence in the SACT team at Public Health England in gathering the data which had to be done by paper, reminder letters and a fair bit of nagging. NHS England regards the rate of 88% return of audit forms as being an outstanding outcome for a large scale real world audit of outcomes and one that it hopes to publish with Public Health England and [redacted].

[redacted]
March 2018

Brentuximab Vedotin Patient Statement – [redacted]

I was diagnosed with Stage IVB Hodgkin's Lymphoma in July 2014 and I have been living with cancer ever since. I have had many treatments since then including three conventional chemotherapies, one allogenic stem cell transplant, several courses of radiotherapy and, for about a year in total, Brentuximab Vedotin.

The difference between Brentuximab Vedotin and a conventional chemotherapy is apparent as soon as the drug is administered. With conventional chemotherapy drugs, sitting in my chair at the chemo ward, I'd track the toxic treacle as it spread around my body and left extreme fatigue and acute nausea in its wake. The experience with Brentuximab was entirely different. It took half an hour to administer, instead of several, which meant less of my precious time was spent on the chemo ward. I was tired afterwards, but never even close to how I felt on chemotherapy.

Whilst on conventional chemotherapy, I was exhausted to the extent that I had to be cared for. Many mornings I couldn't get up and my Mum delivered porridge to me in bed. On Brentuximab, I was up at 6am to drive my partner to the station and my morning started there.

Brentuximab is administered once every three weeks which leaves plenty of time for living in between doses. I worked, almost full-time, as a teacher in a boarding school for three months whilst being treated with Brentuximab. Perhaps more importantly, I had the energy and the fitness to continue doing the things I love; sailing, skiing, walking, running, seeing family and friends and travel.

I am living with cancer and Brentuximab has enabled me to do that.

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma in adults with relapsed or refractory disease after at least two previous therapies when ASCT or multi-agent chemotherapy is not an option

ERG's assessment of the company's new evidence and response to the Cancer Drugs Fund review

[redacted]

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma in adults with relapsed or refractory disease after at least two previous therapies when ASCT or multi-agent chemotherapy is not an option – Cancer Drugs Fund review

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Rider on responsibility for report
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Contributions of authors:

Steve Edwards	Read and commented on draft versions of the ERG report. Guarantor of the report
Mariana Bacelar	Critical appraisal of the company's re-submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and wrote the health economic section of the report.
Charlotta Karner	Critical appraisal of the company's re-submission; critical appraisal of the clinical evidence; and wrote the clinical section of the report.

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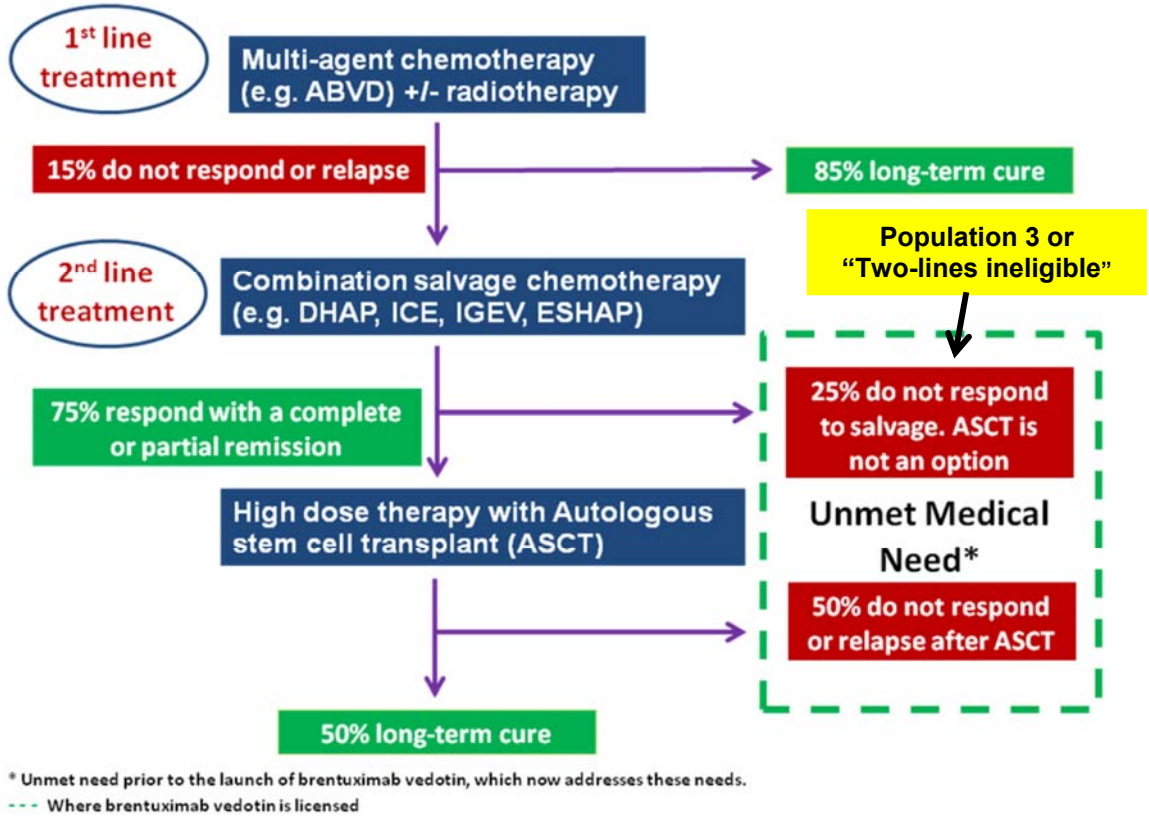
1 BACKGROUND

1.1 Critique of company's overview of service provision

Brentuximab vedotin (hereafter referred to as brentuximab) has been available in England since April 2013 through the Cancer Drugs Fund (CDF) for relapsed or refractory (r/r) CD30+ Hodgkin Lymphoma (HL) following autologous stem cell transplant (ASCT), or, following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. In June 2017, brentuximab was recommended for routine use in the NHS for patients who relapse post ASCT (referred to as 'Population 1' within TA446).[1] Brentuximab for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT ('Population 2' within TA446) was not recommended for use on the NHS. The third population within TA446 was recommended for continued use in the CDF and the current resubmission focuses on this indication, namely the treatment of r/r HL patients who have received at least two prior therapies but are ineligible for an SCT or multi-agent chemotherapy.

The company provides an overview of the treatment pathway for HL and the positioning of brentuximab in the pathway for the population relevant to this appraisal, presented in Figure 1 below. Patients, who do not respond to salvage chemotherapy and therefore would not be eligible for ASCT, would be eligible for treatment with brentuximab which may bridge patients to ASCT (Figure 1). Although not captured in the figure illustrating the treatment pathway, patients eligible for brentuximab also include patients with r/r HL for whom multi-agent chemotherapy is not a treatment option.

Figure 1. Simplified treatment pathway in HL showing where brentuximab vedotin is used for patients in Population 3 of TA446 (reproduced from company submission Figure 1)



1.1 Committee requests

The NICE technology appraisal committee of TA446 concluded that because of the uncertainty in the model structure, overall survival (OS) and progression free survival (PFS) following stem cell transplant (SCT), and post-treatment SCT rates after brentuximab and single-agent chemotherapy, it was difficult to determine a robust estimate of cost-effectiveness.[1] The committee therefore recommended brentuximab for use within the CDF for this indication (i.e. 'Population 3' of TA446) and a Data Collection Agreement was agreed between the company and NHS England (NHSE) for Public Health England (PHE) to undertake a retrospective collection of the post-treatment SCT rate for all relevant patients (i.e. those who were SCT-naïve) who had previously been treated with brentuximab for this indication through the CDF.[2]

It was not deemed feasible to collect data on the post-treatment SCT rate for single-agent chemotherapy, because brentuximab has become the standard treatment used in this setting in the UK (via the CDF).[2] The company, NHSE and NICE, therefore, agreed that these data would instead be informed by a consensus of clinical expert opinion from the National Cancer Research Institute (NCRI) Hodgkin lymphoma clinical study group. This was deemed by NHSE to be the best data source to supplement and/or validate that already provided by the company during TA446.

1.2 Company - new outcome data

As mentioned above, there was substantial uncertainty around OS and PFS following SCT in the original appraisal of brentuximab (TA446).[1] In addition, the company states that the model used to calculate the cost effectiveness of brentuximab for this indication is driven largely by: 1) the percentage of patients that can be successfully bridged to SCT with either brentuximab or single-agent chemotherapy; and 2) the long-term outcomes achieved by these patients following SCT. Therefore, the company has provided alternative data sources in their submission to inform the outcomes that are achieved after SCT.

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

This technology appraisal is a CDF review of TA446, covering one of the indication in the original appraisal: people with CD30+ HL following at least two previous therapies when SCT or multi-agent chemotherapy is not a treatment option, which was referred to as the "two lines ineligible population" or Population 3 in TA446. The company's proposed decision problem and rationale for any differences from the National Institute for Health and Care Excellence (NICE) final scope are presented in Table 1 in the company submission (CS) and discussed below.

The population and intervention, as addressed by the company, are in line with the NICE final scope. The comparator listed in the final scope is best supportive care. According to the company the treatment options for this population prior to the availability of brentuximab in the CDF included single-agent chemotherapy, palliative care (which may include radiotherapy for local relapse) or to attempt an ASCT with a very low probability of success. In TA446 single-agent chemotherapy was agreed to be the most appropriate comparator for brentuximab in this indication and it is the comparator used in this submission. The outcomes of interest listed in the final scope include: OS, PFS, objective response rate, complete remission, adverse effects of treatment, and health-related quality of life. This submission is solely focused on the SCT rate after brentuximab and single-agent chemotherapy, the outcome of the CDF data collection, and key drivers of the original model: OS and PFS post-ASCT and allogeneic SCT (allo-SCT).

3 CLINICAL EFFECTIVENESS

3.1 SCT rates after brentuximab therapy

3.1.1 Data in original review (TA446)

In the last assessment of brentuximab (company's response to the second appraisal committee meeting [ACM], TA446) the clinical effectiveness of brentuximab therapy for patients with two prior therapies and who were ineligible for SCT, was primarily based on data collected retrospectively for patients who were given brentuximab therapy through the CDF at 10 centres in England. This real-world observational evidence including 78 patients for whom data was collected on patient demographics and outcome data, including the rate of post-brentuximab SCT. In this study 58% of patients became eligible for SCT after treatment with brentuximab.

3.1.2 Data Collection of SCT rates post-brentuximab therapy

The retrospective collection of SCT rates was led and reported by the National Cancer Registration and Analysis Service (NCRAS) at PHE. The company provides a summary of the methods for the data collection, based on the report by PHE.[3] In summary, data were extracted from the NHS England CDF database for patients aged 18 or over who had a HL diagnosis and had an approved application through the CDF for the treatment of brentuximab between 1 April 2013 and 31 March 2016. A questionnaire was sent out to consultants named on the original CDF application form to request data on the treatment of these patients. The data collection period lasted for six weeks, and up to five reminders were sent to those consultants who had not returned the questionnaires.

The questionnaire was designed to provide information on:

- If the patient was relevant to this review, that is, if the patient was SCT-naïve and whether or not they received brentuximab;

- Outcome data; if the patients had been given brentuximab with the intention of bridging to an SCT, if the patient had an SCT or not, and whether the patients required salvage chemotherapy after brentuximab to bridge to an SCT.

