NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Takeda
   - Leukaemia CARE
   - National Cancer Research Institute – Association of Cancer Physicians – Royal College of Physicians – Royal College of Radiologists (joint response)

3. Comments on the Appraisal Consultation Document from experts:
   - Dr Christopher Fox – Clinical Expert, nominated by Royal College of Physicians

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Company new evidence appendices -** prepared by Takeda

6. **Evidence Review Group critique of company ACD response and new evidence –** prepared by Aberdeen HTA Group

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

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Single Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Takeda	Takeda does not agree with the ACD draft recommendation of a 'minded no' for the use of brentuximab vedotin for the treatment of relapsed/refractory systemic anaplastic large cell lymphoma (R/R sALCL) and argues that this would not be suitable final guidance to the NHS. Takeda concurs with the committee that R/R sALCL represents a major area of unmet clinical need where there is currently no NICE technology appraisal guidance, limited treatment choices, and patients have a poor prognosis without brentuximab vedotin. Clinical expert opinion in the UK supports the high clinical need for brentuximab vedotin for the treatment of R/R sALCL, and that it has become the standard of care in these patients since it was granted marketing authorisation in late 2012 (with access either through an initial Named patient programme [NPP] or through the Cancer Drugs Fund [CDF] in England since 2013). Removing patient access to brentuximab vedotin, as recommended by the committee in the ACD, would be a hugely retrograde step that could severely impact on health outcomes for R/R sALCL patients and Takeda strongly believes that NICE needs to reconsider and reverse the draft negative recommendation in the ACD. In this ACD response document and two supporting appendices we provide a response to the standard key questions posed by the committee (see page 1 of the ACD). Appendix 1 includes updated cost effectiveness results based on the committee's requests in the ACD for additional analysis; while Appendix 2 provides additional evidence to support that brentuximab vedotin for R/R sALCL satisfies NICE's end of life criteria and thus should qualify for additional flexibility in terms of the final recommendation.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8 and 3.32. Comments noted. The committee considered the response from the company and other consultees and commentators. See FAD sections 3.12, 3.17, 3.19, 3.23, 3.25 and 3.31,

	Although Takeda acknowledge that there is no data directly comparing brentuximab vedotin with chemotherapy for this indication, we do not accept the committee's view that this means there is uncertainty over the clinical efficacy/effectiveness of this medicine. In particular, we disagree fundamentally with the statement on page 4 of the ACD that *"there was uncertainty regarding the extent of PFS and OS because median PFS and OS were not reached"*.[1] Takeda regards this as an illogical statement as the very fact that neither the median PFS (in CR patients) nor OS (in all patients) have been reached after a median of 71.4 months of follow-up actually provides compelling evidence of the very substantial benefits of brentuximab vedotin in R/R sALCL (i.e. that more than 50% of patients in the study are still alive after a median of 6 years of follow up), an aggressive and difficult to control disease (note the comment on page 6 of the ACD that *"People typically have short overall survival after relapse"*).[1] In response to the cost-effectiveness issues raised in the ACD, the company have provided a modified base case and scenario analyses based on the committee's proposed modifications cited in Section 1.2 of the ACD. These modifications include the following: • Use of data from Mak et al. (2013) for extrapolating both progression-free survival (PFS) and overall survival (OS) for chemotherapy • Exploration of a number of parametric models for extrapolating PFS and OS for brentuximab vedotin and chemotherapy, including those already considered in the original submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate • Exploration of a range of excess mortality rates, based on published literature, higher than those used in the base-case analyses. The modified based case assumptions for excess mortality, as identified through a targeted literature review, are an increase of 100% for brentuximab vedotin or chemotherapy without a subsequent transplant, 200% following autologous stem cell transplant and 300% following allogeneic stem cell transplant. The modified base case ICER, including all of the committee's preferred assumptions, is £18,324/QALY. The probabilities of brentuximab vedotin being cost-effective at £20,000, £30,000 and £50,000 per QALY thresholds are 52%, 77% and 97% respectively. A	Comment noted. See FAD section 3.19. Comment noted. See FAD sections 3.17 and 3.19 Comment noted. See FAD section 3.23. Comment noted. See FAD section 3.25.

	confidential patient access scheme (PAS) of [redacted] (in line with the current PAS for relapsed/refractory Hodgkin lymphoma) was applied to all economic analyses. As the base case ICER is well within the cost-effectiveness threshold of £20,000 to £30,000/QALY, Takeda urges the committee to reconsider their initial draft negative recommendation and issue a positive final recommendation for the use of brentuximab vedotin for R/R sALCL. Takeda also requests that the committee reconsiders the eligibility of brentuximab vedotin in R/R sALCL for the end-of-life (EoL) modifier, because we believe there is strong evidence of both the short-life expectancy criterion and the life extension criterion being met. The health economic model (base case) estimates that the median OS for standard care (chemotherapy) in this setting is only 1.26 years (15.18 months), meaning over half of all R/R sALCL patients would have died. Real world evidence from the UK based Haematological Malignancy Research Network (HMRN) showed a mean and median OS of [redacted] respectively; further supporting that patients with R/R sALCL '*normally'* live for less than 24 months, thus satisfying the first criterion. Regarding the second end-of-life criterion of an extension to life that is *"normally at least an additional 3 months"*, we would note that brentuximab vedotin for R/R sALCL easily meets (and exceeds) this requirement. Hence, we would encourage the committee to conclude that brentuximab vedotin is an end-of- life medicine, matching the decision that was reached recently by NICE for nivolumab in R/R Hodgkin lymphoma. Full information on the supporting evidence for the EoL eligibility, including new evidence from HMRN, can be found in Appendix 2. There are a number of additional comments Takeda wish to make in order to support the NICE committee in reversing the draft negative recommendation in the ACD; and these are as follows: • Takeda recognise that the NICE appraisal of brentuximab vedotin in R/R sALCL is challenging. This is because of the limited dataset that exists (in particular for the comparators) and the fact that brentuximab vedotin received an accelerated approval from the EMA based on the high level of unmet patient need and the unprecedented risk-benefit ratio it demonstrated in non-comparative Phase 2 trials. The latter point prevented Phase 3 trials being conducted in the initial indications as it would be unethical to withhold brentuximab vedotin from one	Comment noted. The committee concluded that brentuximab vedotin did not meet the criterion of short life expectancy but did meet the criterion for extension to life. See FAD section 3.29. Comment noted. The committee acknowledged that it would be difficult to do a randomised controlled trial for brentuximab vedotin because of the rarity of systemic anaplastic large cell lymphoma. See FAD section 3.8.

	group of patients. Furthermore, Takeda would like to highlight that the Phase 2 trial in R/R sALCL is the largest prospective interventional trial ever to be conducted in this patient population. Moreover, Takeda challenges many of the clinical arguments that NICE have made on the lack of direct comparative data as it effectively heavily penalises a highly innovative medicine for which the regulators in Europe and USA granted accelerated approval on the basis of the unprecedented patient benefit it provides and the paucity of effective alternative treatment options.	
	• Takeda has sought to address any criticisms within the ACD of the cost effectiveness modelling, and we have remodelled data in line with the ACD recommendations. Scenario analyses have been conducted to further address points of uncertainty. We believe there is sufficient evidence to demonstrate adequately the cost-effectiveness of brentuximab vedotin for R/R sALCL, even at the standard NICE cost effectiveness threshold (and even more so when the EoL decision modifier is applied).	Comment noted. See FAD sections 3.12, 3.17, 3.19, 3.23, 3.25 and 3.31
	• Where clinical uncertainty remains, Takeda has consulted with a number of leading UK lymphoma experts to gain their expert opinion and insight, and this ACD response reflects their feedback.	Comment noted.
	• Brentuximab vedotin for R/R sALCL benefits from a Commercial Access Agreement (confidential discount) which was agreed between Takeda and NHS England in the context of a recent NICE appraisal for the larger R/R HL indication; an indication for which NICE has recently issued positive final guidance in the post-ASCT setting. Clinical expert opinion strongly supports that the clinical efficacy/effectiveness of brentuximab vedotin for R/R sALCL is greater than it is for R/R HL; that the unmet need is at least as large; and that the number of patients affected is significantly smaller, thus limiting the budget impact.	Comment noted. See FAD sections 1.1 and 2.
	Based on the clinical effectiveness and cost effectiveness evidence presented within this ACD response (allied to that in the original company submission), Takeda requests that NICE adopt a positive final recommendation for brentuximab vedotin for R/R sALCL. Finally, we reiterate that failure to do so would be a hugely retrograde step for ALCL patients in England who have had access to this medicine via the CDF since 2013.	Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory

		systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32.
	On the 14th June 2017, the Appraisal committee of the National Institute for Health and Care Excellence (NICE) prepared an Appraisal Consultation Document (ACD) summarising the evidence, views and draft recommendations of the appraisal committee regarding the use of brentuximab vedotin in the NHS in England for treating relapse or refractory systematic anaplastic large cell lymphoma (R/R sALCL). The ACD sets out the draft recommendations made by the committee which currently state that: *"The committee is minded not to recommend brentuximab vedotin, within its marketing authorisation, for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults.* *The committee recommends that NICE requests a revised probabilistic cost-effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and should:* • *Use data from Mak et al. (2013) for extrapolating both progression-free and overall survival for chemotherapy.* • *Explore a number of parametric models for extrapolating progression free and overall survival for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate.* • *Include a range of excess mortality rates higher than those used in the company's base-case analyses. The range should come from published literature identified through a systematic literature review rather than clinical expert opinion."*[1] Takeda does not agree with the draft negative recommendation in the ACD and, in our opinion, if this became the final recommendation, it would not represent a sound and suitable basis for guidance to the NHS. In this document Takeda UK provides a response to the ACD issued in June 2017, strongly requesting that NICE considers a positive final	Comments noted. The committee considered the responses from the company and other consultees and commentators. See FAD sections 3.12, 3.17, 3.19, 3.23, 3.25 and 3.31. Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory

	recommendation for brentuximab vedotin for the R/R sALCL indication, in line with its marketing authorisation. In this response there are updated cost-effectiveness results generated by applying the changes and assumptions specifically requested by the Appraisal Committee in the ACD, including a further exploration of excess mortality risk for long-term survivors (see Appendix 1). Furthermore, Takeda requests that the committee reconsiders the eligibility of brentuximab vedotin in R/R sALCL for the end-of-life modifier, because we believe there is strong evidence that both of the end-of-life criteria are satisfied (see Appendix 2). Please note that an existing confidential patient access scheme (PAS) of [redacted] was applied to all economic analyses.	systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32. Comment noted. The committee concluded that brentuximab vedotin did not meet the criterion of short life expectancy but did meet the criterion for extension to life. See FAD section 3.29. Comment noted. See FAD sections 2 and 3.11.
Takeda	*Please find below the responses of Takeda to the standard questions from the appraisal committee listed on page 1 of the ACD.* ***Has all of the relevant evidence been taken into account?*** Takeda consider that all of the relevant evidence available at the time of the submission has been considered by the committee. However, Takeda do not believe all of the evidence has been interpreted adequately and this is reflected in our response to the question regarding whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence (see Section 3.2 below), and the question as to whether the recommendations are sound and a suitable basis for guidance to the NHS (see Section 3.3 below).	Comment noted. Comments noted. Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of

		0 or 1. See FAD sections 1.1, 3.8.and 3.32.
	The main clinical evidence to support the case for the clinical and cost-effectiveness of brentuximab vedotin for R/R sALCL comes from the SG035-0004 trial which was used to secure the marketing authorisation. The SG035-004 trial is a multicentre, Phase II, prospective, single-arm study in 58 patients with R/R sALCL after treatment failure of at least 1 therapy with curative intent. The study had significant follow-up, with data and analysis presented from 5-years of follow-up (median observation time of 71.8 months) based on investigator assessment.[3]	Comment noted. See FAD sections 3.5 and 3.8.
	Furthermore, the supplementary evidence provided from two retrospective case series (Gopal et al. 2014 and Chihara et al. 2015) and three named patient programmes (Gibb et al. 2013), were accepted by the committee as providing support to the results seen in the SG035-0004 trial. Takeda recognise that the patient population in the aforementioned supplementary data was small, however, given the rarity of R/R sALCL this body of evidence should be considered substantial and valuable to the decision problem at hand. The Mak et al. 2013 data, a historical cohort of 153 patients from the British Columbia Lymphoid Cancer database, was presented as the most appropriate source for outcomes with chemotherapy in R/R sALCL[4]. The committee and Takeda concur that the unadjusted indirect comparison, as presented by Takeda, is the best available evidence for decision making (see page 4 of the ACD) due to the small effective sample size of 4.8 after adjusting for available variables.	Comment noted. See FAD sections 3.6 and 3.8.
	In response to points of discussion raised in the ACD, a number of modifications have been made to the base case economic analysis of brentuximab vedotin for the treatment of R/R sALCL. The following modifications have been made based on comments in the ACD: • Correcting the minor errors identified in the model • Providing a variety of parametric models to fit to both the brentuximab vedotin and chemotherapy data • Use of Mak et al. 2013 data to inform both the PFS and OS of chemotherapy • Exploration of excess mortality rates for the brentuximab vedotin only, chemotherapy only and autologous stem cell transplant and allogenic stem cell transplant cohorts	Comments noted. The committee considered the responses from the company and other consultees and commentators. See FAD sections 3.12, 3.17, 3.19, 3.23, 3.25 and 3.31.

	The results of these analyses are presented in Appendix 1.	
Takeda	***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** There are a number of issues raised in the ACD relating to the analysis and interpretation of the clinical and cost-effectiveness of brentuximab vedotin for patients with R/R sALCL. The Takeda response to these issues and interpretations is provided below: **ACD conclusion on clinical effectiveness - in response to Section 3.1 – 3.9 and Section 3.2 of ACD** **Points of agreement between Takeda and the committee** In relation to Sections 3.1 – 3.9 of the ACD, Takeda agrees with the following statements: *"Patient Experience: Brentuximab vedotin is well tolerated and could significantly improve quality of life"* *"There is an unmet clinical need for people with relapsed or refractory systemic anaplastic large cell lymphoma"* *"People typically have short overall survival after relapse"* *"…brentuximab vedotin would be used as a first-line salvage therapy (that is as second-line therapy after the first-line chemotherapy [for example CHOP]) instead of salvage chemotherapy."* *"People have fewer cycles of brentuximab vedotin in Cancer Drugs Fund clinical practice than in the clinical trial and summary of product characteristics…The committee accepted*	Comment noted. Comments noted.

	that most people in clinical practice would have fewer cycles than specified in the summary of product characteristics and the SG035-0004 trial" *"…the [Gopal and Gibb studies] results largely supported those from SG035-0004"* *"…the committee concluded that the company's unadjusted indirect comparison [with a subset of patients from Mak et.al. with either ALCL specifically or peripheral T-cell lymphoma and a performance status less than 2] was the best available evidence for its decision-making"* In relation to Section 3.24 of the ACD, Takeda agrees with the following statement: *"The committee discussed the company's comments about the innovative nature of brentuximab vedotin. It heard from the clinical and patient expert that treatment with brentuximab vedotin produces high complete remission rates and that results are seen quickly, allowing treatment to be stopped early for most people. They considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. The committee concluded that brentuximab vedotin was an innovative and promising treatment..."* **Points of disagreement between Takeda and the committee** In relation to Sections 3.1 – 3.9 of the ACD which summarise the committee's views on the clinical effectiveness of brentuximab vedotin for R/R sALCL, Takeda disagrees with the committee's interpretation of the clinical efficacy demonstrated in the SG035-0004 trial (Section 3.7 of the ACD). In particular, Takeda requests the committee to reconsider their suggestion that there is uncertainty about the extent of PFS and OS benefit. This presumably links back to the committee's earlier comment on page 4 of the ACD that *"there was uncertainty regarding the extent of PFS and OS because median PFS and OS were not reached"*. As stated earlier in the Executive Summary of this response document, Takeda regards this as an illogical statement as the very fact that the median OS has not been reached after 5-years of follow-up actually provides compelling evidence of the very substantial benefits of brentuximab vedotin in R/R sALCL. The median PFS for patients who achieved a CR was also not reached, however the median	Comments noted. Comments noted. The text in 3.8 has been amended to "there was uncertainty about the full extent of the benefit of treatment with brentuximab vedotin" and the committee acknowledge that brentuximab vedotin is estimated to substantially improve progression-free and overall

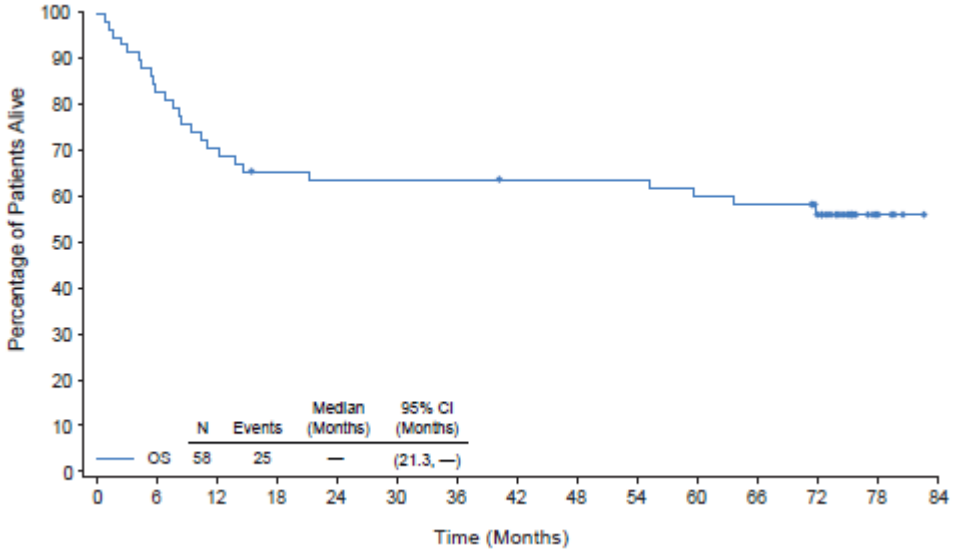
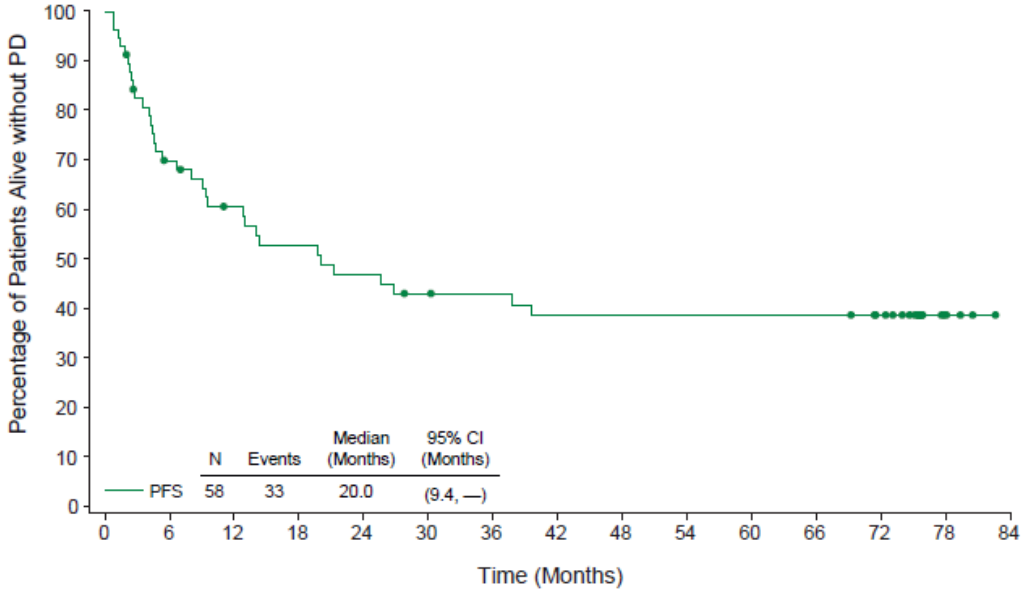
	PFS for all patients was reached during the 5 year follow-up and was 20 months per investigator assessment[3]. In the last forty months of trial follow-up, only two events of progression or death occurred demonstrating the strong disease control provided by brentuximab vedotin. This observed benefit and the flattening of the Kaplan Meyer curve was due to the efficacy of brentuximab vedotin and not due to censoring as 42% of patients were observed until the close of the trial[3]. The more than half of patients treated with brentuximab vedotin who remained alive at the end of the observation period (median follow up of 71.4 months), either with or without a subsequent stem cell transplant, would be considered long-term survivors[3]. According to the clinical community, after 5 years these patients would cease to receive treatment, including regular follow-up by their haematologists for sALCL. **Figure 1: OS following treatment with brentuximab vedotin (Five-Year Follow-Up per Investigator Assessment)[3]**  Source: Pro et al., (2016)	survival. See FAD section 3.8 and 3.20.

Figure 2: PFS following treatment with brentuximab vedotin (Five-Year Follow-Up per Investigator Assessment)[3]



Source: Pro et al., (2016)

The efficacy seen in the SG035-0004 trial has also been observed in real world use of brentuximab vedotin for R/R sALCL in England via the CDF. Since 2013, approximately 45-50 R/R sALCL patients per year have benefited from brentuximab vedotin. Clinical and patient experience has been overwhelmingly positive in support of the effectiveness of brentuximab vedotin, with unanimous clinical and patient expert feedback similar to that described on page 11 of the ACD (Section 3.7). The strong effectiveness observes in UK patients through the CDF and NPP supports the magnitude of PFS and OS benefit and confirms the validity of the outcomes seen in the SG035-0004 trial.

	ACD conclusion on cost-effectiveness in response to Section 3.10 - 3.18 of the ACD In relation to Sections 3.10 – 3.18 of the ACD, Takeda agrees with the following statements: *"The committee accepted the structure of the model as representing the treatment pathway…The committee considered the model appropriate for its decision making"* *"The committee agreed that the company's approach for modelling the rate of stem cell transplant was appropriate for decision making"* *"The committee agreed that the company's approach for modelling progression-free survival and overall survival [based on Smith et al. 2013 data] was appropriate for decision-making"* *"The committee concluded that data for progression-free survival and overall survival based on investigator assessment were appropriate for decision making."* *"…investigator assessment has been used because it provided longer follow-up data (median observation at 71.4 months) and was more reflective of the assessments used in the self-control cohort."* *"The committee concluded that the clinical expert distribution of therapy after progression was the most appropriate for decision-making."* All of the above committee conclusions and assumptions have been included in the company's modified base case cost-effectiveness analysis, presented in Table 1.14 of Appendix 1. Furthermore, Takeda's response to the committee's conclusions and discussions of cost-effectiveness parameters described in Sections 3.14, 3.15, 3.16 and 3.19 of the ACD have been addressed in analysis provided in Appendix 1.	Comment noted.

Takeda	***Are the recommendations sound and a suitable basis for guidance to the NHS?*** Takeda do not agree with the ACD draft negative recommendations as final recommendations, and in our opinion they are not a sound and suitable basis for guidance to the NHS. We have presented in this ACD response a robust case why brentuximab vedotin can be considered both a clinically effective and cost effective treatment for patients with R/R sALCL. The modified base case analysis, including all of the committee's preferred assumptions and a significantly increased excess mortality risk for long-term survivors, yields an ICER of £18,324, as presented in Appendix 1. A full analysis of the impact of each modification to the base case ICER can be found in **Error! Reference source not found.** in Appendix 1. The modified base case ICER is well within the standard threshold considered by NICE to be a cost-effective use of NHS resources (i.e. £20,000 - £30,000/QALY), and therefore brentuximab vedotin for R/R sALCL should be recommended for baseline commissioning within the NHS. This would match the decision recently made by NICE in relation to brentuximab vedotin for the R/R HL post-ASCT indication; we believe such consistency of decision making would be welcomed by Takeda, NHS England, the clinical community, as well as patients and their representatives. Moreover, a compelling case is made within Appendix 2 of this response that brentuximab vedotin for R/R sALCL satisfies NICE's end-of-life criteria and thus should qualify for additional flexibility in terms of NICE's final recommendation.	Comments noted. Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32. Comment noted. The committee concluded that brentuximab vedotin did not meet the criterion of short life expectancy but did meet the criterion for extension to life. See FAD section 3.29.

Takeda	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy or maternity?*** No other aspects relating to unlawful discrimination need particular consideration.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD section 1.1. The committee considered whether its recommendations were associated with any potential issues related to equality. It concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate. See FAD sections 1.2 and 3.30.
Takeda	Takeda does not agree with the ACD draft negative recommendations as final recommendations, and in our opinion they are not a sound and suitable basis for guidance to the NHS. We have presented in this ACD response a robust case why brentuximab vedotin can be considered both a clinically effective and cost effective treatment for adults with R/R sALCL. Based on this response (which builds on the evidence in the original company submission) and a modified base case ICER that is well below the standard cost effectiveness threshold, Takeda requests that NICE adopt a positive final recommendation for brentuximab vedotin for R/R sALCL. The committee should, in our opinion, also take into account the compelling evidence that has been presented within this response to show that brentuximab vedotin for R/R sALCL meets NICE's end-of-life criteria.	Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32.