3.1.3 Results - SCT rate post brentuximab

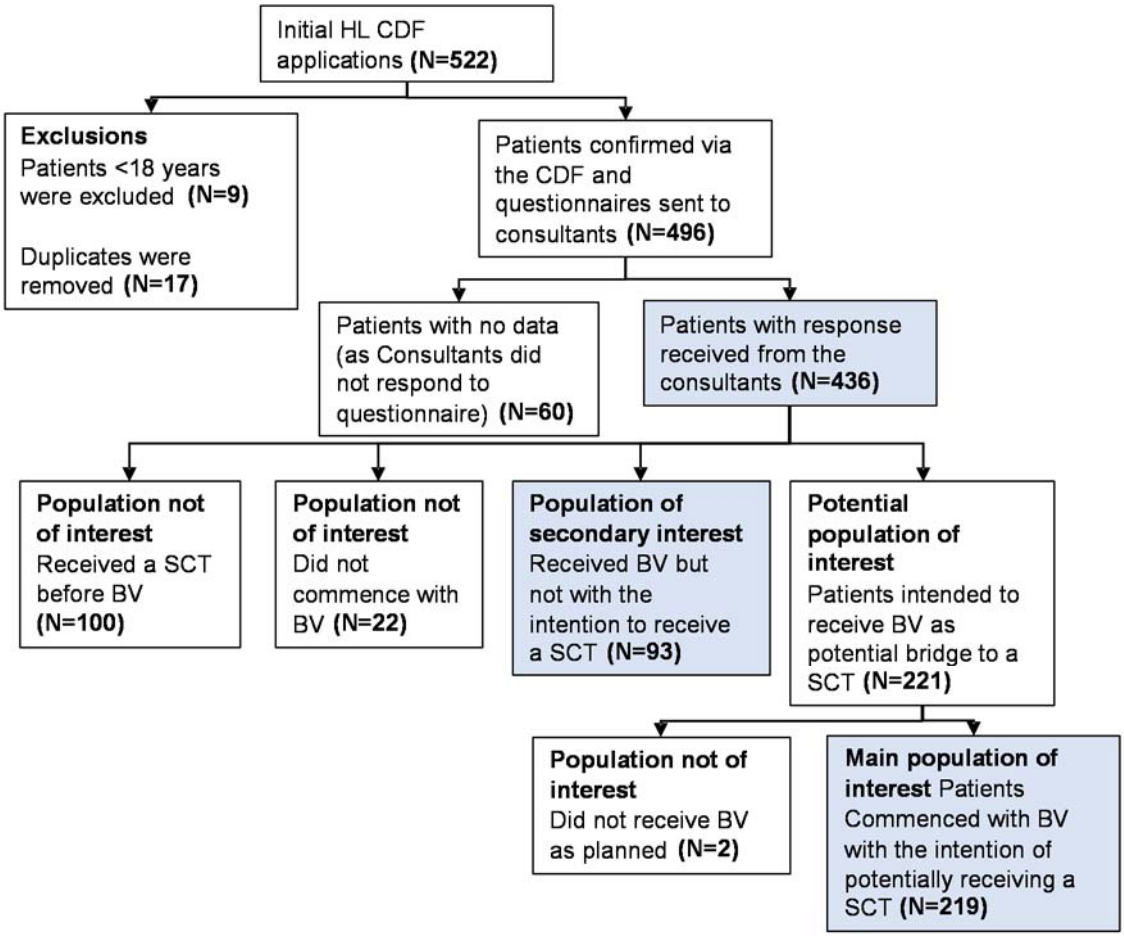
There were 522 initial applications made to the CDF, of which 496 HL patients received CDF funding for brentuximab (Figure 2). Questionnaires were sent to 223 consultants across 106 trusts in England to request data on the treatment of all the HL patients who received brentuximab treatment through the CDF. The response rate to the questionnaire was 88% (436/496), that is, no data are available for 60 patients.

Of the 436 patients for whom data were available, 22 patients did not commence brentuximab treatment and 100 patients received an SCT before brentuximab therapy. The ERG assumes that the 100 people who received an SCT before brentuximab belong to what was referred to as Population 1 (HL patients who relapse post-ASCT) in the original assessment of brentuximab (TA446), as from 2013 to 2016 brentuximab has been available for both Population 1 and 3 through the CDF. However, PHE did not request this information and the indication of these 100 patients can therefore not be confirmed. It is also unclear which population the 22 patients who did not commence brentuximab belonged to.

The remaining patients were all confirmed to be part of Population 3: patients following two prior therapies when SCT or multi-agent chemotherapy was not a treatment option. These patients, who were SCT-naïve when receiving brentuximab, were divided into two groups; patients who received brentuximab with the intention of bridging to SCT (221 patients) and patients who received brentuximab with no intention of bridging to SCT (93 patients). Two of the 221 patients in the former group did not receive brentuximab. Patients from this main population of interest (219 patients who commenced brentuximab therapy with the intention of bridging to SCT), who subsequently did bridge to SCT, were further divided into patients who had an SCT after brentuximab therapy (78 patients) and patients who had brentuximab followed by salvage chemotherapy before bridging to an SCT (50 patients).

Due to the limitations of the data collection questionnaire no baseline characteristics are available for the different groups of patients who applied for brentuximab therapy through the CDF. This means that it is not possible to confirm the population of the 100 patients who received an SCT before brentuximab or the 22 patients who did not commence brentuximab therapy. It is also not possible to confirm if all 219 patients who received brentuximab with the intension of bridging to SCT were PET-negative (i.e. had a complete response) before their SCT, as, according to the company, is standard practice in UK transplant centers. It also makes it impossible to evaluate the applicability of the populations in the Thomson *et al.* 2013[12] and the Reyal *et al*. 2016[13] studies, which inform the outcomes post ASCT and allo-SCT in the company model, to the CDF population (see Section 3.3 and 3.4).

Figure 2. Derivation of the population of interest from the initial CDF applications made for brentuximab for Hodgkin Lymphoma between April 2013 and March 2016 (reproduced from CS Figure 3)



Abbreviations: HL, Hodgkin lymphoma; CDF, Cancer Drugs Fund; SCT, stem cell transplant; BV, brentuximab vedotin

In the CS, the company reported the results as presented in the PHE report of the brentuximab data collection from the CDF. To calculate the rate of patients who bridged to SCT after brentuximab, PHE focused on the 219 patients who were given brentuximab with the intention of bridging to an SCT, which is referred to as the main cohort. The company also describes three sensitivity analyses as presented in the PHE report:

(i) Patients who commenced brentuximab with the intention of receiving an SCT (n=219) plus the 60 patients for whom there were no data (denominator = 279);

(ii) Patients who commenced brentuximab with the intention of receiving an SCT (n=219), plus the 93 patients who received brentuximab with no intention that they would receive an SCT (denominator = 312);

(iii) Patients who commenced brentuximab with the intention of receiving an SCT (n=219), plus the 93 patients who received brentuximab but with no intention of bridging to an SCT, plus the 60 patients for whom there were no data (denominator = 372).

Results for the main cohort and the three sensitivity analyses are presented in Table 1.

Table 1. Number and percentage of patients having an SCT for the different sensitivity scenarios, including a breakdown into the type of SCT and whether or not the patients required salvage chemotherapy after the brentuximab before the SCT (adapted form CS Table 5)

Number and percentage of patients having a SCT for the different scenarios				
	Main cohort: BV with intention of getting a SCT	(i) Main cohort plus Patients with no data	**(ii) Main cohort plus those given BV with no intention of a SCT**	(iii) Main cohort plus combination of (i) and (ii)
Denominator for each cohort	**219**	279	**312**	372
Underwent an allogeneic SCT	45 (21%)	45 (16%)	**45 (14%)**	45 (12%)
Underwent an autologous SCT	33 (15%)	33 (12%)	**33 (11%)**	33 (9%)
Had salvage CT after BV before SCT	50 (23%)	50 (18%)	**50 (15%)**	50 (13%)
Underwent SCT after BV[a]	**78 (36%)**	**78 (28%)**	**78 (25%)**	**78 (21%)**
Underwent SCT after BV +/- salvage[b]	**128 (58%)**	**128 (46%)**	**128 (41%)**	**128 (34%)**
[a] Patients who had BV and then a SCT straight afterwards [b] Patients who had BV then a SCT or BV then salvage chemotherapy and then a SCT				

The company focuses on the results from the second sensitivity analysis, of patients who were treated with brentuximab with or without the intension of bridging to SCT in their base case (SCT rate 25%), as this population is in line with the marketing authorisation of brentuximab; HL patients with two prior therapies who are ineligible for SCT or multi-agent chemotherapy. The company also presents a scenario analysis using sensitivity analysis (ii) including patients who received salvage therapy following brentuximab treatment (SCT rate 41%).

As the company highlights in the CS, the retrospective CDF data collection provides more robust evidence on the real world SCT rate that is achievable for patients who receive brentuximab than the data presented in the original STA, TA446. Interestingly, the data has also provided important

information about patients who aren't able to bridge directly to SCT after brentuximab, but brentuximab therapy has acted as a bridge to salvage therapy and subsequently SCT, which these patients otherwise would not have been eligible for.

The ERG agrees with the company that the most relevant population to the decision problem includes patients who were treated with brentuximab with and without the intention of bridging to SCT, as this reflects the population in the marketing authorisation. The ERG also agrees with the company that, to capture the full benefit of brentuximab, the rate of SCT post-brentuximab should be based on patients that did and did not have salvage therapy after brentuximab. That is, patients who had an SCT, whether it was straight after brentuximab or brentuximab therapy followed by salvage therapy, would not have received an SCT without brentuximab bridging to salvage or SCT. However, the ERG also considers that missing data needs to be accounted for and, therefore, the ERG considers the most relevant population to be based on sensitivity analysis (iii) including patients who received salvage therapy after brentuximab to bridge to SCT (SCT rate 34%). As PHE and the company points out, this is a conservative analysis, as it is highly unlikely that no patients for whom data are missing had an SCT after brentuximab. Analysis based on this sensitivity analysis, also builds on the assumption that all of the patients for whom there were no data were eligible for brentuximab in the relevant indication, i.e. SCT-naïve. However, the proportion of missing data is relatively large and therefore introduces a substantial amount of uncertainty in the accuracy of the estimated post-brentuximab SCT rate. The ERG has therefore taken a conservative approach in using this population as its base case, including the 60 patients with no data as no events (no SCT), to account for the uncertainty in the data and provide an estimate which should lower the risk for decision making.

3.2 SCT rates after single-agent chemotherapy

3.2.1 Data in original review (TA446)

In TA446, the company identified four studies published between 1982 and 2000, which assessed the efficacy of single-agent chemotherapy in HL patients similar to the population in the marketing authorisation for brentuximab in this indication.[4-7] The company pooled the study results of three of the studies (one study was excluded due to poor reporting), estimating the proportion of patients receiving SCT after single-agent chemotherapy to 5.3%. This was based on three events in 57 patients across the studies. The ERG considered the most recent of the studies, Zinzani *et al.* 2000,[8] likely to be the least flawed source for estimating the proportion of patients receiving SCT after single-agent chemotherapy. The proportion of patients receiving SCT reported in this paper was 14%, which the committee accepted as the most likely SCT rate, but highlighted the substantial uncertainty around this estimate.

3.2.2 Data collection of SCT rates post single-agent chemotherapy

The UK NCRI Hodgkin study group was approached by the company and NHSE and asked to form an opinion on the SCT rate that could be expected for r/r HL patients treated with single-agent chemotherapy, that is, patients that have had two prior therapies and are ineligible for SCT or multi-agent chemotherapy. In their response,[9] it was stated that the group had no experience of using single-agent chemotherapy with the intention of bridging to SCT in the relevant patient group. Single-agent chemotherapy would be used in a palliative setting with no intention of bridging to a potentially curative transplant. The group therefore did not feel able to estimate the SCT rate after single-agent chemotherapy. Instead the group reviewed the four studies put forward by the company for the second ACM.

Similar to the ERG in TA446, the group concluded that the quality of the evidence in these studies is low. The group went on to conclude that the studies could be considered equally representative in terms of the efficacy of the single-agent chemotherapy used. Therefore, the group did not agree with the decision at the second ACM of TA446, to focus solely on Zinzani *et al.* 2000,[8] as this study was not found to be more representative in this setting than the other three studies. All the studies are very old; Zinzani *et al.* 2000, which is the most recent one of the four, was still published 18 years ago. The group noted that the transplantation rate seen in Zinzani *et al.* 2000 with single-agent gemcitabine may be an overestimate of the transplantation rate that would be seen with this agent today; "*Front line and relapse treatments have improved to some extent since then, so patients with multiply relapsed disease now would be considered to have on average worse disease biology than patients relapsing 17 years ago. Outcomes with single-agent gemcitabine now therefore would be expected to be inferior compared with those seen 17 years ago.*" This observation could not be confirmed by any direct evidence, but the group makes a comparison with high grade lymphoma where relapse outcomes are worse in the modern era since the introduction of more efficient front line therapies, which cures more people but results in more of those who relapse having more challenging disease and therefore lower cure rates.

The group concluded that the transplant rate of 5.3% calculated across three of the studies is likely to be more representative than the transplant rate based on Zinzani *et al.* 2000 alone (14% transplant rate). The transplant rate of 5.3% has therefore been used in both the company's and the ERG's base case.

3.3 Outcome data after ASCT

3.3.1 Data in original review (TA446)

In TA446, the company used data from Sureda *et al*. 2001[10] for outcome data after ASCT. Sureda *et al.* 2001 is a retrospective observational study of 494 patients with r/r HL who received an ASCT at transplant centers in Spain between 1984 and 1998. It shows a 5-year survival rate post ASCT of 54.5%. The company highlights that this study is not representative of current UK transplant practice or the outcomes that are achieved following an ASCT in the UK today. The UK has adopted PET-based response adjusted strategies, where only patients who are PET negative, that is, who achieve a complete response prior to ASCT, will go on to receive an ASCT.[11] Sureda *et al.* 2001 included patients in complete remission (41%) as well as patients with sensitive disease (42%) and resistant disease (15%).