	A positive final recommendation would match the decision recently made by NICE in relation to brentuximab vedotin for the R/R HL post-ASCT indication; and we believe such consistency of decision making would be welcomed by Takeda, NHS England, the clinical community, as well as patients and their representatives. On the other hand, failure to recommend brentuximab vedotin would be a hugely retrograde step for ALCL patients in England who have had access to this medicine via the CDF since 2013, during which time it has become established as the preferred first-line salvage therapy for patients with R/R sALCL. 1. National Institute for Health and Care Excellence. Appraisal Consultation Document Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma - [ID512] https://www.nice.org.uk/guidance/gid-ta10086/documents/appraisal-consultation-document 2. Takeda UK Ltd. Data on File UK/DF/1707/0008 – ACADEMIC IN CONFIDENCE 3. Pro B *et al*. Five-Year Survival Data from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma. 58th Annual Meeting of the American Society of Hematology (ASH); 2016; San Diego. 4. Mak VH. Survival of patients eripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;**31**(16):1970-76.	
Leukaemia Care	**Re: Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]** ALCL is an extremely rare condition. In this setting, there is an unmet need for alternatives to chemotherapy. Brentuximab vedotin offers an effective treatment option, with high remission rates, instead of highly toxic chemotherapy.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of

		0 or 1. See FAD sections 1.1, 3.8.and 3.32.
	Uncertainty As acknowledged repeatedly in the ACD, brentuximab vedotin is clinically effective. However, due to the rarity of ALCL, it would be difficult to do a randomised clinical trial. Whilst we accept that parts of the data are uncertain, this uncertainty is a result of the rarity of the condition. We submit that this must be taken into account when assessing brentuximab vedotin, because applying the "standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair." (Sir Andrew Dillon, 20 Feb 2015).	Comments noted. Brentuximab vedotin was appraised through NICE's Single Technology Appraisal (STA) process, rather than NICE's highly specialised technology (HST) programme referred to by Sir Andrew Dillon in February 2015. For further details, please see NICE's Technology appraisal process and methods guides, and NICE's highly specialised technology programme. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab vedotin was an effective treatment. See FAD section 3.8. The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab vedotin would substantially increase both progression-free and overall survival

		compared with chemotherapy. See FAD section 3.20.
	Since it has been funded through the Cancer Drugs Fund, it has become a key therapy in UK clinical practice. As such, to withdraw access to this treatment would be a step backwards, which would result in unnecessary deaths and prevent the NHS participating in future research in this area.	Comment noted. The committee considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. See FAD section 3.31.
	This unfairness is further highlighted by the recent positive NICE guidance of brentuximab vedotin for treating Hodgkin lymphoma patients (TA 446). Brentuximab vedotin is considered a step-change in the treatment of ALCL. To recommend it for the treatment of HL, but not ALCL (because of the data limitations created by the small population size), would be both illogical and inequitable.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32.
	Cost-effective Additionally, all ICERs presented were cost-effective (the highest ICER/QALY listed in the ACD being £21,267). As such, we suggest that brentuximab vedotin is both a clinically and cost-effective use of NHS resources for treating relapsed or refractory systemic anaplastic large cell lymphoma.	Comment noted. See FAD section 3.32.

	Patient Feedback We also want to take this opportunity to input comments on the ACD from an ALCL patient who has been treated with brentuximab vedotin: *"As a patient with relapsed/refractory systemic anaplastic large cell lymphoma, I received five cycles of brentuximab vedotin between July and October 2014. This followed two cycles of CHOP and one cycle of DHAP chemotherapy in May and June 2014 respectively. Both CHOP and DHAP were clinically ineffective in treating my rapid and aggressive symptoms. By contrast, brentuximab vedotin quickly demonstrated its high clinical effectiveness in a matter of days.* *Brentuximab vedotin was responsive, well tolerated and represented a low toxic treatment compared to current chemotherapy regimens. Side effects are minimal, significantly less unpleasant and certainly more manageable. Its innovative, selectively targeted approach greatly improves both access to further treatments and ultimately, the survival outcomes for similar patients.* *From a personal perspective, brentuximab vedotin arrested the progression of my symptoms, bringing them under control. Without it, the chances are that I would not have survived beyond the late summer of 2014. To consider it a step change in the treatment pathway of relapsed/refractory systemic anaplastic large cell lymphoma patients is an understatement. For this alone I implore the committee to arrive at a positive decision.* *From an NHS cost and patient experience perspective, brentuximab vedotin can be administered to outpatients by intravenous infusion in approximately half an hour, compared with hospital admission for other forms of traditional treatments.* *Today, I am living proof that access to effective treatment is fundamental. Notwithstanding the clinical and economic considerations, the implications of a negative decision are unthinkable. I know, through first-hand experience that brentuximab vedotin is clinically effective. Should my symptoms recur, the psychological impact of not having access to it is inconceivable, the kind of thoughts that keep me awake at night."*	Comments noted. The committee considered all the information received from the company as per NICE's process guide (see section 3.7.3 of the NICE guide to the process of technology appraisals).

	We hope that you will bear our comments in mind when considering your final recommendation and urge you to make brentuximab vedotin available to all of those who could benefit from it.	
NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Our experts note that it was stated during the first committee meeting that, brentuximab vedotin is a paradigm shift in the management of patients with r/r sALCL. This view was strongly supported at the appraisal meeting by Professor Peter Clarke, Chair of the NHSE chemotherapy group and cancer drugs fund. Patients with r/r sALCL unequivocally represent a disease area of unmet need; disease progression after first-line chemotherapy invariably translates into short survival times notwithstanding the use of second-line chemotherapy regimens. Our experience in the UK is similar to the published Mak et al dataset from British Columbia; patients with r/r sALCL treated with second-line chemotherapy can expect survival times measured in a small number of months. In recent years, the NHSE cancer drugs fund has permitted use of brentuximab vedotin for r/r sALCL allowing patients access to this transformative medicine. Importantly, this has allowed many patients to 'bridge' to stem cell transplantation. Our experts note that the NICE committee will also be familiar with this approach following the recent NICE approval of the same drug - brentuximab vedotin - for patients with relapsed/refractory Hodgkin lymphoma (NICE TA446). Our experts believe that for patients with r/r sALCL, brentuximab vedotin is an even more significant step-change in clinical management. Our experts make the following comments to points raised in the ACD: Results of a single arm study (SG035-0004) in 58 patients suggest brentuximab vedotin is clinically effective based on response rates and there was uncertainty regarding the	Comment noted. Comments noted. The committee considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. See FAD section 3.31. Comments noted. The text in FAD section 3.8 has been amended to "there was uncertainty about the full extent of the benefit of treatment with brentuximab vedotin." The committee concluded that there was a large degree of uncertainty in

	extent of progression-free survival and overall survival because median progression-free survival and overall survival were not reached. With mature follow-up of the SG035-0004, the fact that median PFS and median OS were not reached can only support the effectiveness of this therapy for patients with relapse/refractory ALCL. Our experts note that it is unclear why the NICE committee regarded this as uncertainty. Taken together, the fact that the median PFS/OS have not been reached over a long observation period, in the context of a highly aggressive malignancy which quickly manifests clinically at disease progression, serves only to underscore the effectiveness of this drug rather than introduce uncertainty.	the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab vedotin was an effective treatment. See FAD section 3.8. The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab would substantially increase both progression-free and overall survival compared with chemotherapy. See FAD section 3.20
	As there were no data directly comparing brentuximab vedotin with current treatment (chemotherapy), an unadjusted indirect comparison was carried out. This was considered to be the best available evidence although there was uncertainty because of differences in age, stage of disease, and performance status in the groups compared. Although an indirect comparison, the Mak et al dataset is the largest real-world chemotherapy comparator available. Of 36 ALCL patients in this analysis, only 5 patients (14%) experienced long-term survival with a median PFS of 1.8 months and OS of 3 months for the ALCL patients treated with chemotherapy. Even for patients with a good performance status (in the whole Mak et al cohort), the median PFS was still only 5	Comments noted. The committee acknowledged that the unadjusted indirect comparison of brentuximab vedotin with the Mak et al. chemotherapy dataset is the best available evidence to be used. See FAD 3.10. Comment noted. The recommendations have been updated

	months. These data absolutely support the clinical experience of brentuximab vedotin in r/r sALCL as an unprecedented step-change in management. We would be grateful if the committee can carefully consider these comments and review their recommendation in the appraisal consultation document	and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32.

Comments received from commentators

None

Comments received from clinical and patient experts

Nominating organisation	Comment [sic]	Response
Royal College of Physicians	With reference to the published ACD for brentuximab vedotin indicated for relapsed/refractory systemic anaplastic large cell lymphoma (r/r sALCL), the following constitutes my response as nominated clinical expert (on behalf of the NCRI and RCP). As I clearly stated during the first committee meeting, brentuximab vedotin is a paradigm shift in the management of patients with r/r sALCL. This view was strongly supported at the appraisal meeting by Professor Peter Clarke, Chair of the NHSE chemotherapy group and cancer drugs fund. Patients with r/r sALCL unequivocally represent a disease area of unmet need; disease progression after first-line chemotherapy invariably translates into short survival times notwithstanding the use of second-line chemotherapy regimens. Our experience in the	Comments noted. The committee considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. See FAD section 3.31.

	UK is similar to the published Mak et al dataset from British Columbia; patients with r/r sALCL treated with second-line chemotherapy can expect survival times measured in a small number of months. In recent years, the NHSE cancer drugs fund has permitted use of brentuximab vedotin for r/r sALCL allowing patients access to this transformative medicine. Importantly, this has allowed many patients to 'bridge' to stem cell transplantation. The NICE committee with also be familiar with this approach following the recent NICE approval of the same drug - brentuximab vedotin - for patients with relapsed/refractory Hodgkin lymphoma (NICE TA446). It is my view, together with many expert colleagues, that for patients with r/r sALCL, brentuximab vedotin is an even more significant step-change in clinical management. Specific comments to points raised in the ACD are as follows: 1. ''Results of a single arm study (SG035-0004) in 58 patients suggest brentuximab vedotin is clinically effective based on response rates and there was uncertainty regarding the extent of progression-free survival and overall survival because median progression-free survival and overall survival were not reached.'' RESPONSE: With mature follow-up of the SG035-0004, the fact that median PFS and median OS were not reached can only support the effectiveness of this therapy for patients with relapse/refractory ALCL. It is unclear why the NICE committee regarded this as uncertainty. Taken together, the fact that the median PFS/OS have not been reached over a long observation period, in the context of a highly aggressive malignancy which quickly manifests clinically at disease progression, serves only to underscore the effectiveness of this drug rather than introduce uncertainty.	Comments noted. The text in FAD section 3.8 has been amended to "there was uncertainty about the full extent of the benefit of treatment with brentuximab vedotin." The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab

		vedotin was an effective treatment. See FAD section 3.8. The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab would substantially increase both progression-free and overall survival compared with chemotherapy. See FAD section 3.20.
	2. "As there were no data directly comparing brentuximab vedotin with current treatment (chemotherapy), an unadjusted indirect comparison was carried out. This was considered to be the best available evidence although there was uncertainty because of differences in age, stage of disease, and performance status in the groups compared". RESPONSE: Although an indirect comparison, the Mak et al dataset is the largest realworld chemotherapy comparator available. Of 36 ALCL patients in this analysis, only 5 patients (14%) experienced long-term survival with a median PFS of 1.8 months and OS of 3 months for the ALCL patients treated with chemotherapy. Even for patients with a good performance status (in the whole Mak et al cohort), the median PFS was still only 5 months. These data absolutely support the clinical experience of brentuximab vedotin in r/r sALCL as an unprecedented step-change in management. I should be grateful if the committee can carefully consider these comments and review their minded recommendation in the appraisal consultation document.	Comment noted. The committee acknowledged that the unadjusted indirect comparison of brentuximab vedotin with the Mak et al. chemotherapy dataset is the best available evidence to be used. See FAD section 3.10. .

Comments received from members of the public

Role*	Comment [sic]	Response
NHS Professional	Relapsed anaplastic large cell lymphoma is a devastating disease. The British Columbia Cancer Agency have reported outcomes of relapsed PTCL (which included ALCL) showing PFS and OS of less than 1 year (Mak et al). This very much reflects the experience of lymphoma doctors treating these patients in the clinic. Brentuximab vedotin has however transformed the outlook for these patients. This has been demonstrated by the largest trial ever performed in this rare patient group, albeit a single arm phase II. It showed very impressive PFS and PS curves which show a convincing plateau. Some of these patients were consolidated with a stem cell transplant, but not all. This drug is therefore transformational and directly leads to the saving of lives. There is no alternative drug which is anywhere near as active. I would thoroughly encourage NICE to approve this drug for relapsed / refractory ALCL. It is clear that it is life saving. If it is not available in the UK, patients will suffer avoidable deaths which would be truly tragic. Thank you for your consideration of this feedback.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32.
NHS Professional	This ACD is for brentuximab vedotin (BV) in r/r ALCL e.g. the marketing authorisation. However section 1.2 regards chemotherapy as a 'standard' second line therapy. This is not supported by any literature of sufficient quality, a fact reflected in both ESMO and BCSH guidance which treat chemo and BV in equipoise for r/r ALCL. This is then stated in section 3.2, which contradicts 1.2.	Comment noted. The text has been amended. See FAD section 'Why the committee made these recommendations'
NHS Professional	This is a rare group of lymphoma where not many options are available and the FAD is a major setback for patients. It is the only T cell lymphoma that responds well to Brentuximab which offers good and lasting remissions. Not allowing patients to receive this drug will no doubt increase the mortality from this disease with no other options proven to be useful or relevant national trials.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32).
NHS Professional	I wholeheartedly disagree with the recent negative ACD for brentuximab in relapsed refractory anaplastic large cell lymphoma (ALCL) setting which is now a standard of care in the management of these patients at our institution. The outcomes for patients	Comment noted. The committee concluded that there was a large degree of uncertainty in the clinical

	with relapsed peripheral T-cell lymphoma (PTCL) including patients with relapsed/refractory ALCL are extremely poor with a reported median OS and PFS of just 5.5 months and 3.1 months respectively (Mak et al, JCO 2013). Brentuximab is a well tolerated therapy and has demonstrated excellent efficacy and durable remissions for this patient population in a phase II study, with the median OS not reached. In contrast RR PTCL patients (including ALCL) treated with chemotherapy have a reported median OS of just 6.5 months. Outcome data from the named patient program further supports the excellent outcomes for this patient population following brentuximab (Zinzani et al, Crit Rev Oncol Hem 2015) and a recently published multi-centre retrospective study reported similar findings (Lamarque et al, Haematologica 2016). In these studies brentuximab has been used successfully as a bridge to either autologous or allogeneic stem cell transplantation which offers patients with RR PTCL an opportunity to achieve long term cure in an otherwise very poor prognosis disease. I would ask the committee to re-consider this decision, which I feel will significantly negatively impact survival for this rare patient subgroup.	evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab vedotin was an effective treatment. See FAD section 3.8. The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab would substantially increase both progression-free and overall survival compared with chemotherapy. See FAD section 3.20. Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32.
NHS Professional	I wish to comment that I feel the recent negative ACD for brentuximab for patients with relapsed/refractory systemic anaplastic large cell lymphoma should be re-considered. The outcomes for this patient population is very poor, even when they are managed with chemotherapy (Mak et al, JCO 2013), but very high rates of overall and complete response have been reported for single-agent brentuximab and remissions are	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic

	frequently prolonged. Brentuximab can be used as a bridge to a potentially-curative transplant for these patients and durable remissions even in the absence of brentuximab have been reported with this approach. Omitting brentuximab from the treatment options for these patients in the relapsed setting will undoubtedly compromise their survival.	anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32.
NHS Professional	ALCL is a rare lymphoma but associated with a poor prognosis. Nearly half of patients relapse and prognosis is a short number of months if there is no salvage treatment available. Patients who are older than 60 years of age are often not able to tolerate intensive chemotherapy salvage and in this situation brentuximab (BV) is the only option available otherwise the expected survival would be 2 to 3 months. Over the last 3 years I have given 14 patients BV for relapse Hodgkin lymphoma but only 2 patients BV for relapsed ALCL. My 60 year old patient who was diagnosed in 2010 and relapsed in 2015 was successfully bridged to allogeneic transplant (allo) and remains well and in remission. She received 7 cycles of BV as a bridge to allo. My 74 year old man relapsed in Dec 2015, had 16 cycles of BV and remains well with an excellent quality of life. For younger patients who relapse, salvage chemo is an option but often doesn't work. It is therefore essential to have BV available for second line salvage, aiming to obtain CR and proceed to autologous or allogeneic stem cell transplant. Using BV as first treatment after relapse also reduces the toxicity of systemic chemotherapy which is important prior to stem cell transplant. For patient bridging to auto or allo I would only use on average 4 to 6 cycles of BV. For older patients, over the age of 65 years, they are not fit for intensive chemotherapy and BV is the only option to obtain response with minimal toxicity. Without BV, patients with R/R ALCL will typically die within a few months. If BV is used as a bridge to transplant then this can be extended to years. BV as treatment for older patients not fit enough for transplant also improves survival from short number of months to years in my clinical experience.	Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32. Comment noted. See FAD section 3.3

	Because of the rare nature of disease large phase III data is not available but my “real world” experience is that BV is effective in both PFS, OS and quality of life in a situation where there are no other options available and I urge you to reconsider you decision for this small number of patients.	
NHS Professional	Anaplastic large cell lymphoma is a rare disorder with limit treatment options at relapse. Brentuximab represents an excellent treatment option for relapsed patients with response rates that are much better than standard chemotherapy. Given the rarity of this disorder and its unmet need, brentuximab should remain an option for these patients. Without the option on brentuximab many more patients will likely die of the disease as very few patients achieve a long term remission with standard chemotherapy options. I strongly disagree with the ACD	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32. .
NHS Professional	I am writing to you to ask if you would kindly reconsider your Appraisal decision in which you are minded not to recommend the use of Brentuximab Vedotin in Relapsed/Refractory Anaplastic large Cell Lymphoma.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8, and 3.32. Comments noted. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab

	This is a life-saving treatment in patients who have no good alternative treatment. Throughout the report comparison to second line chemotherapy is mentioned, yet no once does any survival data from such regimens appear. Throughout the report it is written the committee accepts the reduced data set that the company has been able to provide due to rarity of this disease. The report says it accepts the difficulty in producing randomised data comparing chemotherapy with Brentuximab. When considering an approval in the end of life use, an extension of three months of life allows Brentuximab to be consider, throughout the report it says the committee is happy to accept progression free survival and overall survival data from SGN035-0004 and yet at this point there is a refusal to accept data showing life extension by years not just months that has been supported by other trials as listed in the report. Throughout the report the Mak 2013 trial looking at survival in relapsed/refractory ALCL patients is quoted as the standard of care approach. This trial showed an increase in median overall survival of one month for patients treated with second line chemotherapy, median progression free survival is less than a month. I am part of dedicated lymphoma team treating patients with ALCL, Brentixumab Vedotin offers patients a very real chance at long term survival. In the Mak trial only patients with a performance status of 0 or 1 had any real benefit from second line chemotherapy and even then progression free survival was short, an increase of only two months. For these patients to achieve long term survival or at the very least progression free survival that is measurable in terms of years not months then we need access to new agents. The data from the SGN035-0004 trial is remarkable, even if you do not accept the full extent of this data for the concerns you have listed it is very clear Brentuximab Vedotin is offering these patients both greater overall and progression free survival measurable in years. This drug is currently being used to allow patients to successfully undergo stem cell transplants. It offers very real hope in a disease where even first line treatment is not very successful. It is well tolerated in comparison to the platinum based chemotherapy regimens used as alternative and we have had very real success in treating patients with performance statuses of 3 and 4 who would not be fit enough to be treated with platinum. In the current economic climate we are all aware of the burdens on the NHS and the practical decisions that have to be made but in this case there is clear evidence that	vedotin was an effective treatment. See FAD section 3.8. The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab would substantially increase both progression-free and overall survival compared with chemotherapy. See FAD section 3.20. The committee concluded that brentuximab vedotin did not meet the criterion of short life expectancy but did meet the criterion for extension to life. See FAD section 3.29. Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG)

	Brentixumab Vedotin is superior to chemotherapy and offers patients a far greater chance of achieving long term survival. Delaying a decision on this drug by years to collect more data would be at the detriment of many patients who have a horrendous diagnosis. It is my opinion that the data is already clear and not allowing NHS patients access to Brentixumab Vedotin for treatment of ALCL will lead to worse outcomes in this patient subset.	performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32.
NHS Professional	This treatment offers a potentially curative option for patients with relapsed /refractory ALCL. It is a potentially curative option with minimal toxicity. For those for whom intensive salvage strategy is not suitable /appropriate stopping access to this drug is potentially discriminatory in allowing no realistic salvage option. On behalf of all future ALCL patients with support of patients in my practice with long term post Brentuximab remissions please reconsider 'minded No'	Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8 and 3.32.
Patient organisation	We are disappointed that NICE is proposing not to recommend brentuximab vedotin for routine use on the NHS in England for this group of patients. Although patients with relapsed or refractory systemic ALCL are a small group, there is a high level of unmet need, not least because the symptoms of the disease can be debilitating and distressing, and because 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: 1. 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 2. 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 a transplant may not be able to do so if their lymphoma cannot be controlled again with effective treatment first.	Comments noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32. Comment noted. Benefits, such as productivity benefits, are not included in NICE's 'reference case' that specifies the methods considered by NICE to be appropriate for the Appraisal Committee's purpose. See section 5.1

	Achieving 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.	of NICE's 'Guide to the methods of technology appraisal. The committee agreed that brentuximab vedotin was innovative, but that it had not been presented with any evidence of additional benefits that were not captured in the QALY measure. See FAD section 3.31.
	Patients unsuitable for transplant can also benefit from palliative treatment giving significant and prolonged symptom reduction which cannot be achieved with standard chemotherapy options.	Comment noted. See FAD sections 3.3 and 3.24.
	It seems that innovative treatments for small patient groups such as in this situation are stymied by the shortcomings of an appraisal methodology that struggles to cope with uncertainty (inevitable when small numbers are involved), irrespective of the strength of available evidence. In patient populations of this size Phase III trial data is hard to come by, so without some flexibility in the treatment of available evidence, then few, if any, effective treatments are likely to be approved for patients with rarer forms of cancer. One of the criticisms the appraisal consultation document makes is that the company's evidence relies on a single arm phase II study, but it's hard to see how it would be	Comments noted. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab vedotin was an effective treatment. See FAD section 3.8.

	practical and ethical to provide phase III research data given the size of the patient population and the level of unmet need.	The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab would substantially increase both progression-free and overall survival compared with chemotherapy. See FAD section 3.20.
	In relation to the cost-effectiveness calculations, these seem to be based upon eight cycles of treatment, although standard clinical practice now appears to be either five or six cycles (on the basis that maximal response is seen in clinical practice after 4 to 5 cycles). If this is the right, then the cost-effectiveness calculations will be severely distorted. From a patient perspective, you'd expect the technology appraisal to be based on current clinical practice.	Comment noted. The committee accepted that in practice, people would have fewer cycles than specified in the summary of product characteristics or the SG035-0004 trial, and were reassured that the ICER may plausibly be lower. See FAD sections 3.21, and 3.27.
	In conclusion we call on NICE and the company to review further the evidence and pricing assumptions so that patients can have access to a potentially life-saving treatment that also has significantly fewer side effects and after effects than traditional chemotherapy.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32.
NHS Professional	Brentuximab vedotin represents a major step forward in the management of relapsed/refractory ALCL; response rates are high and toxicity is mild to moderate and easily managed by dose reduction or dose delay. In the younger/fitter population fit for transplant brentuximab vedotin provides a bridge to this potentially curative procedure	Comment noted. The committee considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell

	and in the older/less fit population it can provide prolonged disease control and improved quality of life.	lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. See FAD section 3.31.
	It would be highly concerning in my view if NICE decided against allowing access to this drug for patients in England and be clear evidence of excessively high barriers being placed in the way of introducing new, effective and well tolerated medicines into the NHS. Moreover and worryingly it would place the UK clearly outside international standard practice with respect to the management of ALCL - in circumstances where UK patient outcomes data lag behind those of other developed countries.	Comment noted. The recommendations have been updated and now brentuximab vedotin has been recommended an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See FAD sections 1.1, 3.8.and 3.32.
	The data describing use of brentuximab vedotin in ALCL, a rare disease, is limited and there is an absence of randomised data. I am concerned that too much analysis has been attempted and too many firm conclusions drawn from this limited data set.	Comments noted. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab vedotin was an effective treatment. See FAD section 3.8. The committee was aware that there was uncertainty in the clinical evidence used in the economic model (FAD section 3.8), but concluded that the estimates indicate that treatment with brentuximab would substantially increase both progression-free and

		overall survival compared with chemotherapy. See FAD section 3.20.
	All current survivors of cancer have an excess mortality compared with their untreated peers due to the increased risk of 2nd cancers, cardiopulmonary disease and infection. Radiotherapy and alkylating agent chemotherapy are the main reasons for this increased risk and there is an international consensus to move away from these treatments towards targeted approaches wherever possible. BV is an example of a targeted drug with no data to suggest any increased risk of 2nd cancers or cardiovascular disease linked to its use. The excess mortality argument is therefore highly supportive of the use of BV instead of chemotherapy.	Comment noted. The committee considered it was appropriate to use excess mortality rates sourced from published literature in its decision-making. See FAD sections 3.20 and 3.23.