The ERG agrees with the company that outcomes post-ASCT for the population in Sureda *et al.* 2001 are likely to be worse than would be expected for the population of interest in UK clinical practice today. Although Sureda *et al.* 2001 is a large study, it included no UK centers and it is a historical study (all patients transplanted before 2000), which means that transplant practices are likely to be substantially different from what is used in the UK today.

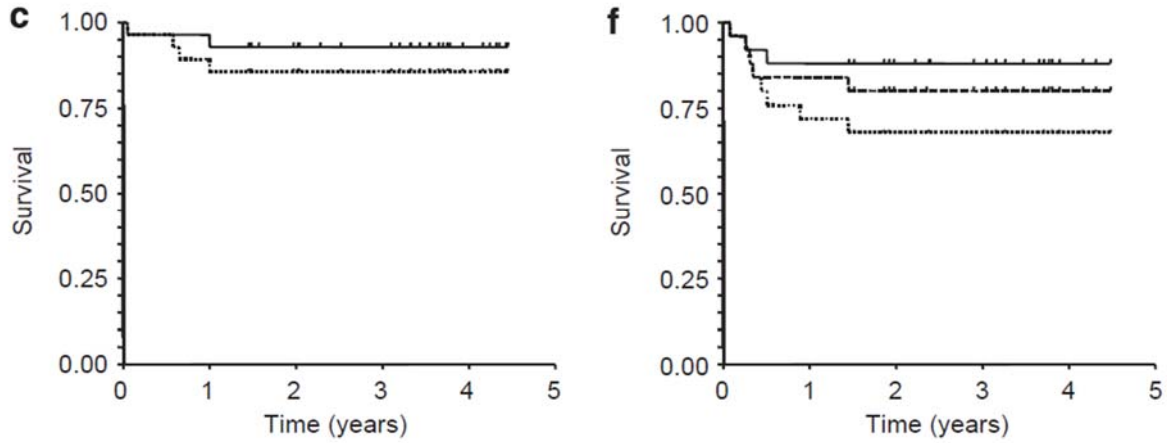
It is not explicitly stated in the publication what was used for determining response, though, as fed back from the ERG's clinical expert, "*PET was not in routine use in 2001 so 'complete remission' was defined by CT. There is a significant discordance between PET and CT results in Hodgkin lymphoma".*

In the original submission of TA446, and in the treatment pathway illustrated by the company Figure 1, the company report the cure rate after ASCT to be around 50%. However, no references were provided for this estimate. According to the ERG's clinical expert, this estimate is likely derived from estimates before PET adaptation, as in Sureda *et al.* 2001. The ERG's clinical expert estimates that for patients who are in complete remission prior to ASCT, the cure rate may be 75-80%.

3.3.2 New data after ASCT

To include outcome data post-ASCT which is more representative of UK clinical practice than the previously used Sureda *et al.* 2001,[10] the company use data from Thomson *et al.* 2013.[12] This study evaluated a PET-directed transplant strategy and included 61 patients with r/r HL who received salvage therapy between November 2007 and December 2010 at University College London. Of these, 28 patients eventually had a complete metabolic response and went on to receive an ASCT. For the patients who received an ASCT, 3-year OS and PFS were 92.9% and 85.7%, respectively (Figure 3). Of the remaining 33 patients, seven patients died of disease progression and 25 patients proceeded to receive an allo-SCT with a 3-year OS and PFS of 88.0% and 68.0%, respectively (Figure 3).

Figure 3. Survival outcomes, OS and PFS, following c) ASCT, and f) allo-SCT (Thomson *et al.* 2013)



c) overall survival (solid), and PFS (dot),
f) overall survival (solid), PFS (dot) and current PFS (dash)
Abbreviations: allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; OS, overall survival; PFS, progression free survival

The ERG agrees with the company that Thomson *et al.* 2013[12] is highly relevant to this appraisal as it is a UK study following UK clinical practice, that is, a PET-response-adjusted transplantation strategy, and as mentioned in the previous section, the results of Thomson *et al.* 2013 are in line with the estimate of the ERG's clinical expert (i.e. 75-80% cure rate for patients who are in complete remission prior to ASCT). However, the ERG notes that the sample size of relevant patients, is very small (28 patients), and although the follow-up is up to 4.5 years, the data are very immature and suffer from substantial censoring, which makes any extrapolation of the data highly uncertain (Figure 3). Due to the inherent uncertainty in the Thomson *et al.* 2013 data, the ERG has taken the conservative approach to use the outcome data after allo-SCT from Reyal *et al*. 2016,[13] described in Section 3.4.2, which is more mature and is based on a larger sample size, to inform the outcomes after ASCT in the economic model (add ref to HE section). As seen in Thomson *et al.* 2013, the outcomes for patients after ASCT are better than those for patients after allo-SCT (Figure 3), and therefore the ERG's analysis using outcome data for allo-SCT to inform the outcomes after ASCT, provides a more robust, although conservative, estimate.

3.4 Outcome data after allo-SCT

3.4.1 Data in original review (TA446)

In TA446, outcomes after allo-SCT were informed by Sureda *et al.* 2012,[14] a prospective phase II study in ten centres in Spain, Switzerland and Sweden, looking at allo-SCT in relapsed HL. A total of 92 patients were recruited from 2000 to 2007. All patients received salvage chemotherapy; 14 patients died from progressive disease and 78 patients proceeded to allo-SCT, of which 50 were in complete or partial

remission and 28 had stable disease. For the allografted population, 4-year PFS and OS rates were 24% and 43%, respectively.

As the company points out, the main issue with Sureda *et al.* 2012 is that 86% of the included patients had failed a previous ASCT prior to receiving allo-SCT, which is in contrast to the population of interest to this appraisal of survival outcomes after allo-SCT for r/r HL patients who are SCT-naïve. No data is reported in Sureda *et al.* 2012 on the subgroup of patients who were SCT-naïve.

The ERG agrees with the company's conclusion that this non-UK study is not representative of the population of interest or the likely outcomes expected in UK clinical practice after allo-SCT.

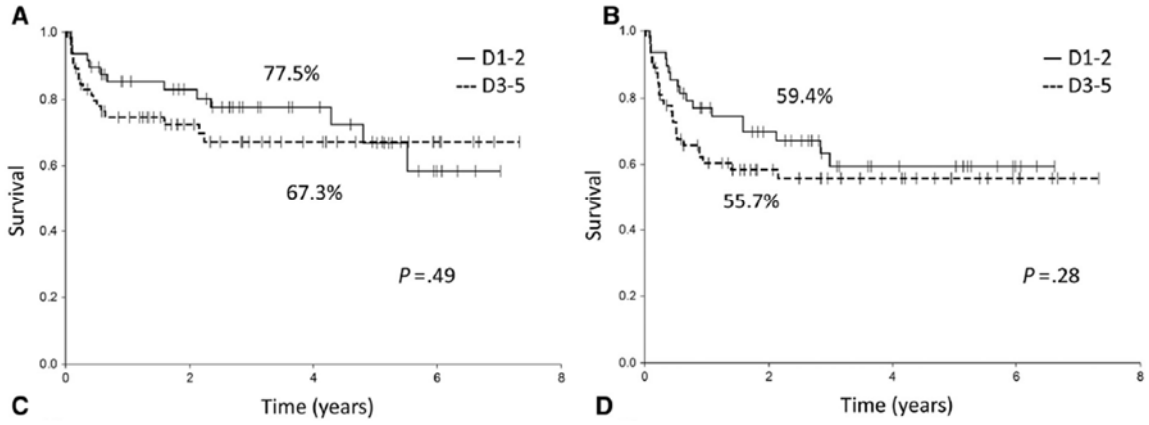
3.4.2 New data after allo-SCT

In the current submission, the company uses an alternative data source to Sureda *et al.* 2012[14] to inform the outcomes post allo-SCT, Reyal *et al.* 2016.[13] This is a retrospective study of 116 HL patients who received allo-SCT at four UK transplant centres between 2005 and 2015. Patients in this study were transplanted using one of two different alemtuzumab-containing regimens. According to the ERG's clinical expert, alemtuzumab is the most frequently used regimen in the UK. According to the company, differences in transplantation platforms are likely to have a substantial effect on survival outcomes. Hence, data on outcomes using an alemtuzumab-based platform, as in Reyal *et al.* 2016, is more relevant to UK practice than the transplant platform used in Sureda *et al.* 2012, which was not alemtuzumab-based.

In Reyal *et al.* 2016, 26% of patients had received a prior ASCT. However, the company uses data for the subgroup of patients who were SCT-naïve, which were provided by one of the authors of Reyal *et al.* 2016. In the full study population, 4-year OS for patients with a complete response (PET-negative) prior to allo-SCT was 77.5%; for patients with residual disease (PET-positive) prior to allo-SCT, the 4-year OS rate was 67.3% (Figure 4). The corresponding rates for PFS at 4 years was 59.4% for PET-negative patients and 55.7% for PET-positive patients (Figure 4). In the subgroup of patients with no prior ASCT, the 4-year OS and PFS rates were [redacted] and [redacted], respectively (Figure 5). [redacted] of the ERG's clinical expert, who estimated long term PFS rate after allo-SCT to 60-70% for patients who have not had a prior ASCT. The ERG's clinical expert also commented that allo-SCT in SCT-naïve patients is fairly unique to UK practice. The ERG's clinical expert also stated that outcomes after allo-SCT are better in patients who are less heavily pre-treated, that is, the long term PFS rate after allo-SCT for patients who have previously failed ASCT is expected to only be 50-60%.

The ERG agrees with the company that the subgroup of Reyal *et al*. 2016, including SCT-naïve patients, provides outcome data for allo-SCT that is highly relevant to current UK transplant practice.

Figure 4. Survival outcomes after allo-SCT, according to pre-transplant Deauville score (Reyal *et al.* 2016)



(A) OS, (B) PFS. Deauville score D1-2, PET-CT negative, mCR; Deauville score D3-5, PET-CT positive, residual disease. Percentages on graph show 4-year rates for each outcome.
Abbreviations: allo-SCT, allogeneic stem cell transplant; mCR, metabolic complete response; OS, overall survival; PFS, progression free survival

Figure 5. Survival outcomes after allo-SCT, according to prior ASCT (Y/N) (Takeda data on file, subgroup analysis from Reyal *et al*. 2016)[13]

[redacted]

3.5 Conclusions of the clinical effectiveness section

- SCT rate after brentuximab therapy:
    - PHE has undertaken a retrospective collection of the post-treatment SCT rate patients who had been treated with brentuximab through the CDF.
    - From the PHE data collection, the company uses the SCT rate of patients who were treated with brentuximab with or without the intension of bridging to SCT in their base case (SCT rate 25%), as this population is in line with the marketing authorisation; patients with r/r HL after at least 2 prior therapies and who are ineligible for SCT or multi-agent chemotherapy. The company also presents a scenario analysis including patients who received salvage therapy following brentuximab treatment (SCT rate 41%).

- The ERG agrees with the company that the most relevant population includes patients who were treated with brentuximab both with and without the intention of bridging to SCT, and to capture the full benefit of brentuximab the rate of SCT post-brentuximab need to include both patients that did and did not have salvage therapy after brentuximab, as in the company's scenario analysis. However, the proportion of missing data is relatively large and therefore introduces a substantial amount of uncertainty in the accuracy of the estimated post-brentuximab SCT rate. The ERG considers using the SCT rate for the same population as in the company's scenario analysis, but also taking into account the 60 patients with missing data (SCT rate 34%), as the estimate associated with the lowest decision risk but acknowledges that it is likely to be a conservative estimate.

- SCT rate after single-agent chemotherapy:
  - The UK NCRI Hodgkin study group was asked to form an opinion on the SCT rate that could be expected for r/r HL patients treated with single-agent chemotherapy. The group concluded that the transplant rate of 5.3%, based on three historical studies put forward in TA446, was reasonable.

- Outcome data after ASCT:
  - Thomson *et al.* 2013 has been presented by the company as a more relevant reflection of current UK transplant practice than Sureda *et al.* 2001, which was used to inform outcomes after ASCT in TA446. However, data from Thomson *et al.* 2013 are very immature and the sample size of the study is small. Therefore, the ERG has preferred approach is to use the outcome data after allo-SCT from Reyal *et al*. 2016, which is more mature and is based on a larger sample size, to inform the outcomes after ASCT.