Brentuximab vedotin (Adcetris®▼) for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]:

Response to the

ACD (June 2017) for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

July 5th 2017

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Table of Contents

List of Abbreviations

ACD	Appraisal consultation document
AE	Adverse event
alloSCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
AWMSG	All Wales Medicines Strategy Group
BSC	Best supportive care
BV	Brentuximab vedotin
CD30+	CD30-positive
CDF	Cancer drugs fund
CR	Complete remission
CT	Computed tomography
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOT	End of treatment
ERG	Evidence Review Group
FDG	Fluorodeoxyglucose
HL	Hodgkin/ Hodgkin's lymphoma
HMRN	Haematological Malignancy Research Network
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
IRF	Independent review facility
ISHL	International Symposium in Hodgkin Lymphoma
ITT	Intent-to-treat
NCCN	National Comprehensive Cancer Network
NPP	Named Patient Programme
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PICOS	Patients, interventions, comparators, outcome and study design
PFS	Progression-free survival
PP	Per-protocol
PR	Partial remission
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RIC	Reduced intensity conditioning

R/R, r/r	Relapsed/ refractory
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Stable disease
SMC	Scottish Medicines Consortium

1. Executive summary

Takeda does not agree with the ACD draft recommendation of a 'minded no' for the use of brentuximab vedotin for the treatment of relapsed/refractory systemic anaplastic large cell lymphoma (R/R sALCL) and argues that this would not be suitable final guidance to the NHS.

Takeda concurs with the committee that R/R sALCL represents a major area of unmet clinical need where there is currently no NICE technology appraisal guidance, limited treatment choices, and patients have a poor prognosis without brentuximab vedotin.

Clinical expert opinion in the UK supports the high clinical need for brentuximab vedotin for the treatment of R/R sALCL, and that it has become the standard of care in these patients since it was granted marketing authorisation in late 2012 (with access either through an initial Named patient programme [NPP] or through the Cancer Drugs Fund [CDF] in England since 2013). Removing patient access to brentuximab vedotin, as recommended by the committee in the ACD, would be a hugely retrograde step that could severely impact on health outcomes for R/R sALCL patients and Takeda strongly believes that NICE needs to reconsider and reverse the draft negative recommendation in the ACD.

In this ACD response document and two supporting appendices we provide a response to the standard key questions posed by the committee (see page 1 of the ACD). Appendix 1 includes updated cost effectiveness results based on the committee's requests in the ACD for additional analysis; while Appendix 2 provides additional evidence to support that brentuximab vedotin for R/R sALCL satisfies NICE's end of life criteria and thus should qualify for additional flexibility in terms of the final recommendation.

Although Takeda acknowledge that there is no data directly comparing brentuximab vedotin with chemotherapy for this indication, we do not accept the committee's view that this means there is uncertainty over the clinical efficacy/effectiveness of this medicine. In particular, we disagree fundamentally with the statement on page 4 of the ACD that *"there was uncertainty regarding the extent of PFS and OS because median PFS and OS were not reached"*.[1] Takeda regards this as an illogical statement as the very fact that neither the median PFS (in CR patients) nor OS (in all patients) have been reached after a median of 71.4 months of follow-up actually provides compelling evidence of the very substantial benefits of brentuximab vedotin in R/R sALCL (i.e. that more than 50% of patients in the study are still alive after a median of 6 years of follow up), an aggressive and difficult to control disease (note the comment on page 6 of the ACD that *"People typically have short overall survival after relapse"*).[1]

In response to the cost-effectiveness issues raised in the ACD, the company have provided a modified base case and scenario analyses based on the committee's proposed modifications cited in Section 1.2 of the ACD. These modifications include the following:

- Use of data from Mak et al. (2013) for extrapolating both progression-free survival (PFS) and overall survival (OS) for chemotherapy

- Exploration of a number of parametric models for extrapolating PFS and OS for brentuximab vedotin and chemotherapy, including those already considered in the original submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate
- Exploration of a range of excess mortality rates, based on published literature, higher than those used in the base-case analyses. The modified based case assumptions for excess mortality, as identified through a targeted literature review, are an increase of 100% for brentuximab vedotin or chemotherapy without a subsequent transplant, 200% following autologous stem cell transplant and 300% following allogeneic stem cell transplant.

The modified base case ICER, including all of the committee's preferred assumptions, is £18,324/QALY. The probabilities of brentuximab vedotin being cost-effective at £20,000, £30,000 and £50,000 per QALY thresholds are 52%, 77% and 97% respectively. A confidential patient access scheme (PAS) of [redacted] (in line with the current PAS for relapsed/refractory Hodgkin lymphoma) was applied to all economic analyses.

As the base case ICER is well within the cost-effectiveness threshold of £20,000 to £30,000/QALY, Takeda urges the committee to reconsider their initial draft negative recommendation and issue a positive final recommendation for the use of brentuximab vedotin for R/R sALCL. Takeda also requests that the committee reconsiders the eligibility of brentuximab vedotin in R/R sALCL for the end-of-life (EoL) modifier, because we believe there is strong evidence of both the short-life expectancy criterion and the life extension criterion being met. The health economic model (base case) estimates that the median OS for standard care (chemotherapy) in this setting is only 1.26 years (15.18 months), meaning over half of all R/R sALCL patients would have died. Real world evidence from the UK based Haematological Malignancy Research Network (HMRN) showed a mean and median OS of [redacted] respectively; further supporting that patients with R/R sALCL '*normally'* live for less than 24 months, thus satisfying the first criterion. Regarding the second end-of-life criterion of an extension to life that is *"normally at least an additional 3 months"*, we would note that brentuximab vedotin for R/R sALCL easily meets (and exceeds) this requirement. Hence, we would encourage the committee to conclude that brentuximab vedotin is an end-of- life medicine, matching the decision that was reached recently by NICE for nivolumab in R/R Hodgkin lymphoma. Full information on the supporting evidence for the EoL eligibility, including new evidence from HMRN, can be found in Appendix 2.

There are a number of additional comments Takeda wish to make in order to support the NICE committee in reversing the draft negative recommendation in the ACD; and these are as follows:

- Takeda recognise that the NICE appraisal of brentuximab vedotin in R/R sALCL is challenging. This is because of the limited dataset that exists (in particular for the comparators) and the fact that brentuximab vedotin received an accelerated approval from the EMA based on the high level of unmet patient need and the unprecedented risk-benefit ratio it demonstrated in non-comparative Phase 2 trials. The latter point prevented Phase 3 trials being conducted in the initial indications as it would be unethical to withhold brentuximab vedotin from one group of patients. Furthermore, Takeda would like to highlight that the Phase 2 trial in R/R sALCL is the largest

prospective interventional trial ever to be conducted in this patient population. Moreover, Takeda challenges many of the clinical arguments that NICE have made on the lack of direct comparative data as it effectively heavily penalises a highly innovative medicine for which the regulators in Europe and USA granted accelerated approval on the basis of the unprecedented patient benefit it provides and the paucity of effective alternative treatment options.

- Takeda has sought to address any criticisms within the ACD of the cost effectiveness modelling, and we have remodelled data in line with the ACD recommendations. Scenario analyses have been conducted to further address points of uncertainty. We believe there is sufficient evidence to demonstrate adequately the cost-effectiveness of brentuximab vedotin for R/R sALCL, even at the standard NICE cost effectiveness threshold (and even more so when the EoL decision modifier is applied).
- Where clinical uncertainty remains, Takeda has consulted with a number of leading UK lymphoma experts to gain their expert opinion and insight, and this ACD response reflects their feedback.
- Brentuximab vedotin for R/R sALCL benefits from a Commercial Access Agreement (confidential discount) which was agreed between Takeda and NHS England in the context of a recent NICE appraisal for the larger R/R HL indication; an indication for which NICE has recently issued positive final guidance in the post-ASCT setting. Clinical expert opinion strongly supports that the clinical efficacy/effectiveness of brentuximab vedotin for R/R sALCL is greater than it is for R/R HL; that the unmet need is at least as large; and that the number of patients affected is significantly smaller, thus limiting the budget impact.

Based on the clinical effectiveness and cost effectiveness evidence presented within this ACD response (allied to that in the original company submission), Takeda requests that NICE adopt a positive final recommendation for brentuximab vedotin for R/R sALCL. Finally, we reiterate that failure to do so would be a hugely retrograde step for ALCL patients in England who have had access to this medicine via the CDF since 2013.

2. Introduction

2.1 Appraisal committee's preliminary recommendations

On the 14th June 2017, the Appraisal committee of the National Institute for Health and Care Excellence (NICE) prepared an Appraisal Consultation Document (ACD) summarising the evidence, views and draft recommendations of the appraisal committee regarding the use of brentuximab vedotin in the NHS in England for treating relapse or refractory systematic anaplastic large cell lymphoma (R/R sALCL). The ACD sets out the draft recommendations made by the committee which currently state that:

"The committee is minded not to recommend brentuximab vedotin, within its marketing authorisation, for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults.

The committee recommends that NICE requests a revised probabilistic cost-effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and should:

- *Use data from Mak et al. (2013) for extrapolating both progression-free and overall survival for chemotherapy.*
- *Explore a number of parametric models for extrapolating progression free and overall survival for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate.*
- *Include a range of excess mortality rates higher than those used in the company's base-case analyses. The range should come from published literature identified through a systematic literature review rather than clinical expert opinion."*[1]

Takeda does not agree with the draft negative recommendation in the ACD and, in our opinion, if this became the final recommendation, it would not represent a sound and suitable basis for guidance to the NHS. In this document Takeda UK provides a response to the ACD issued in June 2017, strongly requesting that NICE considers a positive final recommendation for brentuximab vedotin for the R/R sALCL indication, in line with its marketing authorisation.

In this response there are updated cost-effectiveness results generated by applying the changes and assumptions specifically requested by the Appraisal Committee in the ACD, including a further exploration of excess mortality risk for long-term survivors (see Appendix 1). Furthermore, Takeda requests that the committee reconsiders the eligibility of brentuximab vedotin in R/R sALCL for the end-of-life modifier, because we believe there is strong evidence that both of the end-of-life criteria are satisfied (see Appendix 2).

Please note that an existing confidential patient access scheme (PAS) of [redacted] was applied to all economic analyses.

3. Response to the appraisal committee's key standard questions

Please find below the responses of Takeda to the standard questions from the appraisal committee listed on page 1 of the ACD.

3.1 Has all of the relevant evidence been taken into account?

Takeda consider that all of the relevant evidence available at the time of the submission has been considered by the committee. However, Takeda do not believe all of the evidence has been interpreted adequately and this is reflected in our response to the question regarding whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence (see Section 3.2 below), and the question as to whether the recommendations are sound and a suitable basis for guidance to the NHS (see Section 3.3 below).

The main clinical evidence to support the case for the clinical and cost-effectiveness of brentuximab vedotin for R/R sALCL comes from the SG035-0004 trial which was used to secure the marketing authorisation. The SG035-004 trial is a multicentre, Phase II, prospective, single-arm study in 58 patients with R/R sALCL after treatment failure of at least 1 therapy with curative intent. The study had significant follow-up, with data and analysis presented from 5-years of follow-up (median observation time of 71.8 months) based on investigator assessment.[3]

Furthermore, the supplementary evidence provided from two retrospective case series (Gopal et al. 2014 and Chihara et al. 2015) and three named patient programmes (Gibb et al. 2013), were accepted by the committee as providing support to the results seen in the SG035-0004 trial. Takeda recognise that the patient population in the aforementioned supplementary data was small, however, given the rarity of R/R sALCL this body of evidence should be considered substantial and valuable to the decision problem at hand.

The Mak et al. 2013 data, a historical cohort of 153 patients from the British Columbia Lymphoid Cancer database, was presented as the most appropriate source for outcomes with chemotherapy in R/R sALCL[4]. The committee and Takeda concur that the unadjusted indirect comparison, as presented by Takeda, is the best available evidence for decision making (see page 4 of the ACD) due to the small effective sample size of 4.8 after adjusting for available variables.

In response to points of discussion raised in the ACD, a number of modifications have been made to the base case economic analysis of brentuximab vedotin for the treatment of R/R sALCL. The following modifications have been made based on comments in the ACD:

- Correcting the minor errors identified in the model
- Providing a variety of parametric models to fit to both the brentuximab vedotin and chemotherapy data
- Use of Mak et al. 2013 data to inform both the PFS and OS of chemotherapy
- Exploration of excess mortality rates for the brentuximab vedotin only, chemotherapy only and autologous stem cell transplant and allogenic stem cell transplant cohorts

The results of these analyses are presented in Appendix 1.

3.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There are a number of issues raised in the ACD relating to the analysis and interpretation of the clinical and cost-effectiveness of brentuximab vedotin for patients with R/R sALCL. The Takeda response to these issues and interpretations is provided below:

3.2.1 ACD conclusion on clinical effectiveness - in response to Section 3.1 – 3.9 and Section 3.2 of ACD

Points of agreement between Takeda and the committee

In relation to Sections 3.1 – 3.9 of the ACD, Takeda agrees with the following statements:

"Patient Experience: Brentuximab vedotin is well tolerated and could significantly improve quality of life"

"There is an unmet clinical need for people with relapsed or refractory systemic anaplastic large cell lymphoma"

"People typically have short overall survival after relapse"

"…brentuximab vedotin would be used as a first-line salvage therapy (that is as second-line therapy after the first-line chemotherapy [for example CHOP]) instead of salvage chemotherapy."

"People have fewer cycles of brentuximab vedotin in Cancer Drugs Fund clinical practice than in the clinical trial and summary of product characteristics…The committee accepted that most people in clinical practice would have fewer cycles than specified in the summary of product characteristics and the SG035-0004 trial"

"…the [Gopal and Gibb studies] results largely supported those from SG035-0004"

"…the committee concluded that the company's unadjusted indirect comparison [with a subset of patients from Mak et.al. with either ALCL specifically or peripheral T-cell lymphoma and a performance status less than 2] was the best available evidence for its decision-making"

In relation to Section 3.24 of the ACD, Takeda agrees with the following statement:

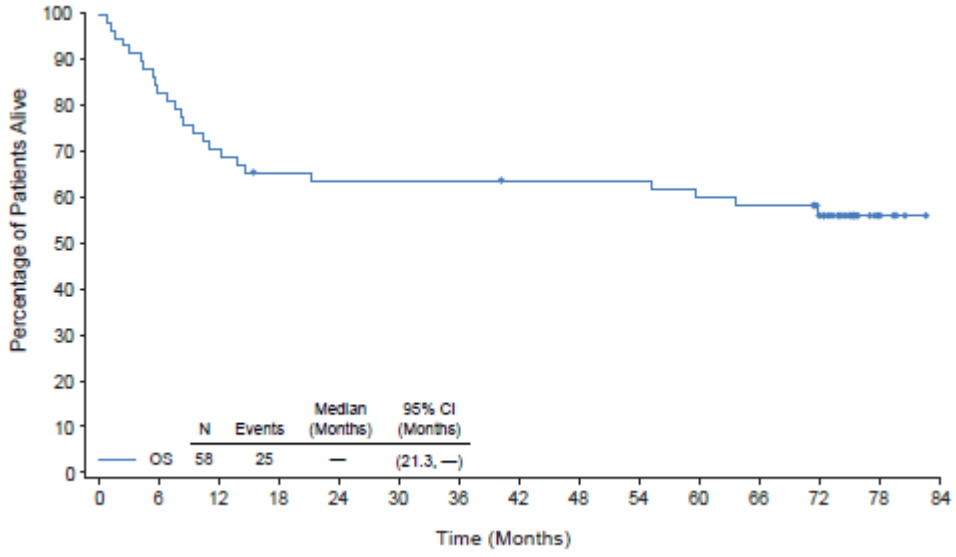
"The committee discussed the company's comments about the innovative nature of brentuximab vedotin. It heard from the clinical and patient expert that treatment with brentuximab vedotin produces high complete remission rates and that results are seen quickly, allowing treatment to be stopped early for most people. They considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. The committee concluded that brentuximab vedotin was an innovative and promising treatment..."

Points of disagreement between Takeda and the committee

In relation to Sections 3.1 – 3.9 of the ACD which summarise the committee's views on the clinical effectiveness of brentuximab vedotin for R/R sALCL, Takeda disagrees with the committee's interpretation of the clinical efficacy demonstrated in the SG035-0004 trial (Section 3.7 of the ACD). In particular, Takeda requests the committee to reconsider their suggestion that there is uncertainty about the extent of PFS and OS benefit. This presumably links back to the committee's earlier comment on page 4 of the ACD that *"there was uncertainty regarding the extent of PFS and OS because median PFS and OS were not reached"*. As stated earlier in the Executive Summary of this response document, Takeda regards this as an illogical statement as the very fact that the median OS has not been reached after 5-years of follow-up actually provides compelling evidence of the very substantial benefits of brentuximab vedotin in R/R sALCL. The median PFS for patients who achieved a CR was also not reached, however the median PFS for all patients was reached during the 5 year follow-up and was 20 months per investigator assessment[3].

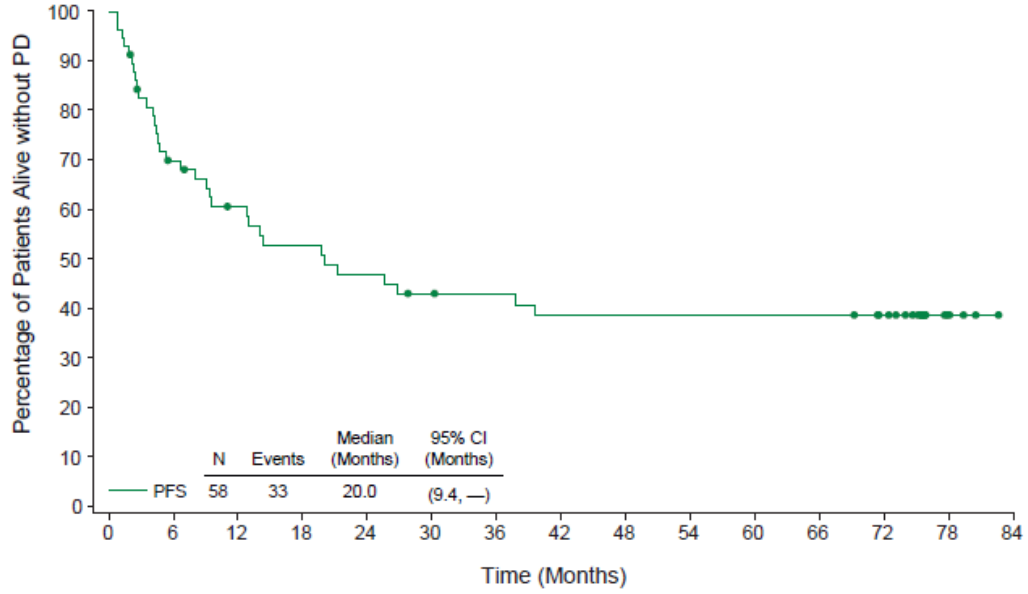
In the last forty months of trial follow-up, only two events of progression or death occurred demonstrating the strong disease control provided by brentuximab vedotin. This observed benefit and the flattening of the Kaplan Meyer curve was due to the efficacy of brentuximab vedotin and not due to censoring as 42% of patients were observed until the close of the trial[3]. The more than half of patients treated with brentuximab vedotin who remained alive at the end of the observation period (median follow up of 71.4 months), either with or without a subsequent stem cell transplant, would be considered long-term survivors[3]. According to the clinical community, after 5 years these patients would cease to receive treatment, including regular follow-up by their haematologists for sALCL.

Figure 1: OS following treatment with brentuximab vedotin (Five-Year Follow-Up per Investigator Assessment)[3]



Source: Pro et al., (2016)

Figure 2: PFS following treatment with brentuximab vedotin (Five-Year Follow-Up per Investigator Assessment)[3]



Source: Pro et al., (2016)

The efficacy seen in the SG035-0004 trial has also been observed in real world use of brentuximab vedotin for R/R sALCL in England via the CDF. Since 2013, approximately 45-50 R/R sALCL patients per year have benefited from brentuximab vedotin. Clinical and patient experience has been overwhelmingly positive in support of the effectiveness of brentuximab vedotin, with unanimous clinical and patient expert feedback similar to that described on page 11 of the ACD (Section 3.7). The strong effectiveness observes in UK patients through the CDF and NPP supports the magnitude of PFS and OS benefit and confirms the validity of the outcomes seen in the SG035-0004 trial.

3.2.2 ACD conclusion on cost-effectiveness in response to Section 3.10 - 3.18 of the ACD

In relation to Sections 3.10 – 3.18 of the ACD, Takeda agrees with the following statements:

"The committee accepted the structure of the model as representing the treatment pathway…The committee considered the model appropriate for its decision making"

"The committee agreed that the company's approach for modelling the rate of stem cell transplant was appropriate for decision making"

"The committee agreed that the company's approach for modelling progression-free survival and overall survival [based on Smith et al. 2013 data] was appropriate for decision-making"

"The committee concluded that data for progression-free survival and overall survival based on investigator assessment were appropriate for decision making."

"…investigator assessment has been used because it provided longer follow-up data (median observation at 71.4 months) and was more reflective of the assessments used in the self-control cohort."

"The committee concluded that the clinical expert distribution of therapy after progression was the most appropriate for decision-making."

All of the above committee conclusions and assumptions have been included in the company's modified base case cost-effectiveness analysis, presented in Table 1.14 of Appendix 1. Furthermore, Takeda's response to the committee's conclusions and discussions of cost-effectiveness parameters described in Sections 3.14, 3.15, 3.16 and 3.19 of the ACD have been addressed in analysis provided in Appendix 1.

3.3 Are the recommendations sound and a suitable basis for guidance to the NHS?

Takeda do not agree with the ACD draft negative recommendations as final recommendations, and in our opinion they are not a sound and suitable basis for guidance to the NHS. We have presented in this ACD response a robust case why brentuximab vedotin can be considered both a clinically effective and cost effective treatment for patients with R/R sALCL.

The modified base case analysis, including all of the committee's preferred assumptions and a significantly increased excess mortality risk for long-term survivors, yields an ICER of £18,324, as presented in Appendix 1. A full analysis of the impact of each modification to the base case ICER can be found in **Error! Reference source not found.** in Appendix 1. The modified base case ICER is well within the standard threshold considered by NICE to be a cost-effective use of NHS resources (i.e. £20,000 - £30,000/QALY), and therefore brentuximab vedotin for R/R sALCL should be recommended for baseline commissioning within the NHS. This would match the decision recently made by NICE in relation to brentuximab vedotin for the R/R HL post-ASCT indication; we believe such consistency of decision making would be welcomed by Takeda, NHS England, the clinical community, as well as patients and their representatives.

Moreover, a compelling case is made within Appendix 2 of this response that brentuximab vedotin for R/R sALCL satisfies NICE's end-of-life criteria and thus should qualify for additional flexibility in terms of NICE's final recommendation.

3.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy or maternity?

No other aspects relating to unlawful discrimination need particular consideration.

4. Conclusion

Takeda does not agree with the ACD draft negative recommendations as final recommendations, and in our opinion they are not a sound and suitable basis for guidance to the NHS. We have presented in this ACD response a robust case why brentuximab vedotin can be considered both a clinically effective and cost effective treatment for adults with R/R sALCL. Based on this response (which builds on the evidence in the original company submission) and a modified base case ICER that is well below the standard cost effectiveness threshold, Takeda requests that NICE adopt a positive final recommendation for brentuximab vedotin for R/R sALCL. The committee should, in our opinion, also take into account the compelling evidence that has been presented within this response to show that brentuximab vedotin for R/R sALCL meets NICE's end-of-life criteria.

A positive final recommendation would match the decision recently made by NICE in relation to brentuximab vedotin for the R/R HL post-ASCT indication; and we believe such consistency of decision making would be welcomed by Takeda, NHS England, the clinical community, as well as patients and their representatives. On the other hand, failure to recommend brentuximab vedotin would be a hugely retrograde step for ALCL patients in England who have had access to this medicine via the CDF since 2013, during which time it has become established as the preferred first-line salvage therapy for patients with R/R sALCL.