- Outcome data after allo-SCT:
  - Data for the subgroup of SCT-naïve patients from Reyal *et al.* 2016, put forward by the company, provides outcome data for allo-SCT that are highly relevant to current UK transplant practice, which is therefore used in the economic model in preference to Sureda *et al.* 2012, which was used to inform outcomes after ASCT in TA446.

4 COST-EFFECTIVENESS

In response to the final appraisal determination of TA446, the company has provided an updated economic model, incorporating the CDF review results. The changes made to the economic model consist on the following:

1. Changing the model structure and data implementation in the model, through the introduction of tunnel states;
2. Changing the model's structure to incorporate a post-SCT progression health state;
3. Estimating the costs and benefits associated with the post-SCT progression health state;
4. Updating the data sources used to model overall survival after alloSCT and ASCT;
5. Updating the estimate relating to the proportion of patients bridging to SCT after brentuximab, and chemotherapy.

4.1 Implementation of tunnel states in the model

The CS reports that while updating the economic model, the company found an implementation error in the model. The company considered the fact that the transitions from health states in the model did not take into account the change in risk over time, depending on when a patient moved into a health state, was a model error. Therefore, the company introduced tunnel states in the model, to account for how long a patient has been in a certain health state.

As a result of this change in the model, the volume of code needed increased substantially and with it, the model complexity. The company decided to extend the cycle length from seven to 28 days, in order to minimise the number of tunnel states required. The increase in model complexity means that running the model results now takes 90 minutes and probabilistic sensitivity analysis (PSA) is no longer feasible as it would take two months to run.

ERG's critique

The ERG is extremely concerned with the structural, and implementation changes applied by the company to "correct" the model. The changes implemented by the company led to an extreme loss in model efficiency, leaving the ERG's ability to change model parameters severely impaired. Furthermore, and linked to the latter issue, the ERG could not conduct a proper review of the updated model. The volume of code, size of the model and its running time turned the model into a "black box", which the ERG could not validate in the time available.

More importantly, the ERG sees no possible justification for the rationale behind the changes in the economic model. In their reply to the clarification questions, the company stated that, "*It was necessary to change the model to account for changes in risk over time* […]. *For example, the hazard of dying after SCT is clearly not constant (the KM curves plateau). The risk of death post-SCT is therefore conditional on the duration of time that has elapsed since the patient has had an SCT. If this correction had not been implemented, the model estimation process would have been incorrect with a direction of bias that is difficult to predict and which could change depending on model settings.*"

The change in the risk of death over time after SCT, is accounted for in the underlying hazard of the survival curve fitted to the overall survival (OS) KM data. It is rare to see constant hazards in most survival models used in technology appraisals, yet this is an issue mitigated through fitting different, and appropriate survival curves to KM data, which can take into account time-changing hazards. The introduction of tunnel states in the model to address this issue is highly flawed, considering its detrimental impact on model efficiency and transparency. Furthermore, the fact that the new model does not allow PSA to be run within a reasonable amount of time is concerning, as joint parameter uncertainty cannot be explored in the analysis.

Finally, the ERG cannot guarantee that additional changes (other than the ones reported in the CS) were not incorporated into the updated model. The incorporation of the tunnel states in the model meant that most data implementation is now through VBA coding, which would be unfeasible to fully review in the available time.

In conclusion, the ERG considers that basing the economic analysis in the new model carries a very high risk, and thus the model submitted by the company is unfit for purpose. Therefore, the ERG had to revert to the previous version of the company's model. This approach is to some extent, problematic, as the company's old model has structural issues related with the treatment pathway. Namely, the previous model did not follow patients' disease progression after SCT. The ERG tried to mitigate this issue, to some extent, and describes the approach taken in the following sections.

4.2 Changing the model structure to incorporate a post-SCT progression state

The company's updated model is reported in Figure 6. The company added the post-SCT health state into the economic model and replaced the palliative care state by the end of life (EOL) state. While conceptually the updated model structure provides an improvement from the company's previous model (Figure 7), as it incorporates the post-SCT disease progression (PD) state, the ERG advises against the use of this model to run the cost-effectiveness analysis, for the reasons explained in the previous section.

Figure 6. Revised model diagram

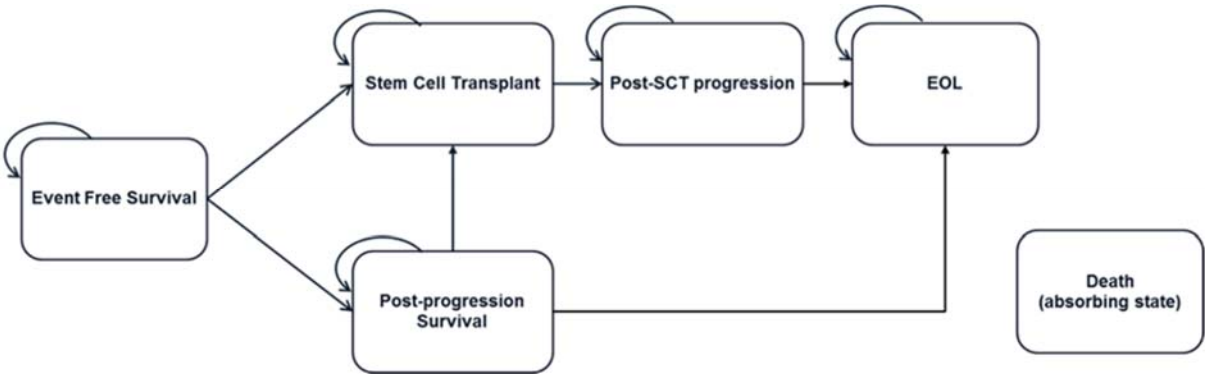
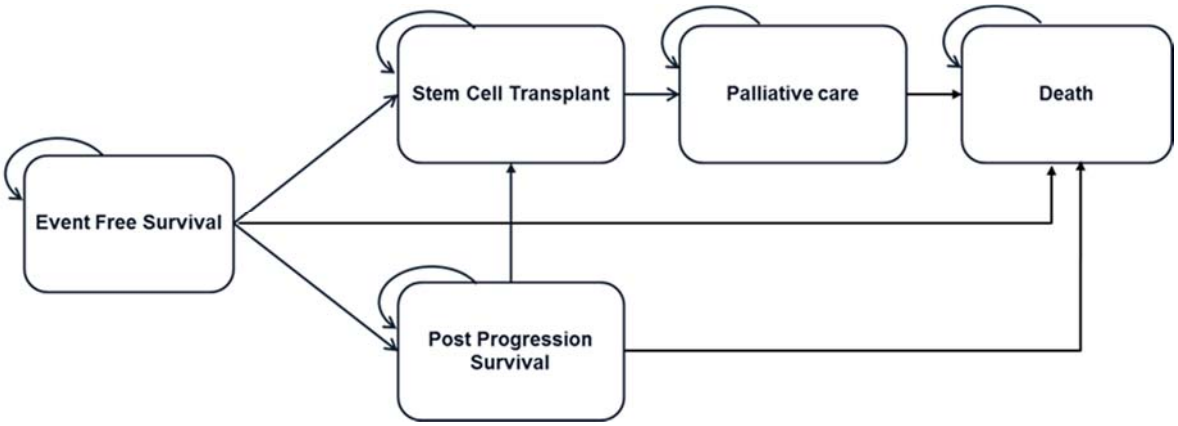


Figure 7. Previous model diagram



Nonetheless, the new data used to model the post-SCT PD state are useful, as they provide insight on patients' time to progression after ASCT (Thomson *et al*. 2013)[12] and alloSCT (Reyal *et al*. 2016).[13] These data are described in Section 3.3 and Section 3.4, respectively.

The company fitted survival models to the KM progression-free survival (PFS) from Thomson *et al*. 2013 and Reyal *et al*. 2016. A Gompertz model was used to model PFS after alloSCT and after ASCT. The company provided measures of statistical fit and presented different models for visual inspection against KM curves in Appendix A (for alloSCT) and Appendix B (for ASCT) of the CS.

It appears that the KM curves presented in the appendixes of the CS are mislabelled, and not matching the PFS data reported in Reyal *et al*. 2016. The labelled ASCT OS and PFS curves seem to be the alloSCT OS and PFS curves. As the reported Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) do not seem to match the respective curves, therefore, it is unclear if the right fit statistics were derived for the right dataset (i.e. ASCT and alloSCT).

Additionally, it appears that the PFS KM and respective fitted curves for alloSCT are being taken from the entire population in Reyal *et al*. 2016 (Figure 8), as opposed to the subgroup of patients provided in the Peggs subgroup analysis (yellow curves in Figure 5). This is inconsistent with the data taken for OS

post-alloSCT, which is based on the subgroup analysis of Reyal *et al.* 2016, for SCT-naïve patients. The ERG's conclusion is based on the fact that the company uses the entire population curve from Reyal *et al*. 2016 to compare to the fitted Gompertz curve in the model (Figure 9).

Figure 8. Kaplan-Meier data used in the company's model for alloSCT

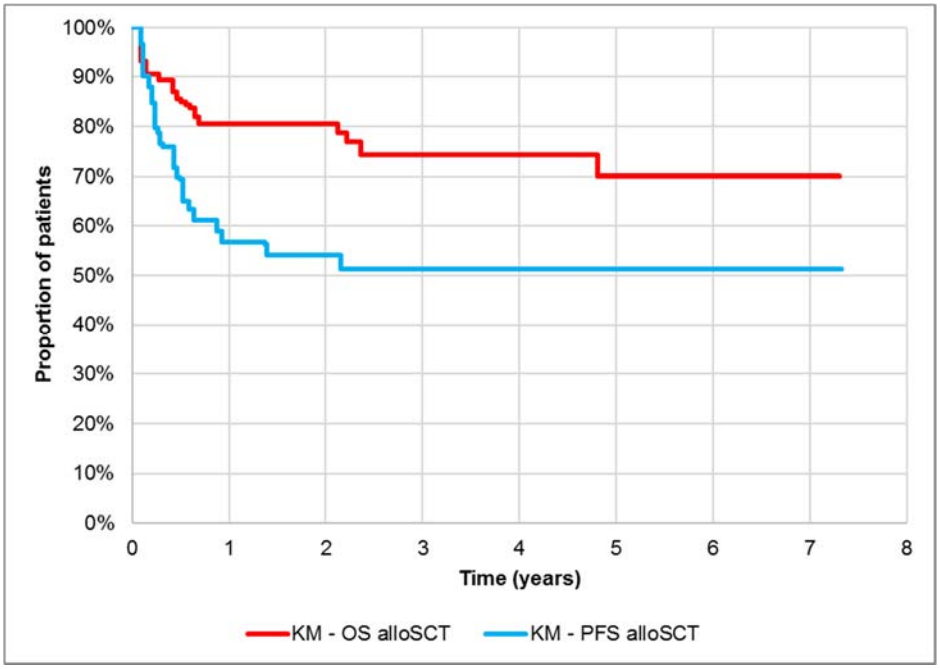


Figure 9. Survival curves used in the company's model for alloSCT

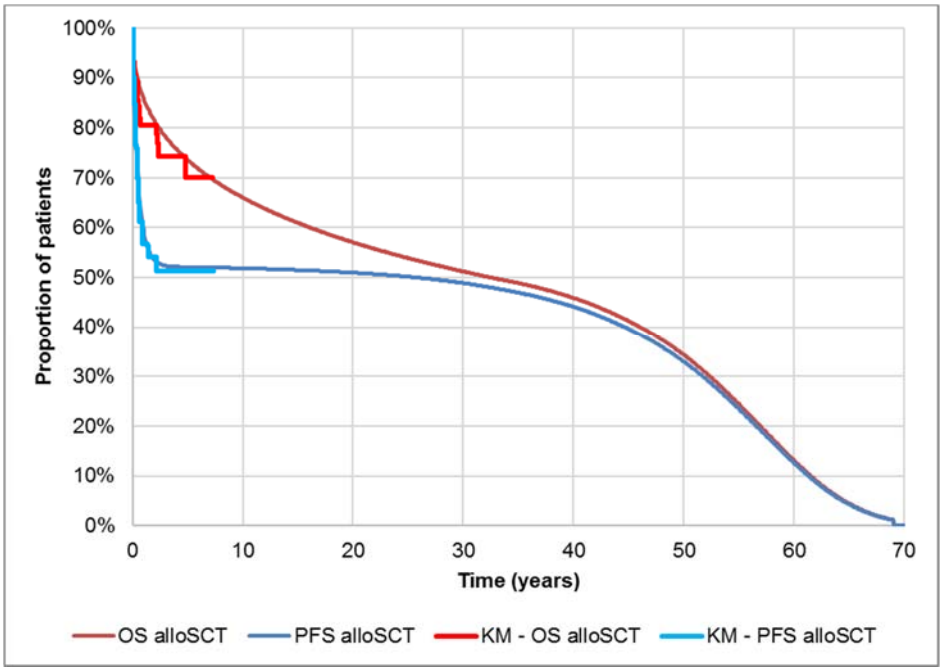


Figure 10. Takeda data on file (subgroup analysis from Peggs on Reyal *et al*. 2016 data)

Overall, the ERG notes that the KM PFS data in Reyal *et al*. 2016 are more pessimistic than the PFS predictions for the naïve group of patients in the Peggs subgroup analysis. Therefore, using the former in the analysis leads to conservative results, as patients progress quicker than expected if the former were used. Thus, the impact on using the correct patient population would likely decrease the final ICER.

Given that the issues aforementioned are based on ERG's assumptions resulting from the investigation of the economic model, the ERG notes that the results may be substantially different depending on if:

1. The AIC and BIC statistics were derived using the right data;

2. The right dataset was used to model post-alloSCT PD.

ERG's critique

The ERG disagrees with the method used to implement disease progression into the economic model. The PD state was not directly modelled from the PFS and OS datasets from Thomson *et al*. 2013 and Reyal *et al*. 2016, but instead derived as a mean value. After estimating mean time to progression (from the PD survival curve) the company then used this value to estimate the proportion of time spent in PD in relation to the time spent alive. Then in each model cycle, the proportion of patients estimated to be in the post-SCT state is calculated as per the following formula:

(proportion of patients who received a SCT– number of patients who go into the EOL state) * proportion of time spent in progressed disease

The company justifies this approach by stating that applying a proportion of time spent in the PD state every cycle, to estimate the proportion of patients progressing after SCT was a means to avoid the further multiplication of tunnel states in the model. This reinforces the ERG's view on the lack of appropriateness of employing tunnel states. The trade-off between not properly modelling PFS and PD states post-SCT; and having tunnel states in the model is completely unjustified given that modelling disease progression after SCT was one of the priorities for the updated analysis.

Given the practical impossibility of changing the company's updated model, the ERG used the post-alloSCT and post-SCT data provided in the CS to update the estimated costs and QALYs expected after SCT. In order to use the OS and PFS survival data for post-SCT patients, the ERG had to adapt the time unit of the estimated Gompertz curves, to match the 7-days cycle in the previous model, compared to

the 28-days cycle employed by the company in the updated model. The ERG's method is described in more detail in the next section.

4.3 Costs and benefits associated with post-SCT PD

4.3.1 Costs associated with post-SCT PD

The company's analysis incorporated costs of disease progression after ASCT (Table 2) and after alloSCT (Table 3). The proportion of patients receiving each treatment, and the associated costs were informed by clinical expert opinion provided to the company. It was also assumed that after progression, patients receive the treatments reported in Table 2 and Table 3 for a mean duration of two months.

Table 2. Cost of disease progression after ASCT

Item	Proportion of patients	Cost per treatment cycle
GEM-P (Gemcitabine, cisplatin, methylprednisolone)	33%	£119
IVE (Ifosfamide, epirubicin, etoposide)	33%	£1,659
Bendamustine + steroids (assumed dexamethasone)	33%	£6,240
Treatment administration	100%	£322
Total	-	£8,340
Weighted total	-	**£2,995**

Table 3. Cost of disease progression after alloSCT

Item	Proportion of patients	Cost per treatment cycle
Gemcitabine & methylprednisolone	25%	£101
Bendamustine + steroids (assumed dexamethasone)	25%	£6,240
Donor lymphocyte infusion	50%	£7,100
Treatment administration	50%	£322
Total	-	£5,457
Weighted total	-	**£5,296**

ERG's critique

The ERG could not obtain clinical expert opinion to validate the assumptions made by the company to estimate the costs related with post-SCT PD. Therefore, the ERG recommends that the Appraisal Committee discusses the clinical validity of the assumptions made by the company in terms of the distribution of patients receiving each treatment; the costs of treatment; and treatment duration (two months) as these assumptions are likely to have a considerable impact on the final ICER.

In order to incorporate these costs into the company's previous model, the ERG had to make a few assumptions, as the model did not include the post-SCT PD health state. Therefore, the ERG had to calculate mean PD costs, to add to the total costs associated with brentuximab and chemotherapy.

Firstly, the ERG calculated the total cost of PD after ASCT and alloSCT by taking the total weighted costs reported in Table 2 and Table 3, respectively, and multiplying these by mean time on treatment (two months as per company's assumption). The ERG then calculated the number of newly progressed patients in each model cycle, after SCT, and multiplied the proportion of newly progressed patients in each cycle by the total cost of PD after ASCT and alloSCT. Newly progressed patients were estimated through the manipulation of the OS and PFS data provided by the company for SCT (fitted with the Gompertz model and adjusted to reflect the 7-days model cycle length in the previous model).

The ERG used the OS and the PFS data provided in the company's updated model from Reyal *et al*. 2016 to estimate newly progressed patients after alloSCT. The ERG used the same data to estimate newly progressed patients after ASCT. The reason for using the OS and PFS data from Reyal *et al*. 2016 to model survival outcomes after ASCT (and not Thomson *et al*. 2013) relates to the immaturity and uncertainty around the Thomson *et al*. 2013 study (as discussed in Section 3.3.2).

Finally, the ERG discounted, and summed all the cycle costs and then weighted the final sum by the proportion of patients receiving ASCT (42.2%) and alloSCT (57.8%) and subsequently, by the proportion of patients bridging to SCT in the brentuximab arm and in the chemotherapy arm, respectively. These costs were then added to the final costs associated with each treatment. The impact of the ERG's analysis is reported in Section 6.

4.3.2 Utility associated with post-SCT PD

The company used a utility of 0.38 to estimate quality of life in the post-SCT PD health state. This value was chosen as it is the same estimate as the one used in the disease progression state (before SCT) in the company's original model.

ERG's critique

The ERG agrees with the value used by the company. Similar to the cost estimation, the ERG had to incorporate the quality of life estimation into the previous company's model. Therefore, the ERG estimated the PD curve by subtracting the PFS from the OS curve from Reyal *et al*. 2016, in order to estimate the proportion of progressed patients after alloSCT in each model cycle. These data were also used to estimate the proportion of progressed patients after ASCT (as explained in the previous subsection of the report). The ERG proceeded to estimate the mean time spent on the progression-free state and on the progression state (taken from the PFS and PD curves, respectively) after SCT. These values amounted to 30 and 3 years, respectively.

These values were then used to generate a weighted post-SCT PD utility value as reported in Table 4. The final utility value of 0.73 compares with the company's previous utility value of 0.77 and the ERG's

previous exploratory utility value of 0.50 (as discussed in the final appraisal determination document of TA447). The key driver of the weighted utility estimate is the mean time spent in the PFS and in the PD sates. Considering that the company's new data for survival outcomes after SCT show a considerable survival benefit compared with the ones used in the previous submission (Sureda *et al.* 2012), the ERG's estimated utility value increased substantially.[10] The impact on the final ICER is reported in Section 6.

Table 4. Estimation of post-SCT PD value undertaken by the ERG

Time	Utility value	Source	Time spent (in years)	Source	Proportion of patients	Source	Weighted total
Up to 14 days following SCT	0.42	Company's previous submission	0.04	Calculation 14 / 365.5	0.13%	Post-SCT PFS curve	0.00
14 days-3 months following SCT	0.60	Company's previous submission	0.21	Calculation (30.5*3 – 14) / 365.5	0.68%	Post-SCT PFS curve	0.00
After 3 months following SCT and progression-free	0.77	Company's previous submission	29.41	Calculation 30 - (30.5*3 - 14)] / 365.5	99.19%	Post-SCT PFS curve	22.46
Post-SCT disease progression	0.38	Company's previous submission	3.16	PD curve	100.00%	Post-SCT PD curve	1.20
Total	-	-	32.57	-	-	-	23.67
Final utility	-	-	-	-	-	-	23.67 / 32.57 = **0.73**
Abbreviations: SCT: stem cell transplant; PD: disease progression; PFS: progression-free survival							

4.4 Overall survival after alloSCT and ASCT

The company fitted survival models to the KM OS data from Thomson *et al*. 2013 and Reyal *et al*. 2016 (Peggs subgroup). A Weibull model was used to estimate OS after alloSCT and a Gompertz model was used to estimate OS after ASCT. The company provided measures of statistical fit and presented different models for visual inspection against KM curves in Appendix A (for alloSCT) and Appendix B (for ASCT) of the CS.

Figure 11 shows the OS KM curve from the Peggs analysis of the SCT-naïve patients in Reyal *et al*. 2016, together with the Weibull curve fitted to the data; and the final curve used in the model. The Weibull curve was capped by the general population background survival curve, hence the divergence in the curves from about 40 years onwards.

The ERG incorporated the post-SCT OS curve from Reyal *et al.* 2016 in the company's previous economic model to replace the Sureda *et al.* 2012 data. The results are presented in Section 6.

Figure 11. Overall survival KM data from Reyal *et al*. 2016 and modelled curves (alloSCT)

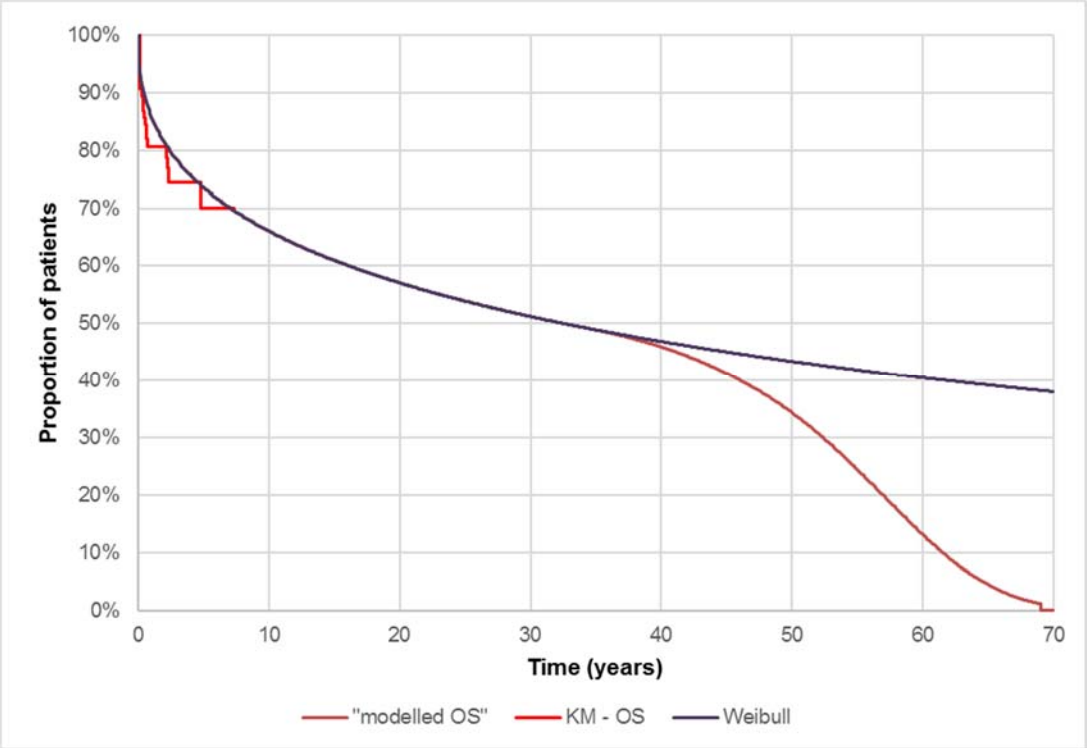
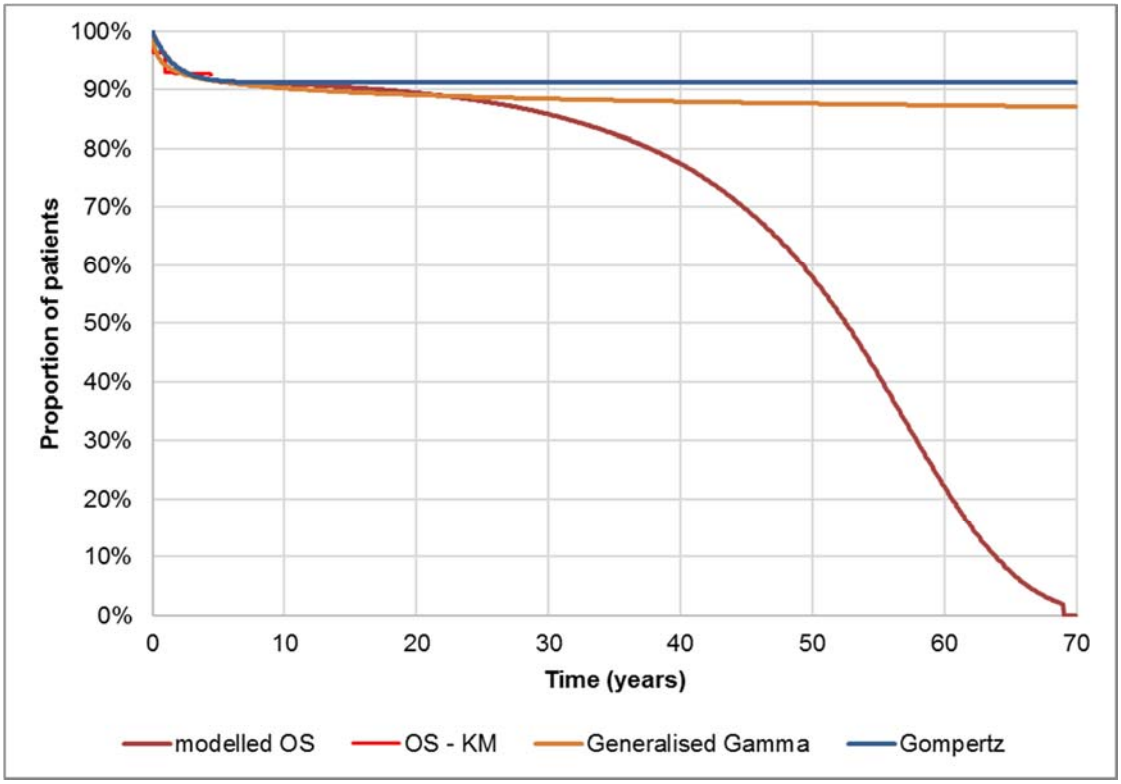