5. References

1. National Institute for Health and Care Excellence. Appraisal Consultation Document Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma - [ID512] https://www.nice.org.uk/guidance/gid-ta10086/documents/appraisal-consultation-document
2. Takeda UK Ltd. Data on File UK/DF/1707/0008 – ACADEMIC IN CONFIDENCE
3. Pro B *et al*. Five-Year Survival Data from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma. 58th Annual Meeting of the American Society of Hematology (ASH); 2016; San Diego.
4. Mak VH. Survival of patients eripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;**31**(16):1970-76.

One Birch Court,
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Worcester, WR3 8SG
[redacted]
[redacted]

5th Julv 2017

Dear NICE Technology Appraisal Committee C,

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

ALCL is an extremely rare condition. In this setting, there is an unmet need for alternatives to chemotherapy. Brentuximab vedotin offers an effective treatment option, with high remission rates, instead of highly toxic chemotherapy.

Uncertainty

As acknowledged repeatedly in the ACD, brentuximab vedotin is clinically effective. However, due to the rarity of ALCL, it would be difficult to do a randomised clinical trial. Whilst we accept that parts of the data are uncertain, this uncertainty is a result of the rarity of the condition. We submit that this must be taken into account when assessing brentuximab vedotin, because applying the "standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair." (Sir Andrew Dillon, 20 Feb 2015).

Since it has been funded through the Cancer Drugs Fund, it has become a key therapy in UK clinical practice. As such, to withdraw access to this treatment would be a step backwards, which would result in unnecessary deaths and prevent the NHS participating in future research in this area.

This unfairness is further highlighted by the recent positive NICE guidance of brentuximab vedotin for treating Hodgkin lymphoma patients (TA 446). Brentuximab vedotin is considered a step-change in the treatment of ALCL. To recommend it for the treatment of HL, but not ALCL (because of the data limitations created by the small population size), would be both illogical and inequitable.

Cost-effective

Additionally, all ICERs presented were cost-effective (the highest ICER/QALY listed in the ACD being £21,267). As such, we suggest that brentuximab vedotin is both a clinically and cost-effective use of NHS resources for treating relapsed or refractory systemic anaplastic large cell lymphoma.

Patient Feedback

We also want to take this opportunity to input comments on the ACD from an ALCL patient who has been treated with brentuximab vedotin:

"As a patient with relapsed/refractory systemic anaplastic large cell lymphoma, I received five cycles of brentuximab vedotin between July and October 2014. This followed two cycles of CHOP and one cycle of DHAP chemotherapy in May and June 2014 respectively. Both CHOP and DHAP were clinically ineffective in treating my rapid and aggressive symptoms. By contrast, brentuximab vedotin quickly demonstrated its high clinical effectiveness in a matter of days.

Brentuximab vedotin was responsive, well tolerated and represented a low toxic treatment compared to current chemotherapy regimens. Side effects are minimal, significantly less unpleasant and certainly more manageable. Its innovative, selectively targeted approach greatly improves both access to further treatments and ultimately, the survival outcomes for similar patients.

From a personal perspective, brentuximab vedotin arrested the progression of my symptoms, bringing them under control. Without it, the chances are that I would not have survived beyond the late summer of 2014. To consider it a step change in the treatment pathway of relapsed/refractory systemic anaplastic large cell lymphoma patients is an understatement. For this alone I implore the committee to arrive at a positive decision.

From an NHS cost and patient experience perspective, brentuximab vedotin can be administered to outpatients by intravenous infusion in approximately half an hour, compared with hospital admission for other forms of traditional treatments.

Today, I am living proof that access to effective treatment is fundamental. Notwithstanding the clinical and economic considerations, the implications of a negative decision are unthinkable. I know, through first-hand experience that brentuximab vedotin is clinically effective. Should my symptoms recur, the psychological impact of not having access to it is inconceivable, the kind of thoughts that keep me awake at night."

We hope that you will bear our comments in mind when considering your final recommendation and urge you to make brentuximab vedotin available to all of those who could benefit from it.

Yours Sincerely,

[redacted]
Leukaemia CARE

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From The Registrar
[redacted]

4 July 2017

Dear Sir or Madam

Re: ACD - Consultees & Commentators: Lymphoma (anaplastic large cell, systemic, relapsed, refractory) - brentuximab vedotin ID 512

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.

Our experts note that it was stated during the first committee meeting that, brentuximab vedotin is a paradigm shift in the management of patients with r/r sALCL. This view was strongly supported at the appraisal meeting by Professor Peter Clarke, Chair of the NHSE chemotherapy group and cancer drugs fund.

Patients with r/r sALCL unequivocally represent a disease area of unmet need; disease progression after first-line chemotherapy invariably translates into short survival times notwithstanding the use of second-line chemotherapy regimens. Our experience in the UK is similar to the published Mak *et al* dataset from British Columbia; patients with r/r sALCL treated with second-line chemotherapy can expect survival times measured in a small number of months.

In recent years, the NHSE cancer drugs fund has permitted use of brentuximab vedotin for r/r sALCL allowing patients access to this transformative medicine. Importantly, this has allowed many patients to 'bridge' to stem cell transplantation. Our experts note that the NICE committee will also be familiar with this approach following the recent NICE approval of the same drug - brentuximab vedotin - for patients with relapsed/refractory Hodgkin lymphoma (NICE TA446). Our experts believe that for patients with r/r sALCL, brentuximab vedotin is an even more significant step-change in clinical management.

Our experts make the following comments to points raised in the ACD:

Results of a single arm study (SG035-0004) in 58 patients suggest brentuximab vedotin is clinically effective based on response rates and there was uncertainty regarding the extent of progression-free survival and overall survival because median progression-free survival and overall survival were not reached.

With mature follow-up of the SG035-0004, the fact that median PFS and median OS were not reached can only support the effectiveness of this therapy for patients with relapse/refractory ALCL. Our experts note that it is unclear why the NICE committee regarded this as uncertainty. Taken together, the fact that the median PFS/OS have not been reached over a long observation period, in the context of a highly aggressive malignancy which quickly manifests clinically at disease progression, serves only to underscore the effectiveness of this drug rather than introduce uncertainty.

As there were no data directly comparing brentuximab vedotin with current treatment (chemotherapy), an unadjusted indirect comparison was carried out. This was considered to be the best available evidence although there was uncertainty because of differences in age, stage of disease, and performance status in the groups compared.

Although an indirect comparison, the Mak et al dataset is the largest real-world chemotherapy comparator available. Of 36 ALCL patients in this analysis, only 5 patients (14%) experienced long-term survival with a median PFS of 1.8 months and OS of 3 months for the ALCL patients treated with chemotherapy. Even for patients with a good performance status (in the whole Mak et al cohort), the median PFS was still only 5 months. These data absolutely support the clinical experience of brentuximab vedotin in r/r sALCL as an unprecedented step-change in management.

We would be grateful if the committee can carefully consider these comments and review their recommendation in the appraisal consultation document

Yours faithfully

Nottingham University Hospitals NHS
NHS Trust

City Hospital Campus
Centre for Clinical Haematology
Hucknall Road
Nottingham
NG5 1PB

Tel: [redacted]

3rd July 2017

Response to NICE: ACD - Consultees & Commentators: Lymphoma (anaplastic large cell, systemic, relapsed, refractory) - brentuximab vedotin [512]

Dear NICE Appraisal Committee C,

With reference to the published ACD for brentuximab vedotin indicated for relapsed/refractory systemic anaplastic large cell lymphoma (r/r sALCL), the following constitutes my response as nominated clinical expert (on behalf of the NCRI and RCP).

As I clearly stated during the first committee meeting, brentuximab vedotin is a paradigm shift in the management of patients with r/r sALCL. This view was strongly supported at the appraisal meeting by Professor Peter Clarke, Chair of the NHSE chemotherapy group and cancer drugs fund.

Patients with r/r sALCL unequivocally represent a disease area of unmet need; disease progression after first-line chemotherapy invariably translates into short survival times notwithstanding the use of second-line chemotherapy regimens. Our experience in the UK is similar to the published Mak *et al* dataset from British Columbia; patients with r/r sALCL treated with second-line chemotherapy can expect survival times measured in a small number of months.

In recent years, the NHSE cancer drugs fund has permitted use of brentuximab vedotin for r/r sALCL allowing patients access to this transformative medicine. Importantly, this has allowed many patients to 'bridge' to stem cell transplantation. The NICE committee with also be familiar with this approach following the recent NICE approval of the same drug - brentuximab vedotin - for patients with relapsed/refractory Hodgkin lymphoma (NICE TA446). It is my view, together with many expert colleagues, that for patients with r/r sALCL, brentuximab vedotin is an even more significant step-change in clinical management.

Specific comments to points raised in the ACD are as follows:

1. *"Results of a single arm study (SG035-0004) in 58 patients suggest brentuximab vedotin is clinically effective based on response rates and there was uncertainty regarding the extent of progression-free survival and overall survival because median progression-free survival and overall survival were not reached."*

RESPONSE: With mature follow-up of the SG035-0004, the fact that median PFS and median OS were not reached can only support the effectiveness of this therapy for patients with relapse/refractory ALCL. It is unclear why the NICE committee regarded

this as uncertainty. Taken together, the fact that the median PFS/OS have not been reached over a long observation period, in the context of a highly aggressive malignancy which quickly manifests clinically at disease progression, serves only to underscore the effectiveness of this drug rather than introduce uncertainty.

2. *"As there were no data directly comparing brentuximab vedotin with current treatment (chemotherapy), an unadjusted indirect comparison was carried out. This was considered to be the best available evidence although there was uncertainty because of differences in age, stage of disease, and performance status in the groups compared".*

RESPONSE: Although an indirect comparison, the Mak et al dataset is the largest real-world chemotherapy comparator available. Of 36 ALCL patients in this analysis, only 5 patients (14%) experienced long-term survival with a median PFS of 1.8 months and OS of 3 months for the ALCL patients treated with chemotherapy. Even for patients with a good performance status (in the whole Mak et al cohort), the median PFS was still only 5 months. These data absolutely support the clinical experience of brentuximab vedotin in r/r sALCL as an unprecedented step-change in management.

I should be grateful if the committee can carefully consider these comments and review their minded recommendation in the appraisal consultation document.

Yours faithfully,

Dr Christopher P Fox
MBChB(Hons) MRCP FRCPath PhD
Consultant Haematologist
Nottingham University Hospitals

Clinical Haematology 3rd Floor
City Campus
Hucknall Road
NG5 1PB
[redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Haematologist
Organisation	Lymphoma Special Interest Group of the British Society of Haematology
Location	England
Conflict	No
Notes	I have received honoraria from Takeda for advisory work and speaking at symposia.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Relapsed anaplastic large cell lymphoma is a devastating disease. The British Columbia Cancer Agency have reported outcomes of relapsed PTCL (which included ALCL) showing PFS and OS of less that 1 year (Mak et al). This very much reflects the experience of lymphoma doctors treating these patients in the clinic. Brentuximab vedotin has however transformed the outlook for these patients. This has been demonstrated by the largest trial ever performed in this rare patient group, albeit a single arm phase II. It showed very impressive PFS and PS curves which show a convincing plateau. Some of these patients were consolidated with a stem cell transplant, but not all. This drug is therefore transformational and directly leads to the saving of lives. There is no alternative drug which is anywhere near as active. I would thoroughly encourage NICE to approve this drug for relapsed / refractory ALCL. It is clear that it is life saving. If it is not available in the UK, patients will suffer avoidable deaths which would be truly tragic. Thank you for your consideration of this feedback.

Name	[redacted]
Role	NHS Professional
Other role	Clinical Research Fellow in Lymphoma
Organisation	The Christie NHS Foundation Trust
Location	
Conflict	Yes
Notes	I have received speaking fees and educational support from Takeda UK
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This ACD is for brentuximab vedotin (BV) in r/r ALCL e.g. the marketing authorisation. However section 1.2 regards chemotherapy as a 'standard' second line therapy. This is not supported by any literature of sufficient quality, a fact reflected in both ESMO and BCSH guidance which treat chemo and BV in equipoise for r/r ALCL. This is then stated in section 3.2,

	which contradicts 1.2

Name	[redacted]
Role	NHS Professional
Other role	Consultant in haematology and Haemato-Oncology
Organisation	Kent Cancer Network Haemato-Oncology Group
Location	England
Conflict	No
Notes	I have received educational grant to attend a scientific meeting from Takeda
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is a rare group of lymphoma where not many options are available and the FAD is a major setback for patients. It is the only T cell lymphoma that responds well to Brentuximab which offers good and lasting remissions. Not allowing patients to receive this drug will no doubt increase the mortality from this disease with no other options proven to be useful or relevant national trials.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Medical Oncologist
Organisation	Royal Marsden Hospital
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear NICE, I wholeheartedly disagree with the recent negative ACD for brentuximab in relapsed refractory anaplastic large cell lymphoma (ALCL) setting which is now a standard of care in the management of these patients at our institution. The outcomes for patients with relapsed peripheral T-cell lymphoma (PTCL) including patients with relapsed/refractory ALCL are extremely poor with a reported median OS and PFS of just 5.5 months and 3.1 months respectively (Mak et al, JCO 2013). Brentuximab is a well-tolerated therapy and has demonstrated excellent efficacy and durable remissions for this patient population in a phase II study, with the median OS not reached. In contrast RR PTCL patients (including ALCL) treated with chemotherapy have a reported median OS of just 6.5 months. Outcome data from the named patient program further supports the excellent outcomes for this patient population following brentuximab (Zinzani et al, Crit Rev Oncol Hem 2015) and a recently published multi-centre retrospective study reported similar findings (Lamarque et al, Haematologica 2016). In these studies brentuximab has been used successfully as a bridge to either autologous or allogeneic stem cell transplantation which offers patients with RR PTCL an opportunity to achieve long term cure in an otherwise very poor prognosis disease. I would

	ask the committee to re-consider this decision, which I feel will significantly negatively impact survival for this rare patient subgroup. Yours sincerely, [redacted]

Name	[redacted]
Role	NHS Professional
Other role	Clinical research fellow
Organisation	The Royal Marsden
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear NICE, I wish to comment that I feel the recent negative ACD for brentuximab for patients with relapsed/refractory systemic anaplastic large cell lymphoma should be re-considered. The outcomes for this patient population is very poor, even when they are managed with chemotherapy (Mak et al, JCO 2013), but very high rates of overall and complete response have been reported for single-agent brentuximab and remissions are frequently prolonged. Brentuximab can be used as a bridge to a potentially-curative transplant for these patients and durable remissions even in the absence of brentuximab have been reported with this approach. Omitting brentuximab from the treatment options for these patients in the relapsed setting will undoubtedly compromise their survival. Kind Regards, [redacted]

Name	[redacted]
Role	NHS Professional
Other role	Consultant Haematologist
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	ALCL is a rare lymphoma but associated with a poor prognosis. Nearly half of patients relapse and prognosis is a short number of months if there is no salvage treatment available. Patients who are older than 60 years of age are often not able to tolerate intensive chemotherapy salvage and in this situation brentuximab (BV) is the only option available otherwise the

	expected survival would be 2 to 3 months. Over the last 3 years I have given 14 patients BV for relapse Hodgkin lymphoma but only 2 patients BV for relapsed ALCL. My 60 year old patient who was diagnosed in 2010 and relapsed in 2015 was successfully bridged to allogeneic transplant (allo) and remains well and in remission. [redacted] received 7 cycles of BV as a bridge to allo. My 74 year old man relapsed in Dec 2015, had 16 cycles of BV and remains well with an excellent quality of life. For younger patients who relapse, salvage chemo is an option but often doesn't work. It is therefore essential to have BV available for second line salvage, aiming to obtain CR and proceed to autologous or allogeneic stem cell transplant. Using BV as first treatment after relapse also reduces the toxicity of systemic chemotherapy which is important prior to stem cell transplant. For patient bridging to auto or allo I would only use on average 4 to 6 cycles of BV. For older patients, over the age of 65 years, they are not fit for intensive chemotherapy and BV is the only option to obtain response with minimal toxicity. Without BV, patients with R/R ALCL will typically die within a few months. If BV is used as a bridge to transplant then this can be extended to years. BV as treatment for older patients not fit enough for transplant also improves survival from short number of months to years in my clinical experience. Because of the rare nature of disease large phase III data is not available but my "real world" experience is that BV is effective in both PFS, OS and quality of life in a situation where there are no other options available and I urge you to reconsider you decision for this small number of patients.

Name	[redacted]
Role	NHS Professional
Other role	Consultant haematologist
Organisation	King's College Hospital
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Anaplastic large cell lymphoma is a rare disorder with limit treatment options at relapse. Brentuximab represents an excellent treatment option for relapsed patients with response rates that are much better than standard chemotherapy. Given the rarity of this disorder and its unmet need, brentuximab should remain an option for these patients. Without the option on brentuximab many more patients will likely die of the disease as very few patients achieve a long term remission with

	standard chemotherapy options. I strongly disagree with the ACD

Name	[redacted]
Role	NHS Professional
Other role	Clinical Research Fellow
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Response to NICE recommendations over use of Brentuximab Vedotin in ALCL By Dr [redacted] - Clinical Research Fellow, The Christie NHS Foundation Trust I am writing to you to ask if you would kindly reconsider your Appraisal decision in which you are minded not to recommend the use of Brentuximab Vedotin in Relapsed/Refractory Anaplastic large Cell Lymphoma. This is a life-saving treatment in patients who have no good alternative treatment. Throughout the report comparison to second line chemotherapy is mentioned, yet no once does any survival data from such regimens appear. Throughout the report it is written the committee accepts the reduced data set that the company has been able to provide due to rarity of this disease. The report says it accepts the difficulty in producing randomised data comparing chemotherapy with Brentuximab. When considering an approval in the end of life use, an extension of three months of life allows Brentuximab to be consider, throughout the report it says the committee is happy to accept progression free survival and overall survival data from SGN035-0004 and yet at this point there is a refusal to accept data showing life extension by years not just months that has been supported by other trials as listed in the report. Throughout the report the Mak 2013 trial looking at survival in relapsed/refractory ALCL patients is quoted as the standard of care approach. This trial showed an increase in median overall survival of one month for patients treated with second line chemotherapy, median progression free survival is less than a month. I am part of dedicated lymphoma team treating patients with ALCL, Brentixumab Vedotin offers patients a very real chance at long term survival. In the Mak trial only patients with a performance status of 0 or 1 had any real benefit from second line chemotherapy and even then progression free survival was short, an increase of only two months. For these patients to achieve long term survival or at the very least progression free survival that is measurable in terms of years not months then we need access to new agents. The data from the SGN035-0004 trial is remarkable, even if you do not accept the full extent

	of this data for the concerns you have listed it is very clear Brentuximab Vedotin is offering these patients both greater overall and progression free survival measurable in years. This drug is currently being used to allow patients to successfully undergo stem cell transplants. It offers very real hope in a disease where even first line treatment is not very successful. It is well tolerated in comparison to the platinum based chemotherapy regimens used as alternative and we have had very real success in treating patients with performance statuses of 3 and 4 who would not be fit enough to be treated with platinum. In the current economic climate we are all aware of the burdens on the NHS and the practical decisions that have to be made but in this case there is clear evidence that Brentixumab Vedotin is superior to chemotherapy and offers patients a far greater chance of achieving long term survival. Delaying a decision on this drug by years to collect more data would be at the detriment of many patients who have a horrendous diagnosis. It is my opinion that the data is already clear and not allowing NHS patients access to Brentixumab Vedotin for treatment of ALCL will lead to worse outcomes in this patient subset.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Medical Oncologist - [redacted] for Lymphoma
Organisation	Portsmouth Hospitals NHS Trust
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This treatment offers a potentially curative option for patients with relapsed /refractory ALCL. It is a potentially curative option with minimal toxicity. For those for whom intensive salvage strategy is not suitable /appropriate stopping access to this drug is potentially discriminatory in allowing no realistic salvage option On behalf of all future ALCL patients with support of patients in my practice with long term post Brentuximab remissions please reconsider 'minded No'

Name	[redacted]
Role	Patient Organisation
Other role	[redacted]
Organisation	Lymphoma Association
Location	
Conflict	Yes
Notes	We have received grant support from the manufacturer for specific projects. The financial sum involved is ~£10,000 out of a total organisational annual income of ~£1.7m, which is

	predominantly generated from public donations.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We are disappointed that NICE is proposing not to recommend brentuximab vedotin for routine use on the NHS in England for this group of patients. Although patients with relapsed or refractory systemic ALCL are a small group, there is a high level of unmet need, not least because the symptoms of the disease can be debilitating and distressing, and because 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: 1. 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 2. 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 a transplant may not be able to do so if their lymphoma cannot be controlled again with effective treatment first. Achieving 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. Patients unsuitable for transplant can also benefit from palliative treatment giving significant and prolonged symptom reduction which cannot be achieved with standard chemotherapy options. It seems that innovative treatments for small patient groups such as in this situation are stymied by the shortcomings of an appraisal methodology that struggles to cope with uncertainty (inevitable when small numbers are involved), irrespective of the strength of available evidence. In patient populations of this size Phase III trial data is hard to come by, so without some flexibility in the treatment of available evidence, then few, if any, effective treatments are likely to be approved for patients with rarer forms of cancer. One of the criticisms the appraisal consultation document makes is that the company's evidence relies on a single arm phase II study, but it's hard to see how it would be practical and ethical to provide phase III research data given the size of the patient population and the level of unmet need. In relation to the cost-effectiveness calculations, these seem to be based upon eight cycles of treatment, although standard clinical practice now appears to be either five or six cycles (on

	the basis that maximal response is seen in clinical practice after 4 to 5 cycles). If this is the right, then the cost-effectiveness calculations will be severely distorted. From a patient perspective, you'd expect the technology appraisal to be based on current clinical practice. In conclusion we call on NICE and the company to review further the evidence and pricing assumptions so that patients can have access to a potentially life-saving treatment that also has significantly fewer side effects and after effects than traditional chemotherapy.

Name	[redacted]
Role	NHS Professional
Other role	Professor of Medical Oncology,
Organisation	University of Manchester and the Christie NHS Foundation Trust, Manchester
Location	England
Conflict	Yes
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Brentuximab vedotin represents a major step forward in the management of relapsed/refractory ALCL; response rates are high and toxicity is mild to moderate and easily managed by dose reduction or dose delay. In the younger/fitter population fit for transplant brentuximab vedotin provides a bridge to this potentially curative procedure and in the older/less fit population it can provide prolonged disease control and improved quality of life. It would be highly concerning in my view if NICE decided against allowing access to this drug for patients in England and be clear evidence of excessively high barriers being placed in the way of introducing new, effective and well tolerated medicines into the NHS. Moreover and worryingly it would place the UK clearly outside international standard practice with respect to the management of ALCL - in circumstances where UK patient outcomes data lag behind those of other developed countries. The data describing use of brentuximab vedotin in ALCL, a rare disease, is limited and there is an absence of randomised data. I am concerned that too much analysis has been attempted and too many firm conclusions drawn from this limited data set.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	All current survivors of cancer have an excess mortality compared with their untreated peers due to the increased risk of 2nd cancers, cardiopulmonary disease and infection. Radiotherapy and alkylating agent chemotherapy are the main reasons for this increased risk and there is an international consensus to move away from these treatments towards targeted approaches wherever possible. BV is an example of a targeted drug with no data to suggest any increased risk of 2nd cancers or cardiovascular disease linked to it's use. The

	excess mortality argument is therefore highly supportive of the use of BV instead of chemotherapy.

Brentuximab vedotin (Adcetris®▼) for treating relapsed or refractory systematic anaplastic large cell lymphoma [ID512]:

Appendix 1: Additional Economic Analyses – in response to the ACD (June 2017) for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

5th July 2017

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Table of Contents

1. Additional analyses

1.1 Overview

In this part of the response, the company provides the additional evidence and analyses cited by the committee in order to facilitate a final recommendation on the cost-effectiveness of brentuximab vedotin in the R/R sALCL indication. This presents an updated cost-effectiveness analysis of brentuximab vedotin and includes presentation of a modified base case. This is discussed further in Section 1.2.

All of the analyses presented in Appendix 2 include a confidential patient access scheme (PAS) of a [redacted] straight discount off the NHS list price, in line with the currently existing PAS.

1.2 Updated analysis on the cost-effectiveness of brentuximab vedotin

1.2.1 Overview

As per Section 3.2.1 of the ACD, the incremental cost-effectiveness ratio (ICER) for brentuximab vedotin vs chemotherapy estimated by the company was £12,873 per QALY gained compared to the ERG base case estimate of £21,267 per QALY gained. The company base case ICER of £12,873 was based on the model settings presented in Table 1.1.

Table 1.1 Summary of company base case[1]

Component	Company base case approach	Committee view on approach
Rates of SCT	• Calculated by combining response rates with the proportion who actually proceed to transplant and the ratio of autologous stem cell transplant (ASCT) to allogeneic stem cell transplant (alloSCT) • Response rates for brentuximab and chemotherapy based on those achieved in SG35-0004[2] • Proportion of responders who proceed to transplant based on SG35-0004 • Rate of ASCT to alloSCT based on SG35-0004	• SCT rates used in the company's model are appropriate (Section 3.11)
Modelling of PFS and OS for SCT	• PFS and OS based on data from Smith et al. (2013)[3] extrapolated using parametric cure models. • PFS and OS for ASCT and alloSCT are independent of salvage treatment	• Modelling of PFS and OS for SCT is appropriate (Section 3.12)
Assessment of progression for	• Investigator-assessed progression-free survival (PFS) for brentuximab vedotin (no SCT)	• PFS based on the investigator

brentuximab (no SCT)		assessment is appropriate (Section 3.13)
Extrapolation of PFS and OS for brentuximab vedotin (no SCT)	• Parametric cure models used to extrapolate PFS and OS for brentuximab vedotin (no SCT)	• Standard parametric models are preferred (Section 3.14)
Source of PFS data for chemotherapy (no SCT)	• PFS for chemotherapy (no SCT) based on a self-control dataset; PFS achieved with the most recent cancer-related therapy prior to brentuximab vedotin for the subgroup of 39 patients in SG035-0004 whose most recent therapy was for R/R disease	• Mak et al. (2013) is the most appropriate source for both PFS and OS (Section 3.15)
Extrapolation of PFS and OS for chemotherapy (no SCT)	• Standard lognormal model used to extrapolate PFS and OS for chemotherapy (no SCT)	• Alternative distributions should be explored (Section 3.16)
Post-progression therapies	• Post-progression therapy distribution based on a clinical expert opinion	• Clinical expert opinion distribution was the most appropriate for decision-making (Section 3.18)
Excess mortality rates	• Excess mortality rates for brentuximab vedotin (no SCT), chemotherapy (no SCT), ASCT and alloSCT were based on clinical expert opinion	• Higher excess mortality rates should be used and sourced from published literature (Section 3.19)

Based on Sections 3.11, 3.13 and 3.18 of the ACD, the committee agreed with the company's method for estimating rates of SCT, use of investigator-assessed PFS for brentuximab vedotin (no SCT) and use of the clinical expert opinion based post-progression therapy distribution. However, as outlined on page 4 of the ACD, the committee requested that Mak et al. (2013)[4] should be used to inform PFS and OS for chemotherapy (no SCT), a full exploration of parametric models for PFS and OS for brentuximab vedotin (no SCT) and chemotherapy (no SCT) should be conducted, and higher excess mortality rates should be considered.

In response, the company have provided a modified base case and scenario analyses based on the committee's preferred modifications cited in Section 1.2 of the ACD. These modifications include the following:

- "Use data from Mak et al. (2013)[4] for extrapolating both progression-free survival (PFS) and overall survival (OS) for chemotherapy
- Explore a number of parametric models for extrapolating PFS and OS for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate
- Include a range of excess mortality rates higher than those used in the company's base-case analyses. The range should come from published literature identified through a systematic literature review rather than clinical expert opinion."[1]

Further details on the methods relating to the company's modified base case for each of the modifications above are presented in Section 1.2.3.

In addition, the company has made a number of revisions to the model based on comments cited in the ERG report, and some minor errors identified in the company model during implementation of the requested analyses. These include the following:

- Double-discounting of post-progression therapy and follow-up care costs
- Ensuring the distribution of chemotherapies sums to 100% in the probabilistic analysis
- Implementation of general population mortality for chemotherapy (no SCT) PFS
- Calculation of chemotherapy acquisition costs
- Calculation of follow-up care costs in post-progression

These revisions are discussed further in Section 1.2.2. The company would like to highlight that rectification of these errors has had an immaterial impact on the results relative to the company ICER of £12,873 per QALY. The combined impact of these revisions resulted in an increase in the company ICER from £12,873 per QALY gained to £13,002 per QALY gained.

1.2.2 Correction of model errors based on comments in the ERG report

As highlighted in Section 1.2.1, the following were cited in the ERG report as potential errors in the company model:

- Double-discounting of post-progression therapy and follow-up care costs
- Chemotherapy distribution does not sum to 100% in the probabilistic analysis
- Implementation of general population mortality for chemotherapy (no SCT) PFS

In an attempt to replicate the ERG's preferred base case, the company planned to remove double discounting of post-progression costs from the company model to align with the methods implemented in the ERG's model. Upon review of the ERG's model dated 07/04/17, the company believes that removal of double discounting post-progression costs has been implemented incorrectly; reasons for this are summarised in Table 1.2. The company would like to highlight that as per the pro-forma response document, the company believe that the ERG's adjustment with respect to the removal of double discounting may be inappropriate. However, the company recognise that the modification impacts both treatment arms, and hence has minimal impact on the results.

Table 1.2 Summary of double discounting removal implemented by the ERG

Cost component	Cohort(s)	Implementation in the ERG's model
Total undiscounted acquisition costs	Brentuximab vedotin + ASCT and brentuximab vedotin + alloSCT	• These are calculated based on mean cycles received by the brentuximab (no SCT) cohort. • Given these therapies are not considered as post-progression therapies, this will not impact the results.
Total undiscounted administration costs	Brentuximab vedotin + ASCT and brentuximab vedotin + alloSCT	• These are calculated based on mean cycles received by the brentuximab (no SCT) cohort. • Given these therapies are not considered as post-progression therapies, this will not impact the results.
Total undiscounted concomitant medication costs	Brentuximab vedotin + ASCT and brentuximab vedotin + alloSCT	• These are calculated based on mean cycles received by the brentuximab vedotin (no SCT) cohort. • Given these therapies are not considered as post-progression therapies, this will not impact the results.
Total undiscounted adverse event costs	Single-agent chemotherapy and multi-agent chemotherapy	• Includes the impact of discounting
Total undiscounted post-progression therapy costs	Chemotherapy + alloSCT	• Includes the impact of discounting
Total undiscounted follow-up care in post-progression costs	Brentuximab vedotin + ASCT, brentuximab vedotin + alloSCT, chemotherapy + ASCT, brentuximab vedotin + alloSCT	• These are calculated as the weighted average of pre-progression follow-up care costs for brentuximab vedotin + SCT and chemotherapy + SCT. • The company believes that these should be calculated using pre-progression follow-up care costs for brentuximab vedotin (no SCT) and chemotherapy (no SCT) as per the discounted costs

The company has rectified this, and believes that the removal of double discounting has now been implemented in the company model.

Upon removing the impact of double discounting, the company identified the following minor errors in the company model:

- Chemotherapy (no SCT) acquisition costs: Discounting of chemotherapy (no SCT) acquisition costs had not been implemented correctly
- Follow-up care costs in post-progression: Patients receiving multi-agent chemotherapy or BSC in post-progression did not accrue follow-up care costs.

The company would like to apologise for this. These minor errors have now been rectified in the company model.

The impact of these minor errors on the cost-effectiveness of brentuximab vedotin vs chemotherapy are presented in Table 1.3. The combined impact of these revisions resulted in a small increase in the company ICER from £12,873 per QALY gained to £13,002 per QALY gained. Results of the scenarios presented in Section 1.2.4 incorporate the impact of these corrections.

Table 1.3 Impact of each modification on the ICER

Modification	Intervention	LYs	QALYs	Costs	Inc. costs	Inc. QALYs	ICER (per QALY)
Original company base case	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,873
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Ensure chemotherapy distribution sums to 100% in probabilistic analysis	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,873
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Removal of discounting post-progression costs	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,861
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Correction of chemotherapy acquisition costs discounting	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,882
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Revision of follow-up care costs in post-progression	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£13,008
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Implementation of general population mortality for chemotherapy (no SCT) PFS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,867
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Combined impact of above base case modifications	**Chemotherapy**	3.35	[redacted]	[redacted]	-	-	**£13,002**
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	

1.2.3 Methods for the modified base case

1.2.3.1 Use of Mak et al. (2013) to inform PFS and OS for chemotherapy

The company recognises that use of the self-control dataset to inform PFS for chemotherapy (no SCT) excludes the potential for long-term survivors. Moreover, due to the nature of the dataset, the self-control dataset does not include deaths, and hence does not equate to PFS or time-to-progression.

In response to this, and to align with Section 3.15 and Section 3.16 of the ACD, the company used PFS data from Mak et al. (2013)[4] (PS<2) to inform PFS for chemotherapy (no SCT). In the original company submission, these data were used in a scenario analysis to inform PFS for chemotherapy (no SCT) through use of the observed Kaplan-Meier data.

To align with Section 3.16 of the ACD, the company fitted standard parametric survival models to the Mak et al. (2013) (PS<2) PFS data. This was not originally conducted as part of the company submission as the self-control dataset was used to inform chemotherapy (no SCT) in the company base case analysis, whereas the Mak et al. (2013) data was used in a scenario analysis.

Parametric models were fitted in Stata (2014)[5] using the 'streg' command. The process for selecting the most appropriate model replicated that for brentuximab vedotin (no SCT) PFS and OS, and chemotherapy (no SCT) OS presented in Section 5.3.4 of the original company submission. Specifically, the suitability of each parametric model was assessed using the methods described in NICE DSU technical support document (TSD) 14[6, 7] (see Table 5.11 of the company submission). This assessment was used to identify models that provided a good fit to the observed data and clinically and biologically plausible extrapolations.

An overlay of the Kaplan-Meier curve and the parametric curves are presented in Figure 1-2. Overlays of the Kaplan-Meier curve with each separate parametric curve are presented in the the Appendix. The corresponding AIC and BIC statistics, and 99% PFS estimates are presented in Table 1.4. The Cox-Snell Residual plots are presented in

Figure 1-1.

Table 1.4 AIC and BIC statistics and 99% PFS estimates for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

	Exponential	Weibull	Gompertz	Lognormal	Log-logistic	Gamma
99% PFS (years)	7.1	9.9	21.5	16.5	27.9	19.4
AIC	183.89	176.44	177.79	170.39	173.11	172.28
BIC	185.74	180.14	181.49	174.09	176.81	177.83
AIC rank	6	4	5	1	3	2
BIC rank	6	4	5	1	2	3
	AIC, Akaike information criterion; BIC, Bayesian information criterion					

Figure 1-1 Cox-Snell residual plots for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

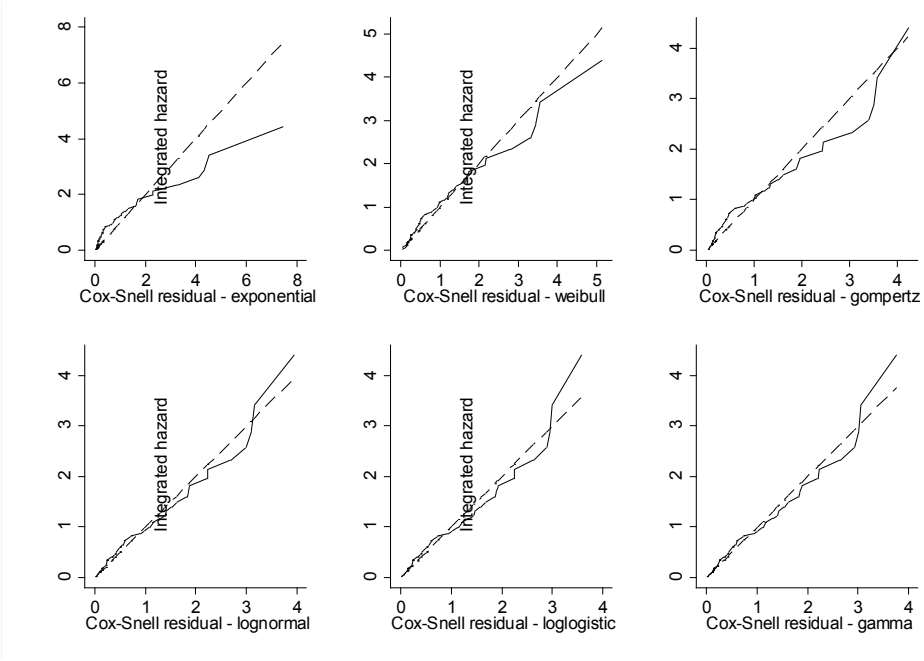


Figure 1-2 Parametric models for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2) – 5 years

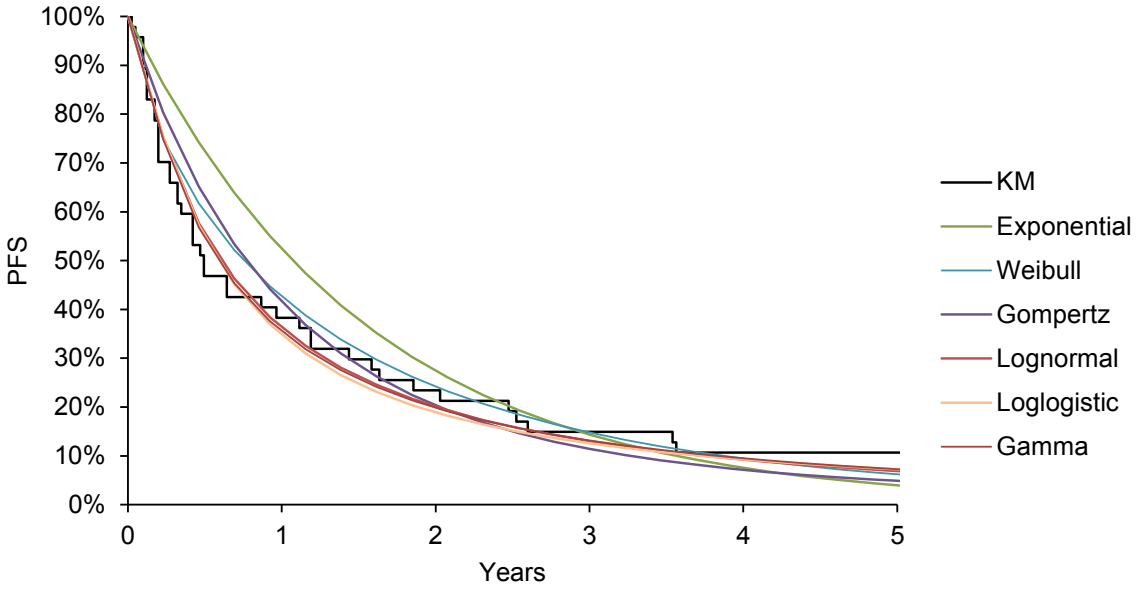
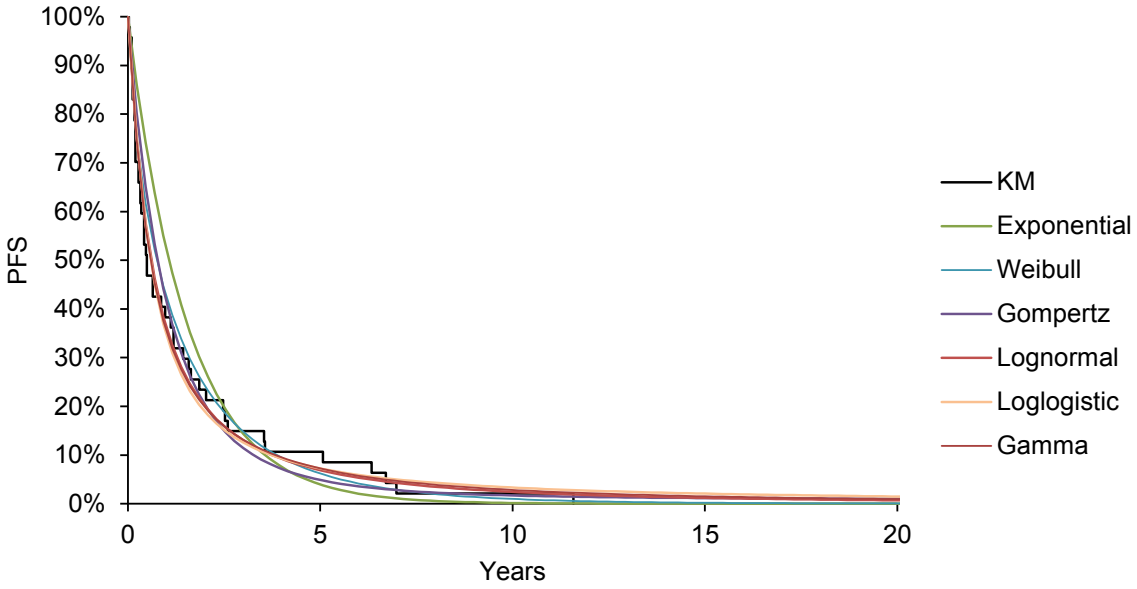


Figure 1-3 Parametric models for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2) – 20 years



The lognormal, log-logistic and gamma models provided the best fit based on visual inspection, Cox-Snell residual plots and AIC and BIC statistics; of which the lognormal model provided the best fit based on BIC.

The lognormal, log-logistic and gamma models predict that 99% of patients experience disease progression or death by approximately 16.5, 27.9 and 19.4 years respectively; whereas the corresponding Kaplan-Meier estimate was approximately 12 years. Given the relatively high 99% PFS estimates generated by the log-logistic and gamma distributions relative to the observed Kaplan-Meier, the lognormal distribution was selected for use in the modified base case. Although the lognormal distribution also over-predicts PFS relative to the observed Kaplan-Meier estimate, the company did not believe that this invalidated use of the lognormal model given the uncertainty in the tail of Kaplan-Meier curve.

The corresponding PFS curves generated by the model by cohort and by comparator are presented in

Figure 1-4 and Figure 1-5 respectively.

Figure 1-4 PFS, by cohort

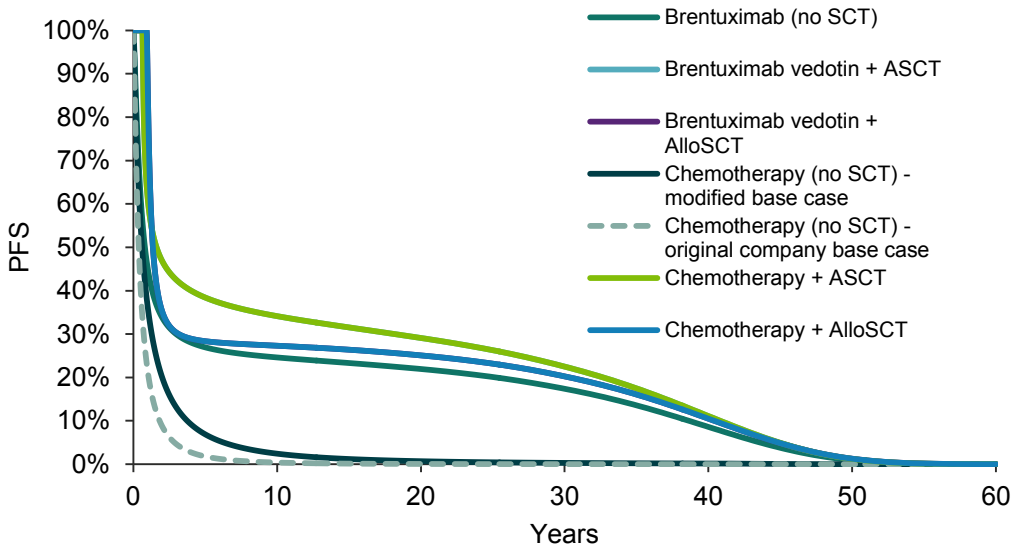
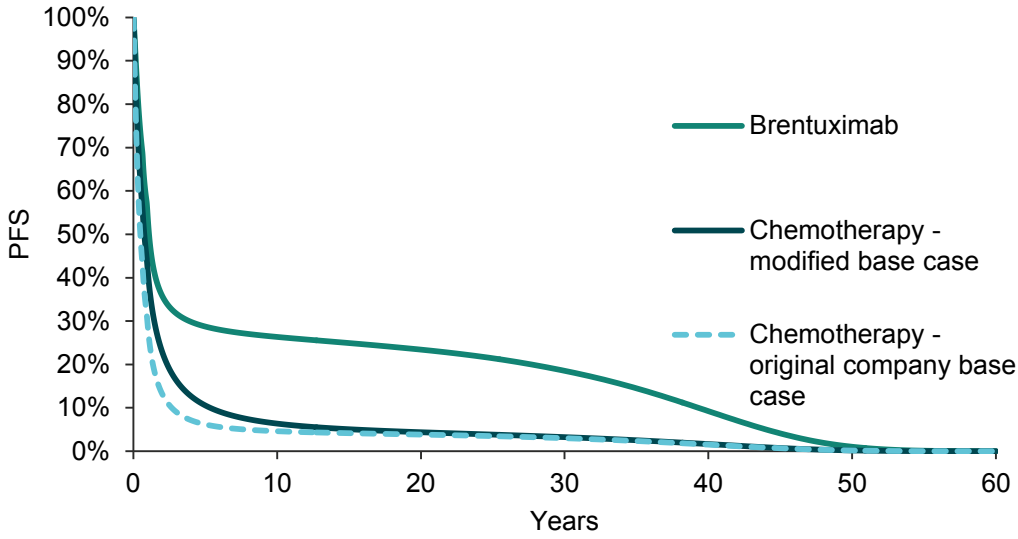


Figure 1-5 PFS, by comparator



Cost-effectiveness results based on use of the observed Kaplan-Meier data and all of the parametric models explored are presented in Section 1.2.4.1. However, the company would like to reiterate that the lognormal model has been selected to model PFS for chemotherapy (no SCT) as part of the modified base case.

1.2.3.2 Explore a number of parametric models for extrapolating PFS and OS for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate

The company recognises that the committee would like to have seen cost-effectiveness analyses based on a number of standard parametric models for brentuximab (no SCT) and chemotherapy (no SCT).

Section 3.16 of the ACD cites that "*the committee concluded that it would have liked to have seen cost-effectiveness analyses based on a number of parametric models including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate*".[1] The company would like to clarify that both accelerated failure time models and proportional hazards models were considered in the original submission for both PFS and OS for both cohorts. For brentuximab vedotin (no SCT), given that mixture cure models were used in the base case of the company submission, ICERs were only presented for the best fitting standard parametric model (gamma).

Brentuximab vedotin (no SCT) - PFS

The company reviewed the original submission, and agrees that it is unclear how the gamma distribution was identified as the best fitting standard parametric model for brentuximab vedotin (no SCT). The company would like to apologise for this. In response, and to align with Section 3.16 of the ACD, the company has presented all of the standard parametric models which were considered as part of the original submission.

The process for selecting the most appropriate parametric model replicated that for chemotherapy (no SCT) PFS (Section 1.2.3.1).

An overlay of the Kaplan-Meier curve and the parametric curves are presented in Figure 1-6. Overlays of the Kaplan-Meier curve with each separate parametric curve are presented in the Appendix. The corresponding AIC and BIC statistics, and 99% PFS estimates are presented in Table 1.5. The Cox-Snell Residual plots are presented in the Appendix.