Figure 12 shows the OS KM curve from Thomson *et al*. 2013, together with the Gompertz curve fitted to the data; and the final curve used in the model. The Gompertz curve was capped by the general population background survival curve, hence the divergence in the curves from about year 5. Due to the immaturity of the survival data in Thomson *et al*. 2013, the background survival curve crossed the fitted OS curve very early on, reflecting the uncertainty in the fitted survival curves. The ERG notes that the Gompertz curve is one of the worst fitting curves to the OS KM data. The company justified using the Gompertz curve due to its more clinically plausible tail. Nonetheless, because the curve crosses with the background survival curve very early in the analysis, the tail of the Gompertz curve is not used in the analysis. The generalised gamma function, for example, would have been a better fit to the KM curve and still provided a very similar survival tail (estimated by the background mortality). Nevertheless, given that the ASCT data were not used in the ERG analysis, the curves used to model the OS KM ASCT data do not have an impact on the ERG's analysis using the company's previous model.

Figure 12. Overall survival KM data from Thomson *et al*. 2013 and modelled curves (ASCT)



4.5 Proportion of patients bridging to SCT after brentuximab and chemotherapy

The company's base case analysis assumed that 25% of brentuximab patients bridge to SCT, reflecting the group of patients in the CDF dataset who bridged to SCT directly from brentuximab. The company also undertook sensitivity analysis using the SCT rate of 41%, reflecting the overall transplantation rate that could be achieved in clinical practice if salvage chemotherapy is given after brentuximab (in this scenario the company has also included the cost of the additional salvage chemotherapy that was administered to 16% of the patients).

The cost of salvage therapy, described in Table 5, was multiplied by the proportion of patients receiving salvage chemotherapy (16% in company's scenario analysis), and by the assumed treatment duration of two cycles of treatment (2 months).

Table 5. Cost of salvage chemotherapy

Item	Proportion of patients	Cost per treatment cycle
GEM-P (Gemcitabine, cisplatin, methylprednisolone)	14%	£119
Bendamustine	32%	£6,211
Mini-BEAM (Carmustine, etoposide, cytarabine, melphalan)	54%	£6,539
Treatment administration	100%	£322
Total	-	£8,340

Weighted total	-	**£5,867**

With regards to the proportion of patients bridging from chemotherapy to SCT, the company used the 5.3% estimate, as agreed with NHS England.

ERG's critique

The ERG could not obtain clinical expert opinion to validate the assumptions made by the company to estimate the costs related with salvage chemotherapy. Therefore, the ERG recommends that the Appraisal Committee discusses the clinical validity of the assumptions made by the company in terms of the distribution of patients receiving each treatment; the costs of treatment; and treatment duration (two months) as these assumptions are likely to have a considerable impact on the final ICER.

During the inspection of the company's updated the model, the ERG found that the company also included the costs of salvage chemotherapy in the comparator arm of the economic model. Given that patients receiving chemotherapy (instead of brentuximab) cannot receive subsequent salvage chemotherapy to bridge to SCT, the ERG does not see a clinical rationale for including these costs in the chemotherapy arm of the model.

As explained in Section 3.1, the ERG's preferred estimate for the proportion of brentuximab patients bridging to SCT is 34% (with 13% of those getting salvage chemotherapy). Therefore, the ERG ran a scenario analysis using this estimate and as a scenario analysis, the ERG changed this parameter to be 21%. Results of the ERG analysis are reported in Section 6.

5 RESULTS

The company's updated results are reported below in

Table 6. The ICER for brentuximab compared with single agent chemotherapy amounts to [redacted] per QALY gained. Brentuximab has a patient access scheme (PAS) of [redacted], driving the ICER down to £16,535 in the company's base case (Table 7). Table 8 shows that the considerable benefit associated with brentuximab, stems mainly from the incremental life years gained through SCT, particularly ASCT (more than 5 years and roughly 4 years, incrementally).

Table 6. Company's base case results

Therapy	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER
Chemotherapy	[redacted]	[redacted]	4.43				
Brentuximab	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	[redacted]
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 7. Company's base case results with PAS

Therapy	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	ICER
Chemotherapy	[redacted]	[redacted]	4.43				
Brentuximab	[redacted]	[redacted]	12.28	[redacted]	[redacted]	7.85	£16,535
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 8. Breakdown of company's results

	Brentuximab	Standard of care	Incremental
Costs			
Drug costs	[redacted]	[redacted]	[redacted]
SCT	[redacted]	[redacted]	[redacted]
Admin costs	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
QALYs (discounted)			

	Brentuximab	Standard of care	Incremental
EFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
alloSCT	[redacted]	[redacted]	[redacted]
ASCT	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Life Years (undiscounted)			
EFS	1.34	1.37	-0.02
PPS	0.09	0.11	-0.02
alloSCT	4.30	1.01	3.29
ASCT	5.12	1.21	3.92
End of life	0.49	0.11	0.37
Total	12.28	4.43	7.85
ICERS			
Cost per QALY gained for brentuximab vs BSC			**£16,535**

6 ADDITIONAL ANALYSIS UNDERTAKEN BY THE ERG

As explained throughout the report the ERG undertook additional analysis to try to address some of the issues identified. The ERG used the company's previous model, given the concerns surrounding the updated model. The model alterations and additional analysis ran by the ERG consist on the following:

1. Incorporating the post-SCT OS curves from Reyal *et al*. 2016;
2. Incorporating the costs associated with the post-SCT PD state in the model;
3. Incorporating the utility associated with the post-SCT PD state in the model;
4. Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these patients receiving salvage chemotherapy, and incurring respective costs);
5. As an alternative to 4, assuming that 21% of brentuximab patients bridge directly to SCT.

Results are reported in Table 9 with list prices and on Table 10 with the brentuximab PAS. The most influential drivers of the economic results are the post SCT survival, and the proportion of patients bridging to SCT with brentuximab (particularly when patients who received salvage chemotherapy are included in this estimate). The ERG's preferred ICER amounts to [redacted] per QALY gained, and £21,478 with the PAS discount applied. These incorporate assumptions 1 to 3 aforementioned, and assuming that 34% of brentuximab patients bridge to SCT (with 13% of these getting salvage chemotherapy). The ICER incorporating the assumption that 21% of brentuximab patients bridge directly to SCT amounts to [redacted] per QALY gained and £19,117 with the PAS included.

Table 9. ERG's analysis

Results per patient	Brentuximab (1)	Chemotherapy (2)	Incremental value (1-2)
Base case (previous model with the Ara utility decrements switch on "yes")			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
1) Incorporating the post-SCT OS curves from Reyal *et al.* 2016			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
2) Incorporating the costs associated with the post-SCT PD state in the model			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
3) Incorporating the utility associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
4) Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
5) Assuming that 21% of brentuximab patients bridge directly to SCT			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

Table 10. ERG's analysis with PAS

Results per patient	**Brentuximab (1)**	**Chemotherapy (2)**	**Incremental value (1-2)**
Base case (previous model – with the Ara utility decrements switch on "yes")			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£29,539**
1) Incorporating the post-SCT OS curves from Reyal et al. 2016			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£15,756**
ICER with all changes incorporated			**£18,135**
2) Incorporating the costs associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£32,314**
ICER with all changes incorporated			**£16,896**
3) Incorporating the utility associated with the post-SCT PD state in the model			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£31,685**
ICER with all changes incorporated			**£18,958**
4) Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£35,413**
ICER with all changes incorporated			**£21,478**
5) Assuming that 21% of brentuximab patients bridge directly to SCT			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£32,027**
ICER with all changes incorporated			**£19,117**
Abbreviation used in the table: Abbreviations used in the table: SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

6.1 Conclusions of the cost-effectiveness section

The ERG considers that using the company's new economic model to analyse the cost-effectiveness of brentuximab carries a very high risk, and that the model submitted by the company is unfit for purpose. Therefore, the ERG had to revert to the previous version of the company's model. This approach is to some extent, problematic, as the company's old model has structural issues related with the treatment pathway. Nonetheless, the ERG tried to mitigate this issue, through implementation of the costs and benefits of post-SCT disease progression, as accurately as possible. The ERG also incorporated the CDF review's results in the analysis to reflect the likely proportion of patients bridging to SCT after brentuximab.

The ERG's base case ICER amounts to [redacted] per QALY gained, and £21,478 with the PAS discount applied. These could be interpreted as conservative estimates, as the ERG is using the Reyal *et al*. 2016 survival data to model survival after ASCT. Given that ASCT is considered to yield better survival outcomes than alloSCT, if the survival estimates associated with ASCT in the analysis were updated to reflect longer survival times, the ERG's final ICER would decrease.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma [ID1366]

You are asked to check the ERG report from BMJ 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 Monday 26 February 2018** 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 committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Applicability of the Thomson *et al.* 2013 and Reyal *et al*. 2016 data to the CDF population

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 11 of the ERG report, it states: *"It is also not possible to confirm if all 219 patients who received brentuximab with the intention of bridging to SCT were PET-negative (i.e. had a complete response) before their SCT, as, according to the company, is standard practice in UK transplant centers. It also makes it impossible to evaluate the applicability of the populations in the Thomson et al. 2013[12] and the Reyal et al. 2016[13] studies, which inform the outcomes post ASCT and allo-SCT in the company model, to the CDF population."*	Takeda request that the ERG consider softening their wording here.	While the statement from the ERG is not necessarily incorrect, it does tend to call into question the post-transplant outcomes data in a manner that may be seen as slightly unfair. The patients included in the CDF data collection were real world patients being treated in England where, as described by Takeda in the Evidence Submission and supported by clinical experts, all SCT centres are following a PET-adapted transplant strategy. There is no reason why, or evidence to suggest that, these patients were not treated according to this standard approach. Takeda's position is that patients would have been treated in this way as per the published UK guidelines. If there is any remaining uncertainty over this point, then Takeda would suggest that it could be addressed with the clinical experts during the NICE AC meeting.	Not a factual error.