Table 1.5 AIC and BIC statistics and 99% PFS estimates for brentuximab (no SCT) PFS

	Exponential	**Weibull**	**Lognormal**	**Log-logistic**	**Gamma**
99% PFS (years)	12.8	34.0	NR	NR	NR
AIC	245.575	234.131	226.364	228.002	220.121
BIC	247.289	237.559	229.792	231.429	225.262
AIC rank	5	4	2	3	1
BIC rank	5	4	2	3	1
	AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reached				

Figure 1-6 Parametric models for brentuximab vedotin (no SCT) PFS – within-trial

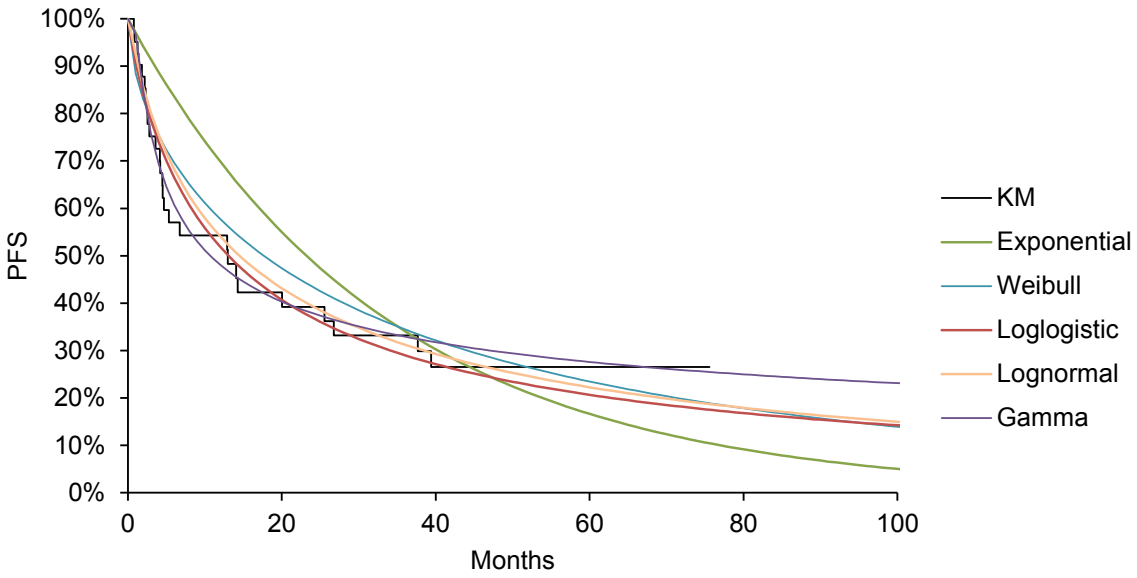
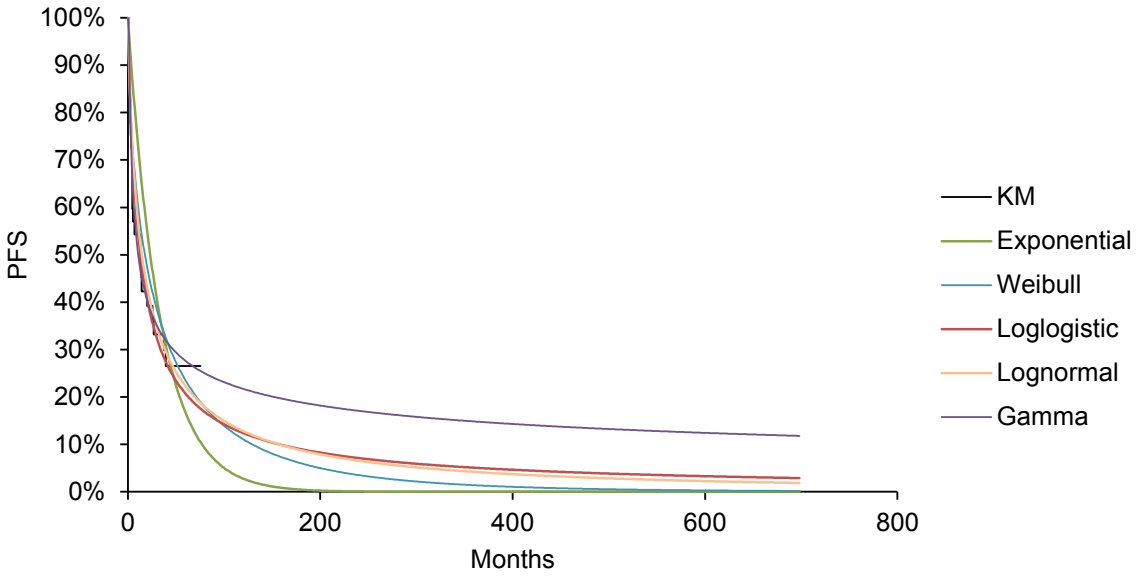


Figure 1-7 Parametric models for brentuximab vedotin (no SCT) PFS – extrapolation



The lognormal, log-logistic and gamma models provided the best fit based on Cox-Snell residual plots and AIC and BIC statistics; of which the gamma model provided the best fit based on BIC. Both the Weibull and exponential models appear to overestimate PFS up to approximately 40 months, and underestimate PFS thereafter. Similarly, the lognormal and log-logistic models appear to fit well to the observed data up to around 40 months, however also underestimate PFS thereafter. In contrast, the gamma model appears to capture the plateau in the KM curve more accurately than the other candidate models. Although the gamma model had not reached 1% by 60 years, these outcomes would not be realised due to the competing risk of general population mortality. As such, the gamma model was selected as the best fitting standard parametric model as per the original company submission.

The corresponding PFS curves generated by the model by cohort and by comparator are presented in Figure 1-8 and Figure 1-9 respectively.

Figure 1-8 PFS, by cohort

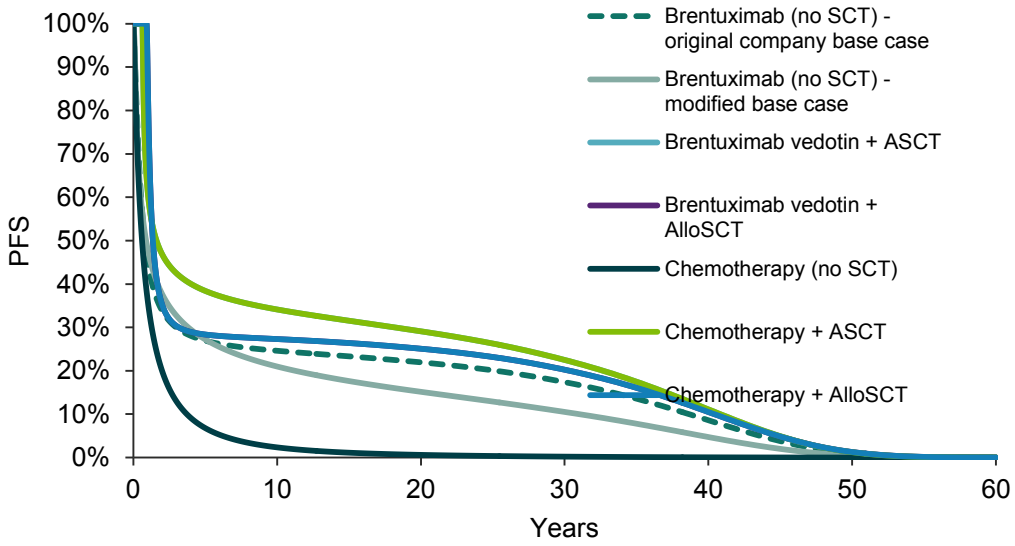
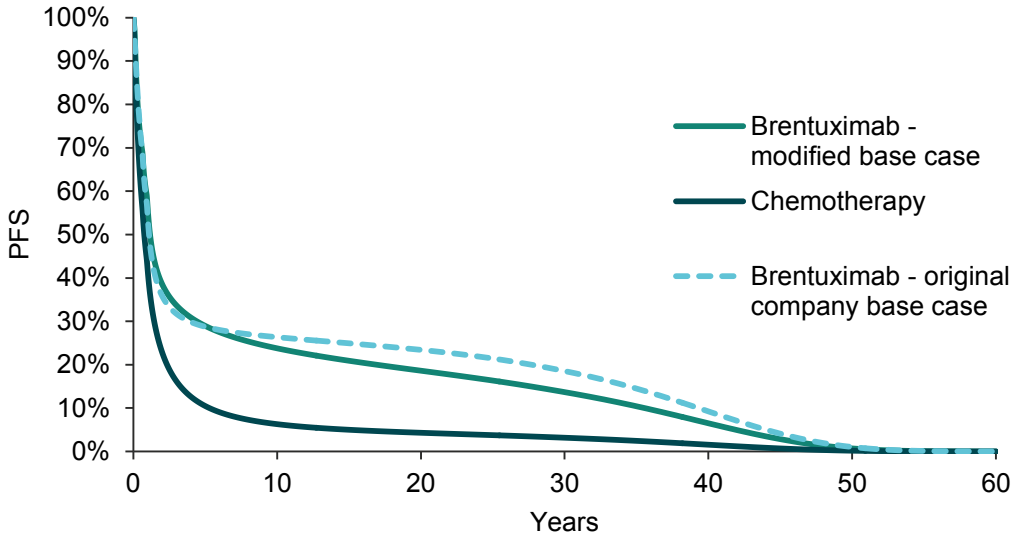


Figure 1-9 PFS, by comparator



Cost-effectiveness results based on all of the parametric models explored are presented in Section 1.2.4.2.

Of note, the company would like to highlight that as per the original company base case; use of a log-logistic cure model is the company's preferred approach to model PFS for brentuximab (no SCT). As per Section 4.2.3.1 of the original submission, the company does not believe that the standard gamma model captures the plateau in the brentuximab (no SCT) KM curve as accurately as the cure model (Appendix 3.3). Notably, Section 3.14 of the

ACD states that “the committee therefore agreed that there was clinical justification for considering the company’s use of mixture cure models further”.

Nevertheless, given the uncertainties expressed by the committee in relation to application of the parametric cure models, the standard gamma distribution was selected to model PFS for brentuximab (no SCT) in the modified base case. Use of a log-logistic cure model is explored in a scenario analysis.

Brentuximab vedotin (no SCT) – OS

The process for selecting the most appropriate parametric model for OS replicated that used for chemotherapy (no SCT) PFS (see Section 1.2.3.1) and brentuximab vedotin (no SCT) PFS.

An overlay of the Kaplan-Meier curve and the parametric curves are presented in

Figure 1-10. Overlays of the Kaplan-Meier curve with each separate parametric curve are presented in the Appendix. The corresponding AIC and BIC statistics, and 99% PFS estimates are presented in Table 1.6. The Cox-Snell Residual plots are presented in the Appendix.

Table 1.6 AIC and BIC statistics and 99% PFS estimates for brentuximab (no SCT) OS

	Exponential	Weibull	Lognormal	Log-logistic	Gamma
99% PFS (years)	32.3	NR	NR	NR	NR
AIC	230.22	219.733	215.634	217.709	211.871
BIC	231.934	223.16	219.061	221.136	217.011
AIC rank	5	4	2	3	1
BIC rank	5	4	2	3	1
	AIC, Akaike information criterion; BIC, Bayesian information criterion				

Figure 1-10 Parametric models for brentuximab vedotin (no SCT) OS – within-trial

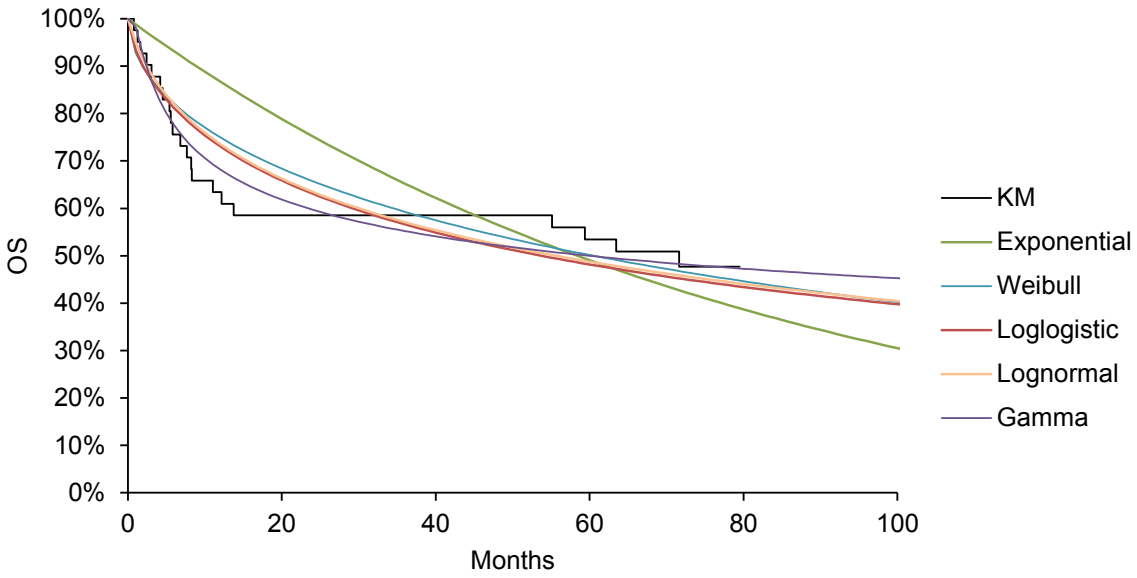
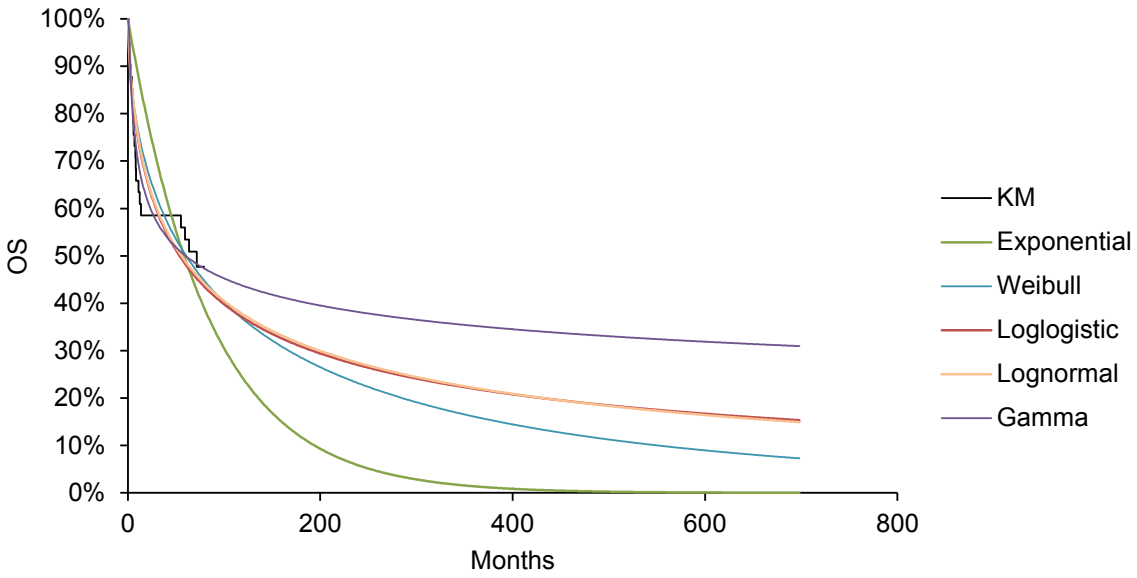


Figure 1-11 Parametric models for brentuximab vedotin (no SCT) OS – extrapolation



As for PFS, the lognormal, log-logistic and gamma models provided the best fit based on Cox-Snell residual plots and AIC and BIC statistics; of which the gamma model provided the best fit based on BIC. All of the candidate models appear to overestimate OS between approximately 10 and 40 months, and underestimate OS thereafter until approximately 80 months. The gamma model appears to fit the data better around approximately 60 months and captures the plateau in the KM curve more accurately than the other candidate models. Although the gamma model had not reached 1% by 60 years, these outcomes would not be realised due to the competing risk of general population mortality. As such, the gamma

model was selected as the best fitting standard parametric model as per the original company submission.

The corresponding OS curves generated by the model by cohort and by comparator are presented in Figure 1-12 and Figure **1-13** respectively.

Figure 1-12 OS, by cohort

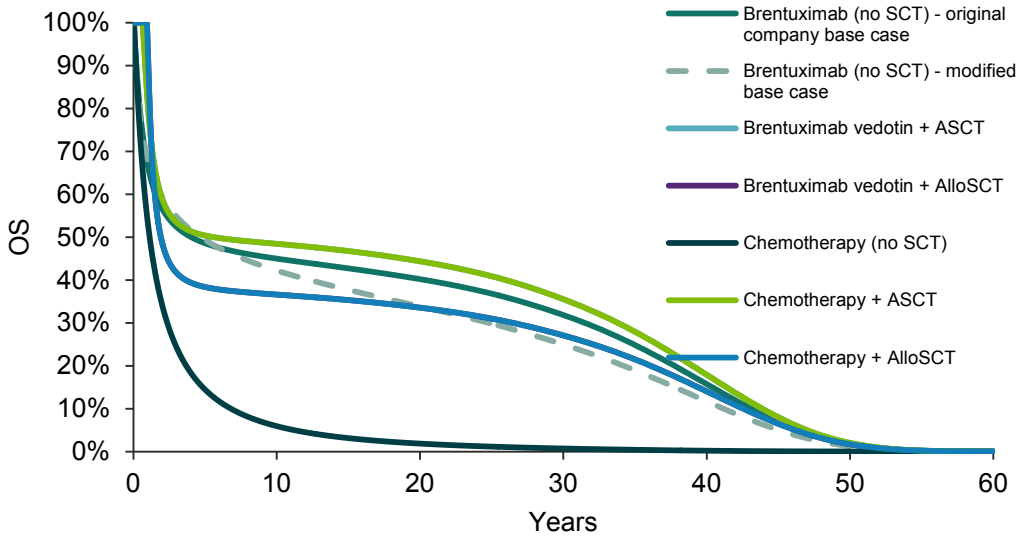
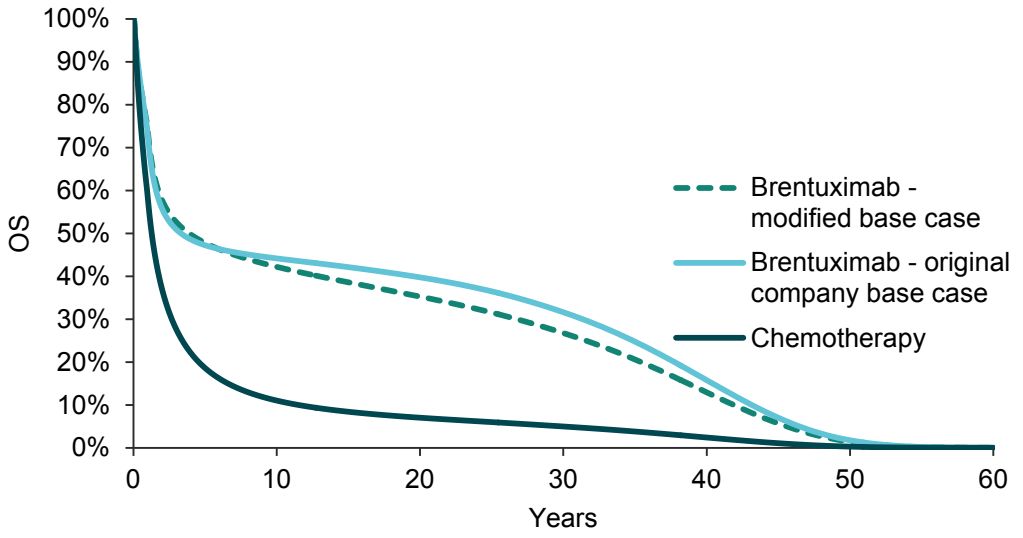


Figure 1-13 OS, by comparator



Cost-effectiveness results based on all of the parametric models explored are presented in Section 1.2.4.2.

Of note, the company would like to highlight that as per the original company base case; use of a log-logistic cure model is the company's preferred approach to model OS for brentuximab vedotin (no SCT). As per Section 4.2.3.1 of the original submission, the company does not believe that the standard gamma model captures the plateau in the brentuximab (no SCT) KM curve as accurately as the cure model (Appendix 3.5). Notably,

Section 3.14 of the ACD states that *"The committee therefore agreed that there was a clinical justification for considering the company's use of mixture cure models further"*.

Nevertheless, given the uncertainties expressed by the committee in relation to application of the parametric cure models, the standard gamma distribution was selected to model OS for brentuximab vedotin (no SCT) in the modified base case. Use of a log-logistic cure model is explored in a scenario analysis.

Chemotherapy (no SCT) - PFS

Parametric models for chemotherapy (no SCT) PFS based on Mak et al. (2013) have been presented in Section 1.2.3.1 of this response document.

Chemotherapy (no SCT) – OS

The process for selecting the most appropriate parametric model for chemotherapy (no SCT) OS was presented in Section 5.3.4.2 of the original submission:

"Models were fitted in Stata using the streg command. The modelling approach and process for selecting the most appropriate model was therefore equivalent to PFS for chemotherapy (no SCT).

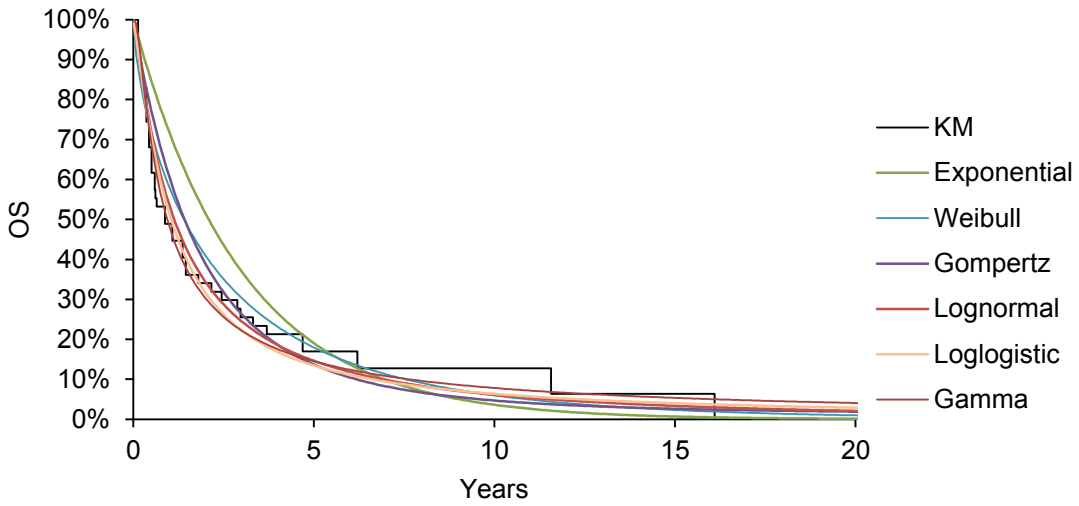
An overlay of the Kaplan-Meier and the parametric curves to demonstrate within-trial fit are presented in

Figure 1-14. The corresponding AIC and BIC statistics and 1% PFS estimates are presented in Table 1.7 and the Cox-Snell Residual plots in the Appendix.

Table 1.7 AIC and BIC statistics & 99% OS estimates for chemotherapy (no SCT) OS

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

Figure 1-14 Parametric models for chemotherapy (no SCT) OS



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

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

Cost-effectiveness results based on all of the parametric models explored are presented in Section 1.2.4.2. However, the company would like to reiterate that the lognormal model has been selected to model OS for chemotherapy (no SCT) as per the original submission.

1.2.3.3 Include a range of excess mortality rates higher than those used in the company's base case analyses

The company acknowledges the uncertainty around the excess mortality rates applied to PFS and OS for brentuximab vedotin (no SCT), chemotherapy (no SCT), ASCT and alloSCT.

Section 3.19 of the ACD states that "The committee concluded that it would have liked to have seen cost-effectiveness analyses based on a range of excess mortality rates higher than those used in the company's base case analyses and that the range should be sourced from published literature identified through a systematic literature review rather than based on clinical expert opinion." As the focus of the discussion on excess mortality during the first appraisal committee meeting was mainly on the post-transplant setting (both alloSCT and ASCT) as opposed to the non-transplant cohorts (brentuximab vedotin only or chemotherapy only), the literature search was focused on the excess mortality in the post-transplant population.

Unfortunately, it was not feasible to conduct a systematic literature review to identify studies reporting excess mortality rates within the timeframe available. Instead, the company identified excess mortality rates based on a targeted online search of publications reporting outcomes for haematological malignancies. Search terms for this search included: stem cell transplant, long term, outcomes, survival, general population, lymphoma, and haematological malignancies. This targeted online search was supplemented by discussions held with clinical experts from a range of hospitals across England. Specifically, ten clinical experts were asked whether they knew of any specific authors/and or centres who had published literature relating to long-term survival in haematological malignancies.

The results of this are presented in Table 1.8.