Issue 2 Use of outcomes from alloSCT to inform outcomes after ASCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 17 of the ERG report it states: *"therefore the ERG's analysis using outcome data for allo-SCT to inform the outcomes after ASCT, provides a more robust, although conservative, estimate"*	Takeda request that the ERG consider deleting the *words "more robust"* here.	On a clinical basis we do not consider it appropriate to use outcomes data from allo-SCT to inform outcomes from ASCT and therefore we do not see how this can be described as *"more robust"*. Autologous SCT (ASCT) and allogeneic SCT (allo-SCT) are fundamentally different procedures, with the former using the patient's own stem cells while the latter uses donor stem cells. Their modes of action in terms of tackling Hodgkin's lymphoma are also fundamentally different. In the context of a PET-adapted transplant strategy which is standard practice in UK SCT centres, these different transplant modalities are also used in patients with different disease profiles. If there is any remaining uncertainty over this point, then Takeda would suggest that it could be addressed with the clinical experts during the NICE AC meeting. Takeda agree with the ERG that using outcomes data from allo-SCT to inform outcomes after ASCT is a conservative approach (we would suggest very conservative). There is no doubt that outcomes are better after ASCT than after allo-SCT. This is supported by the data provided by Takeda and also by clinical expert opinion, including that of the ERG clinical expert (see page 16	Not a factual error.

		and page 18 of the ERG report for ERG clinical expert comments on the likely survival outcomes after ASCT and allo-SCT respectively). Hence, this is a conservative approach. As above, if there is any remaining uncertainty over this point, then Takeda would suggest that it could be addressed with the clinical experts during the NICE AC meeting.	

Issue 3 Requirement for tunnel states in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Throughout the ERG report there is a difference of opinion between the ERG and Takeda on the cause of the model issue which the company believes required the addition of the tunnel states. The following statement on page 23 of the ERG report describes the ERG's interpretation: *"The change in the risk of death over time after SCT, is accounted for in the underlying hazard of the survival curve fitted to the overall survival (OS) KM data.*	It is fair to state that the implementation of tunnel states reduces the transparency of the model, and that in the base case it appears to not make a very large difference to the ICER, and thus a simplifying assumption to use a model without tunnel states may be a legitimate choice. However, the company believes that although curve fitting does provide a simple way to work around the issue, it may not necessarily fully resolve it.	The ERG are correct that decreasing hazards over time can be (and are) accounted for in curve fitting - for example through the shape parameter in the Weibull curve. This assumption however is predicated on all patients beginning to follow the curve at time zero – the case in the three-state cancer models referenced by the ERG where patients follow an overall survival curve whether they are in progression-free or post-progression survival. In this model however, the time to Stem Cell Transplant (SCT) and time to disease progression are also modelled, with patients taking up to one year to reach SCT for example. Post-Progression Survival and SCT are different health states with different survival curves, and patients are being "drip fed" into	Not a factual error.

It is rare to see constant hazards in most survival models used in technology appraisals, yet this is an issue mitigated through fitting different, and appropriate survival curves to KM data, which can take into account time-changing hazards. The introduction of tunnel states in the model to address this issue is highly flawed, considering its detrimental impact on model efficiency and transparency."	The proposed amendment is to remove the last sentence from the quote which states: '*The introduction of tunnel states in the model to address this issue is highly flawed"* as tunnel states are well-recognised in health economic literature and can be used in an effort to solve an issue such as the one here.	the health states each cycle. Hence, in a simplified model without tunnel states, we believe patients would join the survival curves at times not equal to zero, and thus not face the risks in the early part of the curve. This is potentially a problem as SCT in particular has high risks for the first year, which could add a potential bias in favour of SCT. Equally, PPS has a very poor prognosis, with high mortality in the early part of the curve which would not be experienced by patients who do not move there directly at time zero. The overall direction and magnitude of these effects is not possible to predict which provides some rationale and justification for the introduction of tunnel states by the company in an effort to more accurately model outcomes.	

Issue 4 Omission of key assumptions/limitations in the ERG reporting of their conclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
At present, the ERG base case is implied to represent a reasonable midpoint of the various analyses. However, in reality several assumptions are made which are described as highly conservative in the text of the ER report. In aggregate, we consider that these assumptions border	The ERG should revise their wording on page 38 to reflect that rather than being "likely" as is stated, their base case is actually the most conservative analysis possible in relation to the data derived from the CDF data collection.	Data for 60 of 496 patients was not available because the patient's consultant did not return the data collection form. could not be retrieved from consultants from CDF data collection. The ERG make two key assumptions in relation to the patients with missing data: 1) That all 60 patients were part of the population included in this appraisal (i.e. after at least two prior therapies when	Not a factual error.

on being skewed against brentuximab vedotin. In addition, we believe that some of the text in the conclusion of the ERG report (page 38) does not reflect fairly the text in the remainder of the ERG report. For example, it states on page 38 of the ERG report that: *"The ERG also incorporated the CDF review's results in the analysis to reflect the **likely** proportion of patients bridging to SCT after brentuximab." [emphasis added]*	Takeda request that the ERG consider changing the word *"could"* here to *"should"*.	SCT or multi-agent chemotherapy is not a treatment option. 2) That the SCT rate in these 60 patients was 0% (i.e. no data means no SCTs) Takeda note that for the 436 patients where data was collected from the CDF, 100 of these patients (i.e. 23%) were actually post-SCT while the remainder (314 patients, 77%) were in the pre-SCT population. Hence, the ERG's first assumption is highly conservative and, by over-estimating the likely denominator, it has the effect of reducing the SCT rate in the target population for this appraisal. The second ERG assumption is also highly conservative, as stated on page 14 of the ERG report: *"As PHE and the company points out, this is a conservative analysis, as it is highly unlikely that no patients for whom data are missing had an SCT after brentuximab… The ERG has therefore taken a conservative approach in using this population as its base case"* In short, there is no reason to believe that the rate of SCT would be different for the 12% of patients with missing data than for the 88% with available data. Based on these two assumptions, the ERG's conclusion (on page 38 of the ERG report) that the SCT rate used in their base case reflects the "likely" proportion is factually inaccurate. It is in fact the most conservative estimate possible for the SCT rate following brentuximab vedotin,	

The ERG's conclusion further states on page 38 that: *"These* [ICERs] ***could*** *be interpreted as conservative estimates, as the ERG is using the Reyal et al. 2016 survival data to model survival after ASCT"* [emphasis added]		based on the CDF data collection (i.e. a rate of 21%). Takeda believes the estimated SCT rate should be based on the known information from the patients with available data (i.e. a rate of 25%). There is no doubt that the outcomes are better after ASCT than after allo-SCT. This is supported by the data provided by Takeda and also by clinical expert opinion, including that of the ERG clinical expert (see page 16 and page 18 of the ERG report for ERG clinical expert comments on the likely survival outcomes after ASCT and allo-SCT respectively). Hence, there is no reason to use the word *"could"* in this context; use of the word *"should"* better reflects the reality of the situation.	

Issue 5 Requested clarification from Takeda: relevance of the AIC and BIC statistics

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 26 of the ERG's report the manufacturer is asked to clarify whether the AIC and BIC statistics were derived using the correct data.	Takeda can confirm that the AIC and BIC statistics tables found in Appendix A and B of the Takeda submission are correct in the source date and labelling. . However, having re-reviewed Appendices A and B of our submission, Takeda wish to note that there is was mix-up in which images are presented in Figures 9, 10, 12 and 13. Due to a copy and paste error, incorrect Kaplan Meier graphs are located under the figure headings. The images representing the	Response to clarification request from the ERG Report.	The ERG thanks the company for clarifying.

	Thomson et al. (2013) Kaplan Meier curves have been placed under the Reyal et al. (2016) headings and vice versa. Takeda apologises for the confusion caused by this error and would like to emphasises that this error was not made within the model nor for the AIC and BIC statistics, it only impacted the image labels of the Kaplan Meier curves within the Appendices A and B.		

Issue 6 Requested clarification from Takeda: dataset used to model post-alloSCT disease progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 26 of the ERG's report the manufacturer is asked to clarify the dataset used to model post-alloSCT disease progression.	Takeda can confirm that during the process of model construction an error was made regarding the source of data used for PFS from the Reyal et al. (2016) study. The Takeda model incorrectly uses data from the D4-D5 subgroup of the Reyal et al (2016) study for PFS. The ERG is correct in identifying that data from the "no prior SCT" sub-group should be used for PFS as well as OS. The rationale for this is that, by definition, patients included in the target population for this appraisal are undergoing their first SCT as they have previously been ineligible for SCT. However, Takeda agree with the ERG that the incorporation of the wrong PFS data (i.e. D4-D5 subgroup rather than the "no prior SCT" subgroup) will cause the estimated ICERs to be somewhat pessimistic (the ICERs will be "conservative").	Response to clarification request from the ERG Report. The use of the correct data for alloSCT outcomes based on the error identified by the ERG in their report.	The ERG thanks the company for clarifying.

	The correction for this error is described in part ii) of Issue 7 below.		

Issue 7 Suggested alterations to the ERG's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Having reviewed the ERG's amended version of the company's previous model, Takeda believe some minor alterations/corrections would enhance the robustness of the results. Takeda have built in the functionality for the ERG to: • See the results with ERG original approach • See the results for each of the suggested alterations either independently or as a group	*i.) Correctly incorporating the estimated costs post SCT progression* The costs summarised by the ERG in Table 2 and Table 3 of their report are relevant to a 28-day model cycle and not a 7-day model cycle. In the amended ERG model there is the option to apply this change by changing cell G83 on the Controls sheet (and "tracing dependents" will allow the ERG to review all the amended model cells). Cells V1:W2 on sheet PF-Comp have within them an alternate formulae which applies these estimated costs appropriately. *ii.) Incorporation of the most relevant post-alloSCT disease progression data*	Takeda believe the suggested amendments will make the ICERs estimated by the ERG's model more robust as they both address issues raised by the ERG report and also work to correct errors in the ERG model identified by Takeda. To aid this process Takeda have provided a version of the ERG's model that implements these changes in a manner that maximises usability and transparency.	i) The ERG thanks the company for pointing this out and corrected this in the economic model and results; ii) The ERG appreciates the company's new estimation of post-alloSCT disease progression, but highlights that the ERG analysis was undertaken with the available data at the time. As such, the ERG does not consider this to be a factual error. Given that using these

• Trace where the alterations have been implemented Switches for each of these changes are contained on the controls sheet (cells G83: I85). A description of the proposed changes is outlined below. Takeda would like to suggest the following three areas be amended/corrected: *i.) Correctly incorporating the estimated one-off costs post-SCT progression* There is an error in how the ERG have applied the post-ASCT (Table 2) and post- alloSCT (Table 3) relapse cost estimates derived from clinical consultation. As the Takeda re-submitted model had a 28-day cycle, the cost estimates for relapse post-transplant were applicable per 28-day model cycle. However, Takeda note that the ERG have applied the 28-day cycle cost estimates on a weekly cycle basis and therefore overestimate the total costs. *ii.) Incorporation of the most relevant post-alloSCT disease progression data*	According to Takeda's best understanding of the ERG's revised version of the model, we have included the most relevant disease progression data for those receiving alloSCT. This alteration can be selected by changing cell G84 on the Controls sheet (and "tracing dependents" will allow the ERG to review all the amended model cells). Original data is taken from model version 2018 01 16_brentuximab two lines ineligible CE model_base_case.xlsb by completing the following steps: - Amend error in cells F14 and F15 of the PFSSCT sheet where the D4 – D5 subgroup was being selected by changing formulae to =IF(c_allo_curve_choice=$E$2,E3,F3) and =IF(c_allo_curve_choice=$E$2,E4,F4) respectively - Amend column HO of the survival and progression sheet to use a weekly rather than 28-day cycle - Copy out resulting curve in Column HP of the survival and progression sheet *iii.) Correcting the approach to incorporating the brentuximab and standard of care SCT rates within the economic model* In the amended ERG model there is the option to apply this change by changing cell G85 on the Controls sheet (and "tracing dependents" will allow the ERG to review all the amended model cells).		data results in a conservative, but still under the £30,000 threshold, the ERG did not change this in the model; iii) And iv) The ERG appreciates the company's new estimation of post-alloSCT disease progression, but highlights that the ERG analysis was undertaken with the available data at the time. As such, the ERG does not consider this to be a factual error. Given that using these data results in a conservative, but still under the £30,000 threshold, the ERG did not change this in the model; v) Not a factual error. The ERG used the Reyal *et al.* ~~(~~2016~~)~~ study to model time to progression after ASCT as explained in the ERG report.