Table 1.8 Targeted search of long-term survival estimates

Author	Year	Patient population	Treatment	Date of treatment	Excess mortality	Definition	Value	Uncertainty	Additional comments
Hill[8]	2010	DLBCL	ASCT	1994-2006	SMR	Ratio of annual mortality relative to general population mortality	5.1		
Wingard[9]	2011	AML, ALL, MDS, lymphoma and SAA	AlloSCT	Pre-2004	Relative mortality rate	Relative mortality rate vs age, sex, nationality, ethnicity matched general population	Lymphoma returned to general population beyond 8 years		Patients surviving at least 2 years post SCT
Nivison-Smith[10]	2009	AML, lymphoma	ASCT	1992-2001	Relative survival at 5 years	A relative survival ratio of 97% indicates that the annual survival probability is 97% as high as the general population	0.973		Australia and New Zealand
Nivison-Smith[10]	2009	AL, CML, MDS	AlloSCT	1992-2001	Relative survival at 5 years	A relative survival ratio of 97% indicates that the annual survival probability is 97% as high as the general population	0.978		Australia and New Zealand
Nivison-Smith[10]	2009	AML, lymphoma	ASCT	1992-2001	Non-relapse mortality	-	7%	-	-
Nivison-Smith[10]	2009	AL, CML, MDS	AlloSCT	1992-2001	Non-relapse mortality	-	5.60%	-	-
Vanderwalde[11]	2013	Hematological malignancies (AML, HL, NHL and MM)	ASCT	1986-2006	SMR	Risk of death vs general population	3.4	95% CI: 2.9-3.9	5 years post-ASCT
Vanderwalde[11]	2013	NHL	ASCT	1986-2006	SMR	Risk of death vs general population	2.9	95% CI: 2.3-3.6	5 years post-ASCT
Vanderwalde[11]	2013	HL	ASCT	1986-2006	SMR	Risk of death vs general population	6.4	95% CI: 4.6-8.7	5 years post-ASCT

Majhail[12]	2009	HL and NHL	ASCT	1990-1998	Relative mortality	Relative mortality vs age-, gender matched general population (10 year post SCT)	NHL 5.9	95% CI: 3.6-8.2)	10 year post HCT. 5 yr figure for NHL 5.6 (4.4-6.7)
Bhatia[13]	2005	AML, ALL, NHL, HD	ASCT	1981-1998	SMR	-	5.1	95% CI: 3.8-6.6	6-10 years post-ASCT
Bhatia[13]	2005	NHL	ASCT	1981-1998	SMR	-	3.9	95% CI: 2.5-5.6	6-10 years post-ASCT
Bhatia[13]	2005	HL	ASCT	1981-1998	SMR	-	10.2	95% CI: 5.7-16	6-10 years post-ASCT
Bhatia[13]	2005	ALL	ASCT	1981-1998	SMR	-	26.5	95% CI: 6.9-58.9	6-10 years post-ASCT
Martin[14]	2010	ALL, AML, CML, lymphoma, MDS, other	SCT	1970-2002	"Fold higher"	-	4-9	-	-
Goldman[15]	2010	CML	AlloSCT	1978-1998	Relative mortality rates	Relative mortality compared to age-, sex- and race adjusted general population At 6 years At 10 years At 15 years	2.9 2.5 NS	95% CI: 1.9 to 3.9 1.3 to 3.7 0 to 4.9	In patients who survived at least 5 years; Worldwide
Pond[16]	2006	AML, CML	AlloSCT	1970-2002	Ratio of observed vs expected	-	Range 2.86 to 5.16	95% CI crosses 1 for all so NS	10 years to 15+ years post SCT; Canada

Section 3.19 of the ACD states that "*The committee was aware that excess mortality rates considered in appraisals for haematological cancers (such as acute lymphoblastic leukaemia) were much higher (up to four times greater)".* The company would like to highlight that excess mortality rates observed acute lymphoblastic leukaemia (ALL) are unlikely to be reflective of those in sALCL. This is based on the following:

- Clinical expert opinion
    - Ten clinical experts who were consulted confirmed that R/R sALCL and ALL are very different haematological malignancies with different long term outcomes, including those after SCT. They absolutely do not believe that outcomes with ALL can be used as a proxy for RR sALCL.
- Standardised mortality ratios reported in the literature are higher in ALL than lymphoma (NHL or HL)
    - Bhatia et al. (2009) was a retrospective study which assessed late mortality in 854 patients post-ASCT, treated for haematological malignancies. Standardised mortality ratios 6-10 years post-SCT for patients with ALL and NHL were 26.5 (95% CI: 6.9-58.9) and 3.9 (95% CI: 2.5-5.6) respectively
    - Wingard *et al*. (2011). All haematological malignancies saw an increased relative rate of mortality compared with the general population at 2 years following SCT. Although the relative risks declined for all malignancies (including ALL) over time they did not return to expected general population rates except for in patients with lymphoma.

Cost-effectiveness results based on a range of excess mortality rates for all cohorts are presented in Section 1.2.4.3. However, the company would like to highlight that the following excess mortality rates (vs general population) have been selected as part of the modified base case:

- Brentuximab (no SCT): 100% increase (a 2-fold increase vs general population)
- Chemotherapy (no SCT): 100% increase (a 2-fold increase vs general population)
- ASCT: 200% increase (a 3-fold increase vs general population)
- AlloSCT: 300% increase (a 4-fold increase vs general population)

1.2.3.4 Summary of the modified base case

Table 1.9 summarises the changes made to the base case, highlighting the modifications that have been made compared to those listed on page 3 of the ACD, and the rationale for the company modification.

Table 1.9 Summary of company modified base case

ACD modification	Modified company base case	Rationale
Mak et al. (2013)[4] to inform PFS and OS for chemotherapy (no SCT)	Lognormal function to extrapolate progression-free survival and overall survival	• Reflects ACD
Parametric models to extrapolate progression-free	• Lognormal function to extrapolate progression-free survival and	• Reflects ACD for chemotherapy (no

survival and overall survival for brentuximab vedotin and chemotherapy	overall survival for chemotherapy (no SCT) • Standard gamma model to extrapolate progression-free survival and overall survival for brentuximab vedotin (no SCT)	SCT) and brentuximab vedotin (no SCT)
Excess mortality rates	Excess mortality rates of the following: • Brentuximab vedotin (no SCT) – 100% • Chemotherapy (no SCT) – 100% • ASCT – 200% • AlloSCT – 300%	• Reflects ACD • Values based on targeted search of long-term survival of patients with haematological malignancies in published literature
Scenario analysis in which the excess mortality rates of brentuximab vedotin (no SCT), chemotherapy (no SCT), ASCT and alloSCT are varied	A scenario analysis has been applied to the above modified base case presenting a range of excess mortality rates between 0% and 500%.	• Reflects ACD • Range based on targeted search of long-term survival of patients with haematological malignancies in published literature

1.2.4 Results

1.2.4.1 Use of Mak et al. (2013) to inform PFS and OS for chemotherapy

Cost-effectiveness results based on all of the parametric models explored for PFS and OS for chemotherapy (no SCT) are presented in Table 1.10. Use of a lognormal distribution to extrapolate both PFS and OS for chemotherapy (no SCT) increases the ICER from £13,002 to £14,222.

Table 1.10 Impact of each modification on the ICER – Mak et al. (2013) to inform PFS and OS for chemotherapy (no SCT)

Modification	Intervention	Lys	QALYs	Costs	Inc. costs	Inc. QALYs	ICER (per QALY)
Original company base case	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,873
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Revised company base case (errors corrected)	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£13,002
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Observed Kaplan-Meier for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,283
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Exponential distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,208
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Weibull distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,104
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Gompertz distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,169
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,222
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,387
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	

Gamma distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,307
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and observed Kaplan-Meier for OS	Chemotherapy	3.53	[redacted]	[redacted]	-	-	£14,359
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and exponential distribution for OS	Chemotherapy	3.64	[redacted]	[redacted]	-	-	£14,573
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and Weibull distribution for OS	Chemotherapy	3.47	[redacted]	[redacted]	-	-	£14,357
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and gompertz distribution for OS	Chemotherapy	3.39	[redacted]	[redacted]	-	-	£14,275
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and log-logistic distribution for OS	Chemotherapy	3.32	[redacted]	[redacted]	-	-	£14,170
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and gamma distribution for OS	Chemotherapy	3.46	[redacted]	[redacted]	-	-	£14,296
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Observed Kaplan-Meier for PFS and observed Kaplan-Meier for OS	Chemotherapy	3.53	[redacted]	[redacted]	-	-	£14,499
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Exponential distribution for PFS and exponential distribution for OS	Chemotherapy	3.64	[redacted]	[redacted]	-	-	£14,642
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	

Weibull distribution for PFS and Weibull distribution for OS	Chemotherapy	3.47	[redacted]	[redacted]	-	-	£14,276
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Gompertz distribution for PFS and gompertz distribution for OS	Chemotherapy	3.39	[redacted]	[redacted]	-	-	£14,233
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic distribution for PFS and log-logistic distribution for OS	Chemotherapy	3.32	[redacted]	[redacted]	-	-	£14,336
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Gamma distribution for PFS and gamma distribution for OS	Chemotherapy	3.46	[redacted]	[redacted]	-	-	£14,382
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Modified base case setting: Lognormal distribution for PFS and lognormal distribution for OS	**Chemotherapy**	**3.35**	[redacted]	[redacted]	**-**	**-**	**£14,222**
	Brentuximab vedotin	**9.53**	[redacted]	[redacted]	[redacted]	[redacted]	

1.2.4.2 Explore a number of parametric models for extrapolating PFS and OS for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate

Cost-effectiveness results based on all of the parametric models explored for PFS and OS for brentuximab vedotin (no SCT) are presented in Table 1.11. Use of a gamma distribution to extrapolate both PFS and OS for brentuximab vedotin (no SCT) increases the ICER from £13,002 to £14,703.

Table 1.11 Impact of each modification on the ICER – standard parametric models to inform PFS and OS for brentuximab (no SCT)

Modification	Intervention	Lys	QALYs	Costs	Inc. costs	Inc. QALYs	ICER (per QALY)
Original company base case	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,873
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Revised company base case (errors corrected)	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£13,002
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Exponential distribution for PFS and log-logistic cure model for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£19,537
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Weibull distribution for PFS and log-logistic cure model for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£17,660
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and log-logistic cure model for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£17,126
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic distribution for PFS and log-logistic cure model for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£17,350
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Gamma distribution for PFS and log-logistic cure model for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,244
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic cure model for PFS and exponential distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£20,223
	Brentuximab vedotin	6.65	[redacted]	[redacted]	[redacted]	[redacted]	

Log-logistic cure model for PFS and Weibull distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£15,051
	Brentuximab vedotin	7.85	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic cure model for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,275
	Brentuximab vedotin	8.12	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic cure model for PFS and log-logistic distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,373
	Brentuximab vedotin	8.06	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic cure model for PFS and gamma distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£13,391
	Brentuximab vedotin	8.99	[redacted]	[redacted]	[redacted]	[redacted]	
Exponential distribution for PFS and exponential distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£25,355
	Brentuximab vedotin	6.65	[redacted]	[redacted]	[redacted]	[redacted]	
Weibull distribution for PFS and Weibull distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£20,137
	Brentuximab vedotin	7.85	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£19,055
	Brentuximab vedotin	8.12	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic distribution for PFS and log-logistic distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£19,458
	Brentuximab vedotin	8.06	[redacted]	[redacted]	[redacted]	[redacted]	
Gamma distribution for PFS and gamma distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,703
	Brentuximab vedotin	8.99	[redacted]	[redacted]	[redacted]	[redacted]	

Modified base case setting: Gamma distribution for PFS and gamma distribution for OS	**Chemotherapy**	**3.35**	[redacted]	[redacted]	-	-	**£14,703**
	Brentuximab vedotin	**8.99**	[redacted]	[redacted]	[redacted]	[redacted]	

1.2.4.3 Include a range of excess mortality rates higher than those used in the company's base case analyses

Cost-effectiveness results based on excess mortality rates between 0% and 500% excess mortality rates for the ASCT and alloSCT cohorts are presented in Table 1.12. Cost-effectiveness results based on excess mortality rates between 0% and 500% for the brentuximab vedotin (no SCT) and chemotherapy (no SCT) cohorts are presented in Table 1.13.

Table 1.12 Scenario analysis of excess mortality rates for ASCT and alloSCT

	Excess hazard associated with alloSCT									
Excess hazard associated with ASCT	**0%**	**10%**	**20%**	**50%**	**100%**	**150%**	**200%**	**300%**	**400%**	**500%**
0%	£12,970	£12,985	£12,999	£13,037	£13,089	£13,132	£13,170	£13,233	£13,285	£13,329
10%	£12,987	£13,002	£13,016	£13,053	£13,106	£13,149	£13,187	£13,250	£13,302	£13,347
20%	£13,002	£13,017	£13,031	£13,069	£13,121	£13,165	£13,203	£13,266	£13,318	£13,363
50%	£13,044	£13,059	£13,073	£13,111	£13,164	£13,208	£13,246	£13,310	£13,362	£13,407
100%	£13,103	£13,118	£13,132	£13,170	£13,223	£13,268	£13,306	£13,371	£13,424	£13,469
150%	£13,152	£13,167	£13,181	£13,220	£13,274	£13,318	£13,357	£13,422	£13,475	£13,521
200%	£13,195	£13,210	£13,225	£13,263	£13,317	£13,362	£13,401	£13,467	£13,521	£13,566
300%	£13,267	£13,283	£13,297	£13,337	£13,391	£13,437	£13,476	£13,542	£13,597	£13,643
400%	£13,328	£13,343	£13,358	£13,398	£13,453	£13,499	£13,539	£13,605	£13,660	£13,707
500%	£13,380	£13,395	£13,410	£13,450	£13,506	£13,552	£13,592	£13,659	£13,715	£13,762

Table 1.13 Scenario analysis of excess mortality rates for brentuximab vedotin (no SCT) and chemotherapy (no SCT)

	Excess hazard associated with brentuximab (no SCT)									
Excess hazard associated with chemotherapy (no SCT)	**0%**	**10%**	**20%**	**50%**	**100%**	**150%**	**200%**	**300%**	**400%**	**500%**
0%	£12,929	£13,078	£13,220	£13,618	£14,211	£14,746	£15,240	£16,145	£16,972	£17,744
10%	£12,926	£13,074	£13,216	£13,614	£14,206	£14,741	£15,235	£16,140	£16,966	£17,737
20%	£12,922	£13,070	£13,213	£13,610	£14,202	£14,736	£15,230	£16,134	£16,960	£17,730
50%	£12,912	£13,060	£13,202	£13,598	£14,190	£14,723	£15,216	£16,118	£16,942	£17,711
100%	£12,895	£13,043	£13,185	£13,580	£14,170	£14,702	£15,193	£16,093	£16,914	£17,681
150%	£12,880	£13,027	£13,168	£13,563	£14,151	£14,682	£15,172	£16,069	£16,888	£17,652
200%	£12,865	£13,012	£13,153	£13,547	£14,134	£14,663	£15,152	£16,046	£16,863	£17,624
300%	£12,838	£12,984	£13,124	£13,516	£14,100	£14,627	£15,113	£16,003	£16,816	£17,573
400%	£12,812	£12,957	£13,097	£13,487	£14,069	£14,593	£15,078	£15,963	£16,771	£17,525
500%	£12,787	£12,933	£13,072	£13,460	£14,040	£14,562	£15,044	£15,926	£16,730	£17,480

1.2.4.4 Modified base case

The impact of each modification on the cost-effectiveness of brentuximab vedotin is provided in Table 1.14. The combined impact of these modifications has increased the ICER from £12,873 to £18,324.

Table 1.14 Impact of each modification on the ICER and the proposed modified base case

Modification	Intervention	LYs	QALYs	Costs	Inc. costs	Inc. QALYs	ICER (per QALY)
Original company base case	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,873
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Revised company base case (errors corrected)	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£13,002
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Mak et al. (2013): Lognormal distribution for PFS and lognormal distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,222
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Brentuximab (no SCT) Gamma distribution for PFS and gamma distribution for OS	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£14,703
	Brentuximab vedotin	8.99	[redacted]	[redacted]	[redacted]	[redacted]	
Excess mortality SCT cohorts: ASCT: 200% AllosCT: 300%	Chemotherapy	3.12	[redacted]	[redacted]	-	-	£13,467
	Brentuximab vedotin	9.07	[redacted]	[redacted]	[redacted]	[redacted]	
Excess mortality (no SCT) cohorts: Brentuximab (no SCT): 100% Chemotherapy (no SCT): 100%	Chemotherapy	3.31	[redacted]	[redacted]	-	-	£14,170
	Brentuximab vedotin	8.90	[redacted]	[redacted]	[redacted]	[redacted]	
Combined impact of the above settings	**Chemotherapy**	**3.09**	[redacted]	[redacted]	-	-	**£18,324**
	Brentuximab vedotin	**8.02**	[redacted]	[redacted]	[redacted]	[redacted]	

1.2.4.5 Probabilistic sensitivity analysis

PSA was conducted using the same methods as the original submission. The probabilistic ICER generated by this analysis was £20,399.

The cost-effectiveness plane is presented in Figure 1-15. The corresponding CEAC and CEAF are presented in Figure 1-16 and Figure 1-17 respectively. The corresponding probabilities for decision thresholds of £20,000, £30,000 and £50,000 per QALY are presented in Table 1.15.

Figure 1-15 Cost-effectiveness plane

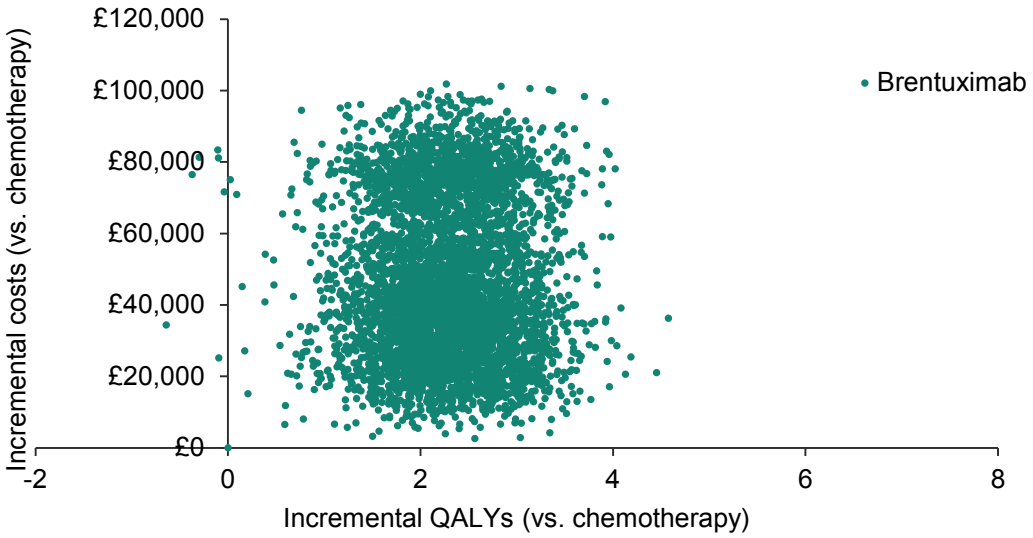


Figure 1-16 Cost-effectiveness acceptability curve

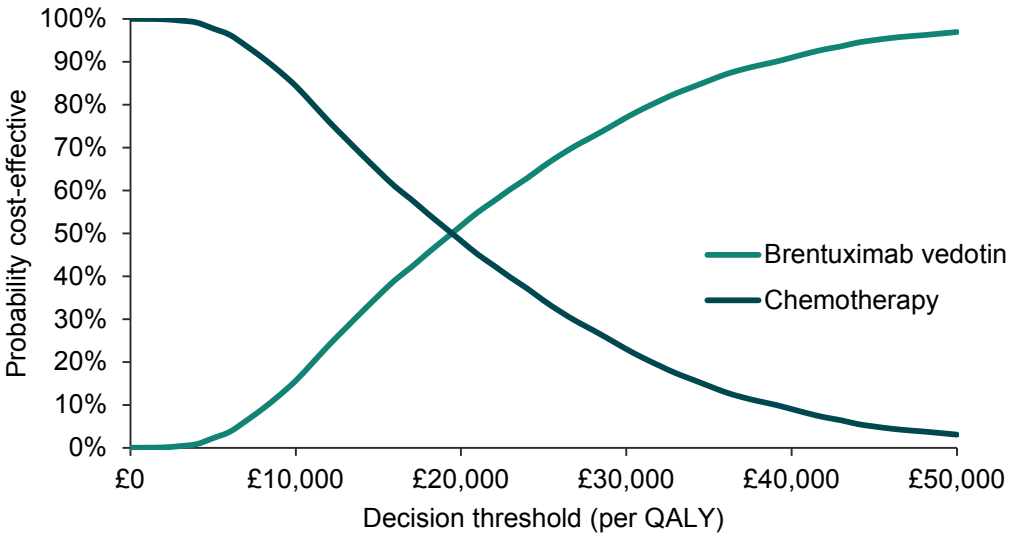


Figure 1-17 Cost-effectiveness acceptability frontier

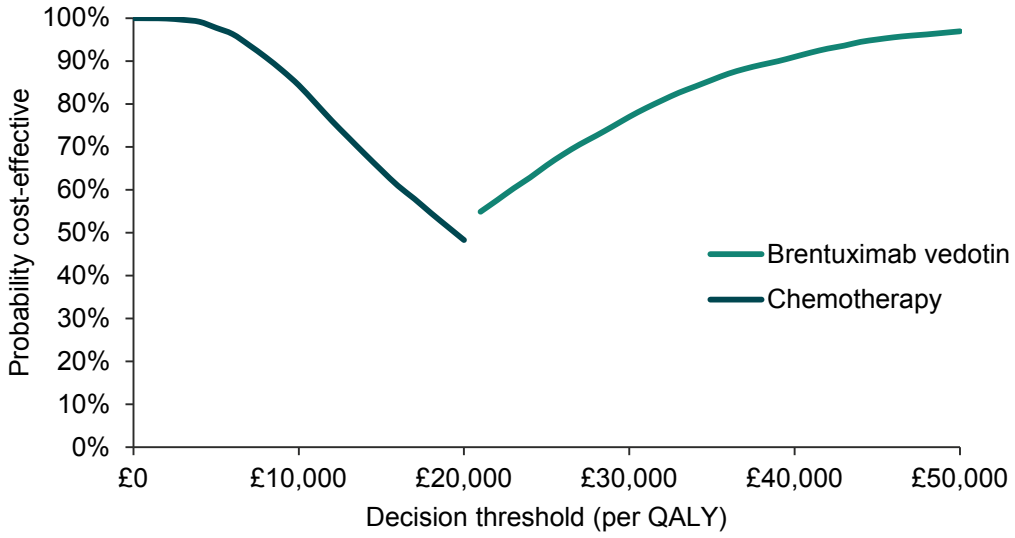


Table 1.15 Probabilities of cost-effectiveness

Decision threshold (per QALY)	Brentuximab	Chemotherapy
£20,000	52%	48%
£30,000	77%	23%
£50,000	97%	3%

1.2.4.6 Deterministic sensitivity analysis

Results of the deterministic sensitivity analyses based on the modified base case are presented in Table 1.16.

Cost-effectiveness results based on excess mortality rates between 0% and 500% excess mortality rates for the ASCT and alloSCT cohorts when adopting the remaining settings for the modified base case are presented in Table 1.17. Cost-effectiveness results based on excess mortality rates between 0% and 500% for the brentuximab vedotin (no SCT) and chemotherapy (no SCT) cohorts when adopting the remaining settings for the modified base case are presented in Table 1.18.