As acknowledged in Issue 6 above, an oversight led to the most relevant data for post-alloSCT disease progression not being incorporated into the manufacturer's model. As such, it has understandably also not been incorporated into the ERG's model. To help make the ERG's model as robust as possible this has now been incorporated into their model and can be selected as an option. *iii.) Correcting the approach to incorporating the brentuximab and standard of care SCT rates within the economic model* In the version of the previous model that was amended by the ERG there is a coding error in the way the SCT rates following either brentuximab or single-agent chemotherapy are incorporated into the model. Takeda only identified and resolved this issue during the current resubmission process (and therefore the correction had not been made in the version of the model that the ERG have adapted). The coding error is related to the manner in which the SCT rates	When this switch is pressed the following transitions are amended in the Survival and Progression sheet: - Column AA and AC: Time to SCT on the brentuximab arm based upon the original pooled dataset of 78 patients is adjusted based upon the difference between SCT rates in the new model using the CDF information (stored in Controls G53) and the SCT rate in the original pooled dataset used to produce the survival curve (58%; Lists sheet cell E163). Two assumptions are made here: o the time to SCT increases proportionately given that fewer patients are expected to receive SCT than were presented in the original dataset in the ERG base case o this proportionate increase applies equally to time to SCT regardless of whether or not the patient has progressed - Column AB and AD: Time to SCT on the standard care arm based upon the original pooled dataset of 78 patients is adjusted based upon the difference between SCT rates in the new model using published literature (stored in Controls J53) and the SCT rate in the original pooled dataset used to produce the survival curve (58%; Lists sheet cell E163). The same two assumptions are made as above *iv.) Correcting approach to implementation of time to SCT for the log logistic curve*		iv) The ERG thanks the company for pointing out this factual error and has corrected this in the economic model and results.

were previously incorporated into the transitions, leading to unexpected results whereby a change of the proportion of people getting a SCT is not properly reflected in the QALY gain for each respective arm. This leads to odd results as can be seen by comparing the results from the ERG's Scenarios 4 and 5 (see Table 9 and Table 10 of the ERG report). One would expect that when the SCT rate for brentuximab increases (while those of the comparator arm remain constant) the QALYs for the brentuximab arm would increase while those in the comparator arm would remain constant. In the ERG's version of the model (as provided to Takeda by NICE on 21st February 2018) this does not happen. Takeda have identified the correction required and have now implemented this as an option within the updated version of the ERG's model which accompanies this factual accuracy check response. *iv.) Correcting approach to implementation of time to SCT for the log logistic curve*	The covariate can now be included in the projections by changing cell G86 on the Controls sheet (and "tracing dependents" will allow the ERG to review all the amended model cells). *v.) Correcting approach to implementation of time to SCT for the log logistic curve* The correct column can now be selected using G87 on the Controls sheet (and "tracing dependents" will allow the ERG to review all the amended model cells). *vi.) Wrong multiplier applied to salvage chemotherapy costs* The correct multiplier can now be selected using G88 on the Controls sheet (and "tracing dependents" will allow the ERG to review all the amended model cells).		

An error was identified on QC which resulted in the covariate for response not being included in the survival projections for time to SCT (based upon the pooled dataset). *v.) Correcting approach to implementation of time to SCT for the log logistic curve* While QC'ing the ERG amendments an error was identified where the proportion of newly progressed ASCT patients using in column Y was mistakenly being taken from the information on newly progressed patients for AlloSCT *vi.) Wrong multiplier applied to salvage chemotherapy costs* While QC'ing the ERG amendments an error was identified where the 28-day cost (meant to be multiplied by 2 to provide the full cost of salvage chemotherapy) was being multiplied by 30.5 in controls K61.			

Issue 8 Commercial In Confidence (CIC) Markings and Redaction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Throughout the ERG report there are inconsistencies with previous documents in how the CIC markings have been carried out. The ERG report marks the "with PAS" ICERs as CIC throughout the document and leaves the "without PAS" ICERs as non-CIC. ; instead the "without PAS" ICERs as well as the total and incremental costs and QALYs should be marked as CIC. The "with PAS" ICERs should be visible as aligned to all other brentuximab vedotin NICE documents.	Please mark the following as CIC (and therefore in need of redaction for any documents made public): • Total and incremental costs ("with PAS" and "without PAS") and cost breakdowns • Total and incremental QALYs • "Without PAS" ICERs • The magnitude of simple discount Please do not mark (or redact) any "with PAS" ICERs as CIC, they should be unmarked throughout the document.	Consistency with all other NICE documents for brentuximab vedotin, both for the current and other appraisals. Inaccurate markings (or redactions) in the ERG report would make it possible to calculate the current level of discount (PAS) which is confidential.	The ERG thanks the company and corrected the CiC marking as requested.

Issue 9 Results arising from the corrected version of the ERG's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Based on the minor alterations/corrections to the ERG model (as summarised in Issue 7 above) there	See revised tables of results below. In addition to the ERG's scenarios in these tables, we also ran the following scenarios to match the company's base case assumptions and also one of our preferred scenarios:	To provide the ERG and NICE with what we believe are more correct cost-effectiveness results.	The ERG presents the updated results according to the reply to issue 7 and issue 8.

is a need to generate updated cost-effectiveness results for Table 9 and Table 10 of the ERG report (see Section 6 of the ERG report – "Additional analysis undertaken by the ERG").	Assuming that 25% of brentuximab vedotin patients bridge directly to SCT (i.e. Takeda base case assumption): ICER (with PAS) = £22,159/QALY. [redacted] Applying the 41% estimate for the proportion of brentuximab vedotin patients bridging to SCT, and 16% of these receiving salvage chemotherapy and respective costs (i.e. Takeda preferred scenario) : ICER (with PAS) = £17,556/QALY. [redacted]		

Equivalent of Table 9 in ERG report (corrected ERG model: without PAS)

Results per patient	Brentuximab (1)	Chemotherapy (2)	Incremental value (1-2)
Base case (previous model – with the Ara utility decrements switch on "yes")			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
1) Incorporating the post-SCT OS curves from Reyal *et al.* 2016			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
2) Incorporating the costs associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
3) Incorporating the utility associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
4) Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]

ICER with all changes incorporated			[redacted]
5) Assuming that 21% of brentuximab patients bridge directly to SCT			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

Equivalent of Table 10 in ERG report (corrected model: with PAS)

Results per patient	Brentuximab (1)	Chemotherapy (2)	Incremental value (1-2)
Base case (previous model – with the Ara utility decrements switch on "yes")			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£26,996**
1) Incorporating the post-SCT OS curves from Reyal *et al.* 2016			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£14,200**
ICER with all changes incorporated			**£14,200**
2) Incorporating the costs associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£27,220**
ICER with all changes incorporated			**£14,365**
3) Incorporating the utility associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£29,004**
ICER with all changes incorporated			**£15,417**
4) Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£32,962**

ICER with all changes incorporated			**£18,984**
5) Assuming that 21% of brentuximab patients bridge directly to SCT			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£42,475**
ICER with all changes incorporated			**£24,839**
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma in adults with relapsed or refractory disease after at least two previous therapies when ASCT or multi-agent chemotherapy is not an option

ERG's rapid review of the company's new evidence and response to the Cancer Drugs Fund review

Erratum

This report was commissioned by the NIHR HTA Programme as project number 15/69/20

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page number	Change
34 - 38	All PAS-including results are no longer highlighted as commercial in confidence, and all non-PAS-including results have been highlighted as such.
36 - 38	All ICERs presented have been updated to reflect the changes made by the ERG in the estimation of disease progression costs after stem cell transplant, and the cost of salvage chemotherapy, as requested by the company.

5 ADDITIONAL ANALYSIS UNDERTAKEN BY THE ERG

As explained throughout the report the ERG undertook additional analysis to try to address some of the issues identified. The ERG used the company's previous model, given the concerns surrounding the updated model. The model alterations and additional analysis ran by the ERG consist on the following:

1. Incorporating the post-SCT OS curves from Reyal *et al*. 2016;
2. Incorporating the costs associated with the post-SCT PD state in the model;
3. Incorporating the utility associated with the post-SCT PD state in the model;
4. Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these patients receiving salvage chemotherapy, and incurring respective costs);
5. As an alternative to 4, assuming that 21% of brentuximab patients bridge directly to SCT.

Results are reported in Table 9 with list prices and on Table 10 with the brentuximab PAS. The most influential drivers of the economic results are the post-SCT survival, and the proportion of patients bridging to SCT with brentuximab (particularly when patients who received salvage chemotherapy are included in this estimate). The ERG's preferred ICER amounts to [redacted] per QALY gained, and £17,885 with the PAS discount applied. These incorporate assumptions 1 to 3 aforementioned, and assuming that 34% of brentuximab patients bridge to SCT (with 13% of these getting salvage chemotherapy). The ICER incorporating the assumption that 21% of brentuximab patients bridge directly to SCT amounts to [redacted] per QALY gained and £18,544 with the PAS included.

Table 9. ERG's analysis

Results per patient	Brentuximab (1)	Chemotherapy (2)	Incremental value (1-2)
Base case (previous model – with the Ara utility decrements switch on "yes")			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
1) Incorporating the post-SCT OS curves from Reyal *et al.* 2016			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
2) Incorporating the costs associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]

ICER with all changes incorporated			[redacted]
3) Incorporating the utility associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
4) Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)		[redacted]	[redacted]
[redacted]			[redacted]
5) Assuming that 21% of brentuximab patients bridge directly to SCT			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER with all changes incorporated			[redacted]
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

Table 10. ERG's analysis with PAS

Results per patient	Brentuximab (1)	Chemotherapy (2)	Incremental value (1-2)
Base case (previous model – with the Ara utility decrements switch on "yes")			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£29,539**
1) Incorporating the post-SCT OS curves from Reyal et al. 2016			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£15,756**
ICER with all changes incorporated			**£15,756**
2) Incorporating the costs associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£30,176**
ICER with all changes incorporated			**£16,198**
3) Incorporating the utility associated with the post-SCT PD state in the model			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£31,685**
ICER with all changes incorporated			**£17,369**
4) Applying the 34% estimate for the proportion of patients bridging to SCT (and 13% of these receiving salvage chemotherapy and respective costs)			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£30,751**
ICER with all changes incorporated			**£17,885**
5) Assuming that 21% of brentuximab patients bridge directly to SCT			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£32,027**
ICER with all changes incorporated			**£18,544**
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

5.1 Conclusions of the cost-effectiveness section

The ERG considers that using the company's new economic model to analyse the cost-effectiveness of brentuximab carries a very high risk, and that the model submitted by the company is unfit for purpose. Therefore, the ERG had to revert to the previous version of the company's model. This approach is to some extent, problematic, as the company's old model has structural issues related with the treatment pathway. Nonetheless, the ERG tried to mitigate this issue, through implementation of the costs and benefits of post-SCT disease progression, as accurately as possible. The ERG also incorporated the CDF review's results in the analysis to reflect the likely proportion of patients bridging to SCT after brentuximab.

The ERG's base case ICER amounts to [redacted] per QALY gained, and £17,885 with the PAS discount applied. These could be interpreted as conservative estimates, as the ERG is using the Reyal *et al*. 2016 survival data to model survival after ASCT. Given that ASCT is considered to yield better survival outcomes than alloSCT, if the survival estimates associated with ASCT in the analysis were updated to reflect longer survival times, the ERG's final ICER would decrease.

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma in adults with relapsed or refractory disease after at least two previous therapies when ASCT or multi-agent chemotherapy is not an option

Addendum

March 2018

This report was commissioned by the NIHR HTA Programme as project number 15/69/20

BMJ Technology Assessment Group

SUMMARY

The following scenarios were requested by NICE as a result of discussion during the pre-meeting briefing. The scenarios are based on the ERG's alternative base case analysis including the company's patient access scheme (PAS) discount of [redacted].

Scenario 1: 5.3% stem cell transplant (SCT) rate post standard chemotherapy and 41% SCT rate post brentuximab vedotin (BV). According to Table 5 of the company submission, 26% of patients bridge directly from BV to SCT and 15% of patients receive salvage chemotherapy after BV to bridge to SCT.

Scenario 2: 14.3% SCT rate post standard chemotherapy, based on Zinzani et al. 2000, and 34% SCT rate post BV (including 13% of patients receiving salvage chemotherapy after BV).

Results per patient	Brentuximab (1)	Chemotherapy (2)	Incremental value (1-2)
ERG alternative base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£17,885**
1) 5.3% SCT rate post standard chemotherapy & 41% SCT rate post BV (and 15% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£17,738**
2) 14.3% SCT rate post standard chemotherapy & 34% SCT rate post BV (and 13% of these receiving salvage chemotherapy and respective costs)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£21,339**
Abbreviations used in the table; SCT, stem cell transplant; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.			

The ERG wishes to highlight that any changes made to the BV SCT rate impacts the standard chemotherapy arm. This is due to the structure of the model, whereby the post-progression survival post SCT (PPSSCT) for BV is fixed and instead an adjustment is made to the standard chemotherapy arm PPSSCT using a ratio of the proportion of patients bridging to SCT on BV and standard chemotherapy, to calculate the impact in terms of quality adjusted life years (QALYs). As a consequence of this, the results for BV remain static, whereas the results for standard chemotherapy change. However, the incremental costs, QALYs, and resulting ICER demonstrate the overall impact of the change.