Table 1.16 Scenario analyses results

Deterministic sensitivity analysis	Base case value	DSA value	ICER for brentuximab vedotin (per QALY)
Base case	-	-	£18,324
Discount rate (costs, benefits)	3.5%	1.5%	£14,254
Assessment type	Investigator	IRF	£26,091
Source of response data for brentuximab patients receiving SCT	SGN35-0004 (self-control)	Equivalent to chemotherapy	£18,428
Brentuximab (no SCT) PFS per INV distribution	Gamma standard model	Exponential	£16,432
Brentuximab (no SCT) PFS per IRF distribution	Log-logistic	Exponential	£21,999
Brentuximab (no SCT) OS distribution	Gamma standard model	Kaplan-Meier	£17,079
Brentuximab (no SCT) PFS and OS distribution	Gamma standard model	Log-logistic cure model	£16,253
Source of chemotherapy (no SCT) PFS data	Mak (2013) PS<2 (n=47)	Mak (2013) ALCL (n=17)	£18,324
Source of chemotherapy (no SCT) PFS data	Mak (2013) PS<2 (n=47)	Self-control	£16,421
Chemotherapy (no SCT) PFS distribution	Lognormal	Log-logistic	£18,562
Chemotherapy (no SCT) PFS hazard	Original data	Increased 25%	£18,324
Chemotherapy (no SCT) PFS hazard	Original data	Decreased 25%	£18,324
Source of chemotherapy (no SCT) OS data	Mak (2013) PS<2 (n=47)	Mak (2013) ALCL (n=17)	£16,898
Source of chemotherapy (no SCT) PFS and OS data			£18,938
Chemotherapy (no SCT) OS distribution	Lognormal	Kaplan-Meier	£18,627
Chemotherapy (no SCT) OS hazard	Original data	Increased 25%	£17,386
Chemotherapy (no SCT) OS hazard	Original data	Decreased 25%	£20,182
Chemotherapy (no SCT) PFS and OS hazards			£20,182
ASCT PFS distribution	Gamma	Lognormal	£18,158
ASCT OS distribution	Lognormal	Gamma	£18,349
ALCL calibration for ASCT	Exclude	Include	£17,177
Allo-SCT PFS distribution	Lognormal	Gamma	£18,365
Allo-SCT OS distribution	Lognormal	Gamma	£18,326

ALCL calibration for Allo-SCT	Exclude	Include	£17,950
ALCL calibration for ASCT and Allo-SCT			£16,847
Rate of stem cell transplant	Response-based (SGN35-0004)	Response-based (clinical opinion)	£25,929
Rate of stem cell transplant	Response-based (SGN35-0004)	Equal in both arms (Mak et al.)	£19,287
Proportion receiving ASCT vs. Allo-SCT	Base case (SGN35-0004)	AlloSCT = 75%	£19,508
Cured time-point (years)	5 years	2 years	£18,175
Relative dose intensity	On	Off	£18,324
Chemotherapy relative dose intensity	100%	Equivalent to BV	£18,415
Drug wastage	Off	On	£16,497
Cost of ASCT	Clinical expert	NHS reference costs	£17,127
Cost of Allo-SCT	Clinical expert	NHS reference costs	£16,763
Adverse event disutilities	Include	Exclude	£18,312
Chemotherapy costs; all patients receive cheapest	Mix	ESHAP	£16,733
Chemotherapy costs; all patients receive most expensive	Mix	Gem-P	£17,955
Radiotherapy	5%	40%	£18,099

Table 1.17 Scenario analysis of excess mortality rates for ASCT and alloSCT

	Excess hazard associated with alloSCT									
Excess hazard associated with ASCT	**0%**	**10%**	**20%**	**50%**	**100%**	**150%**	**200%**	**300%**	**400%**	**500%**
0%	£17,423	£17,449	£17,474	£17,542	£17,636	£17,715	£17,784	£17,899	£17,994	£18,075
10%	£17,452	£17,479	£17,504	£17,572	£17,666	£17,746	£17,814	£17,930	£18,025	£18,106
20%	£17,479	£17,506	£17,532	£17,600	£17,695	£17,774	£17,843	£17,959	£18,054	£18,136
50%	£17,554	£17,581	£17,607	£17,676	£17,771	£17,852	£17,921	£18,038	£18,134	£18,216
100%	£17,659	£17,687	£17,712	£17,782	£17,879	£17,960	£18,030	£18,149	£18,246	£18,330
150%	£17,748	£17,776	£17,802	£17,872	£17,970	£18,052	£18,123	£18,242	£18,341	£18,425
200%	£17,825	£17,853	£17,879	£17,950	£18,049	£18,132	£18,204	£18,324	£18,424	£18,509
300%	£17,956	£17,985	£18,011	£18,083	£18,184	£18,268	£18,340	£18,463	£18,564	£18,650
400%	£18,066	£18,094	£18,121	£18,194	£18,296	£18,381	£18,455	£18,578	£18,681	£18,768
500%	£18,160	£18,189	£18,216	£18,290	£18,392	£18,478	£18,553	£18,678	£18,782	£18,870

Table 1.18 Scenario analysis of excess mortality rates for brentuximab vedotin (no SCT) and chemotherapy (no SCT)

	Excess hazard associated with brentuximab (no SCT)									
Excess hazard associated with chemotherapy (no SCT)	**0%**	**10%**	**20%**	**50%**	**100%**	**150%**	**200%**	**300%**	**400%**	**500%**
0%	£16,910	£17,083	£17,251	£17,722	£18,435	£19,087	£19,697	£20,829	£21,883	£22,882
10%	£16,900	£17,073	£17,240	£17,711	£18,423	£19,074	£19,683	£20,814	£21,866	£22,864
20%	£16,890	£17,063	£17,230	£17,700	£18,411	£19,061	£19,670	£20,799	£21,850	£22,846
50%	£16,861	£17,034	£17,200	£17,669	£18,377	£19,025	£19,631	£20,756	£21,802	£22,794
100%	£16,816	£16,988	£17,153	£17,620	£18,324	£18,968	£19,570	£20,688	£21,728	£22,713
150%	£16,774	£16,945	£17,110	£17,573	£18,274	£18,915	£19,513	£20,625	£21,658	£22,637
200%	£16,734	£16,904	£17,068	£17,530	£18,227	£18,864	£19,460	£20,565	£21,592	£22,565
300%	£16,659	£16,828	£16,991	£17,448	£18,139	£18,770	£19,359	£20,454	£21,469	£22,431
400%	£16,590	£16,758	£16,919	£17,372	£18,057	£18,683	£19,267	£20,351	£21,356	£22,307
500%	£16,526	£16,692	£16,852	£17,302	£17,981	£18,601	£19,181	£20,255	£21,251	£22,193

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3. Appendix

3.1 Chemotherapy (no SCT) PFS – Mak et al. (2013) parametric extrapolations

Figure 3-1 Exponential distribution for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

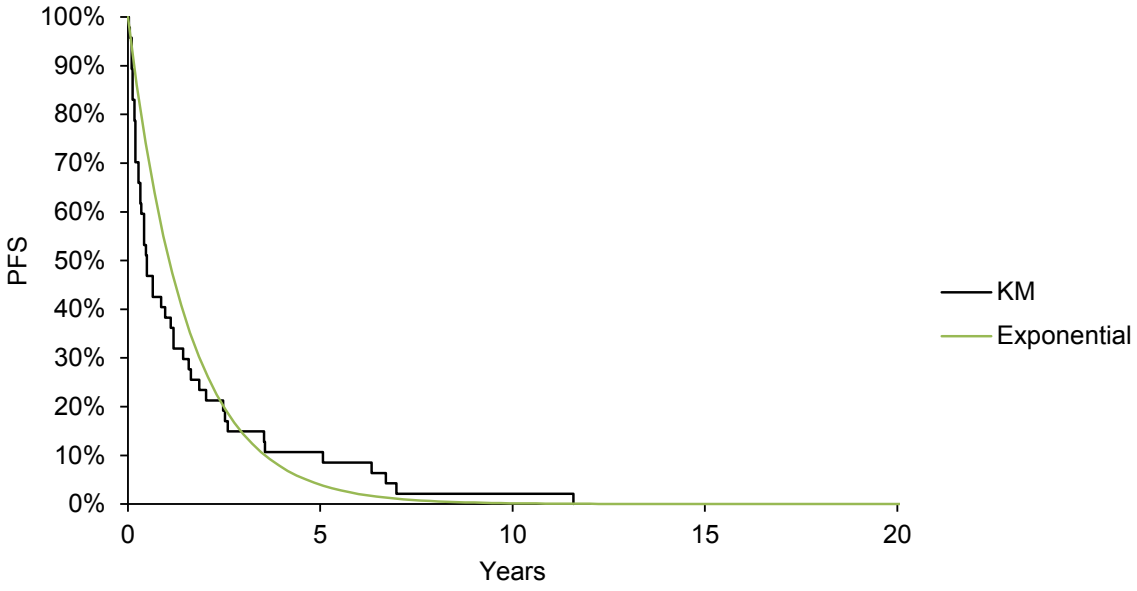


Figure 3-2 Weibull distribution for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

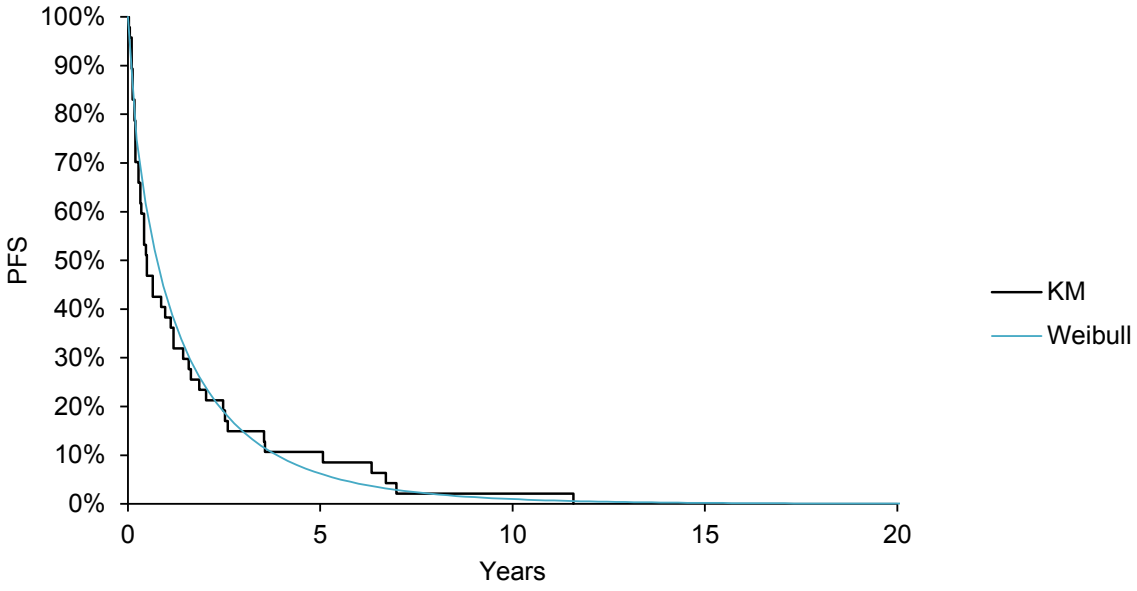


Figure 3-3 Gompertz distribution for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

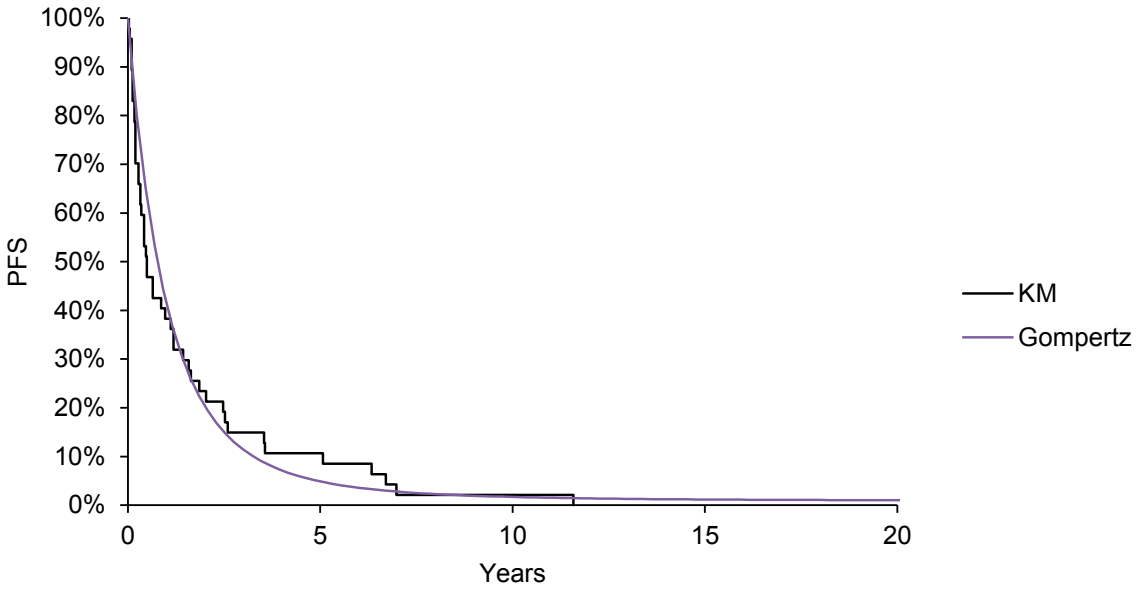


Figure 3-4 Lognormal distribution for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

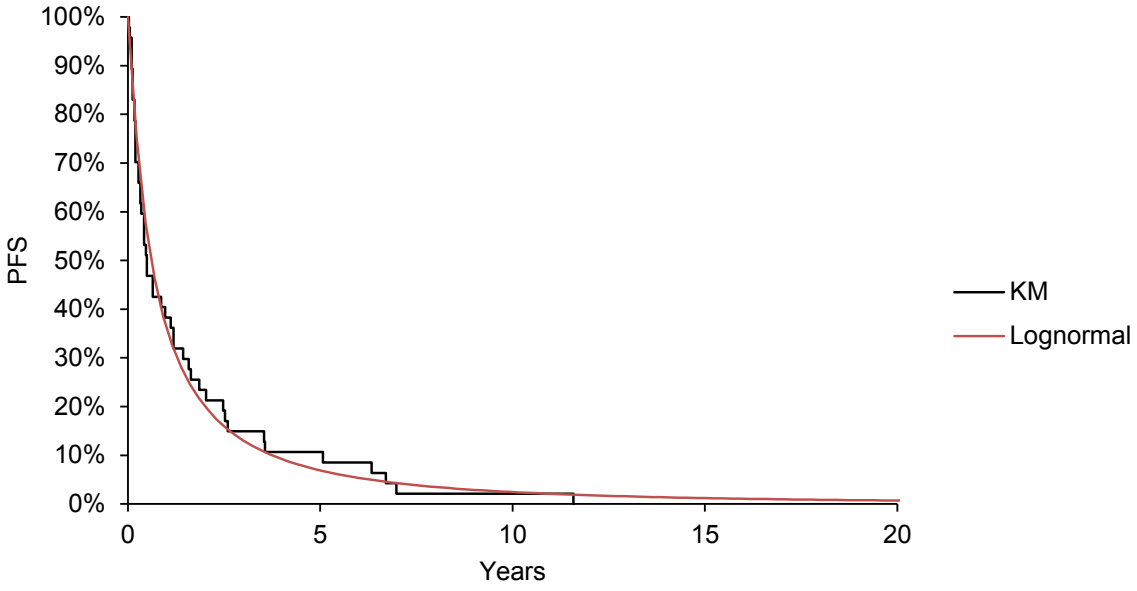


Figure 3-5 Log-logistic distribution for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)

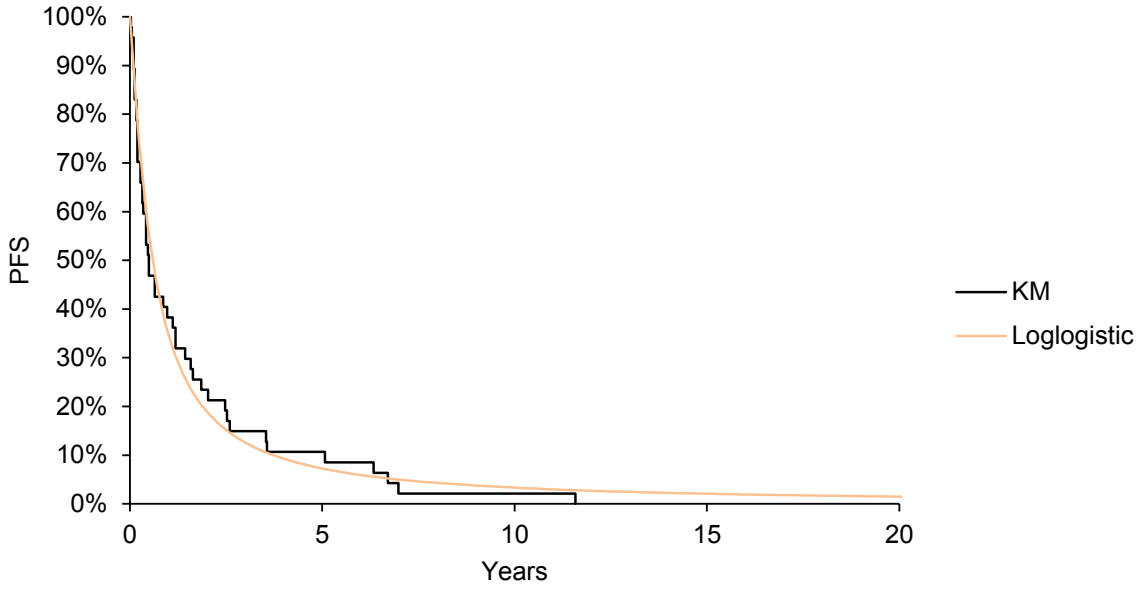
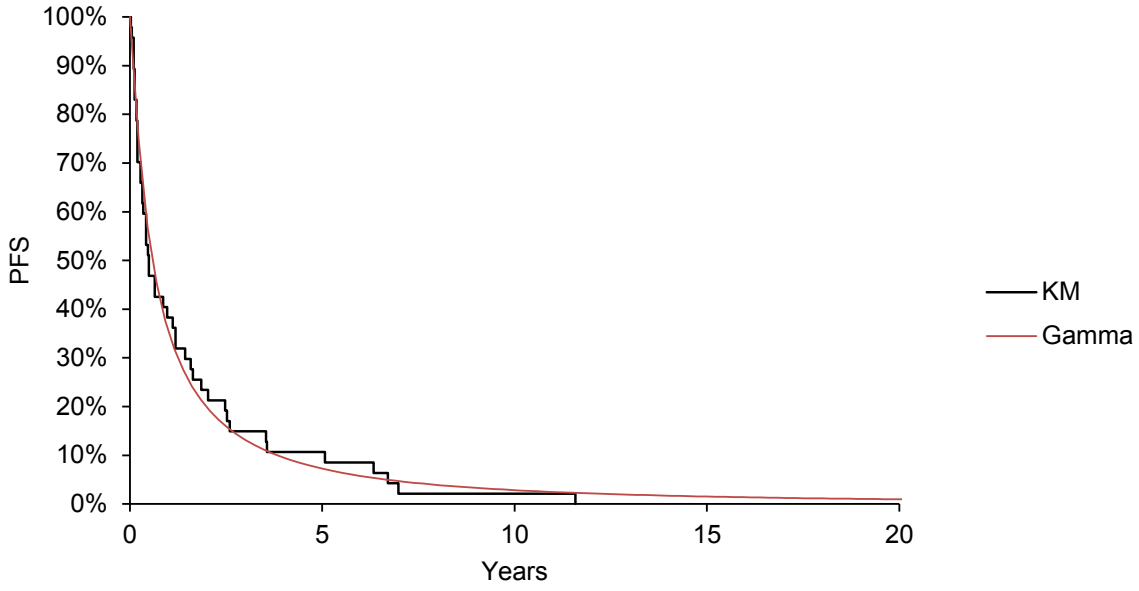


Figure 3-6 Gamma distribution for chemotherapy (no SCT) PFS from Mak et al. (2013) (PS<2)



3.2 Brentuximab (no SCT) PFS – Cox-Snell Residual plots

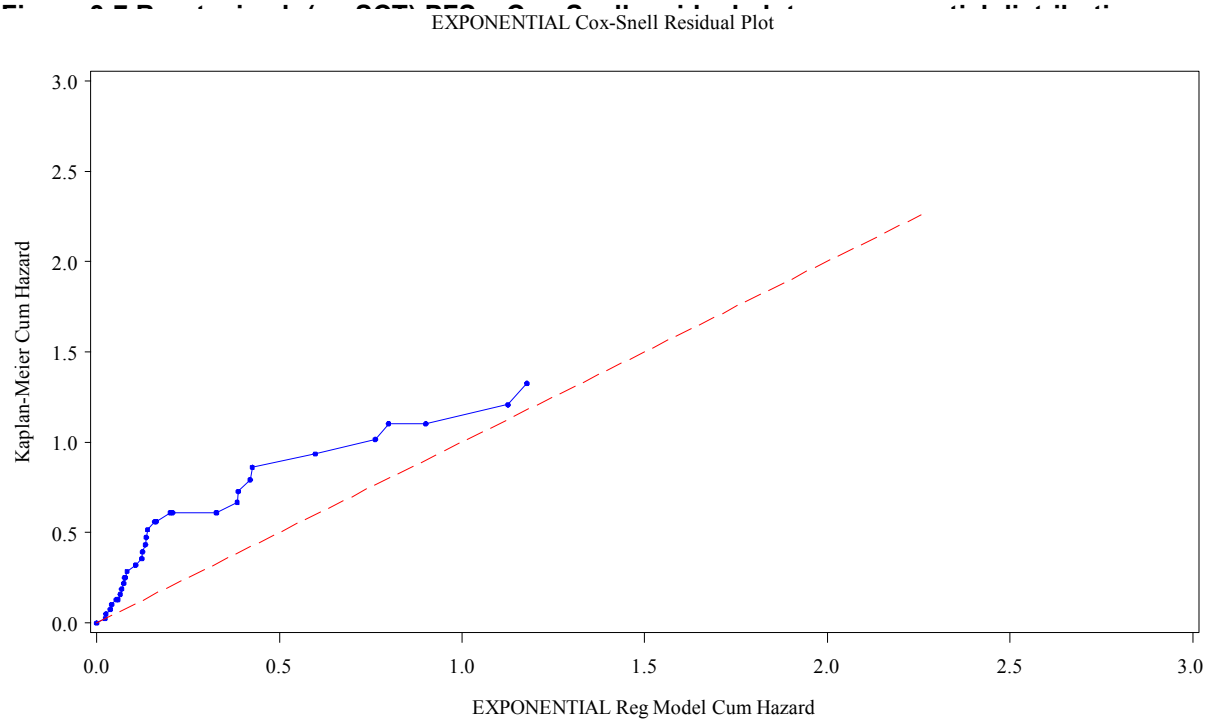
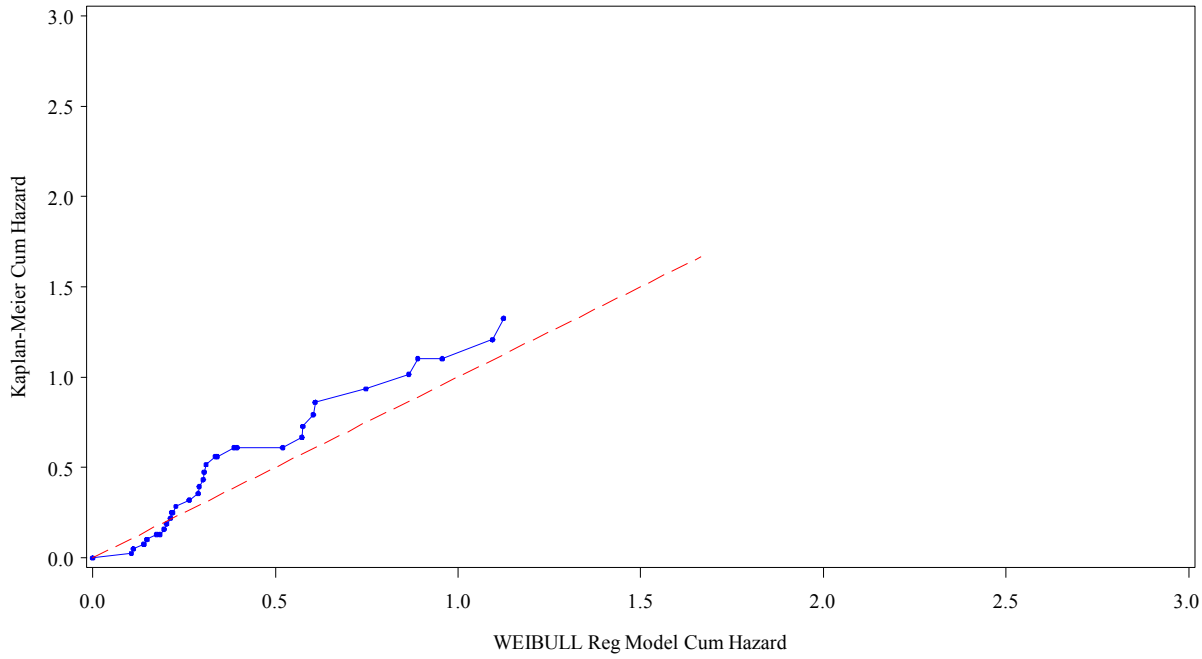


Figure 3-8 Brentuximab (no SCT) PFS – Cox-Snell residual plots – Weibull distribution



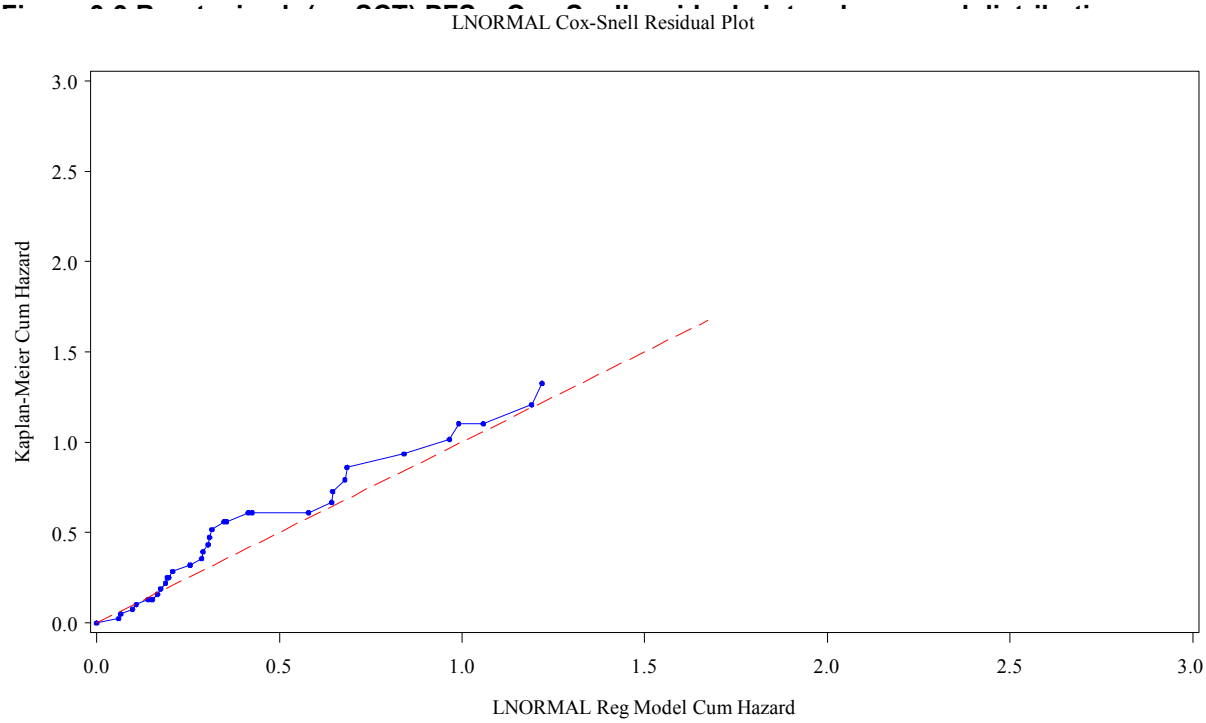
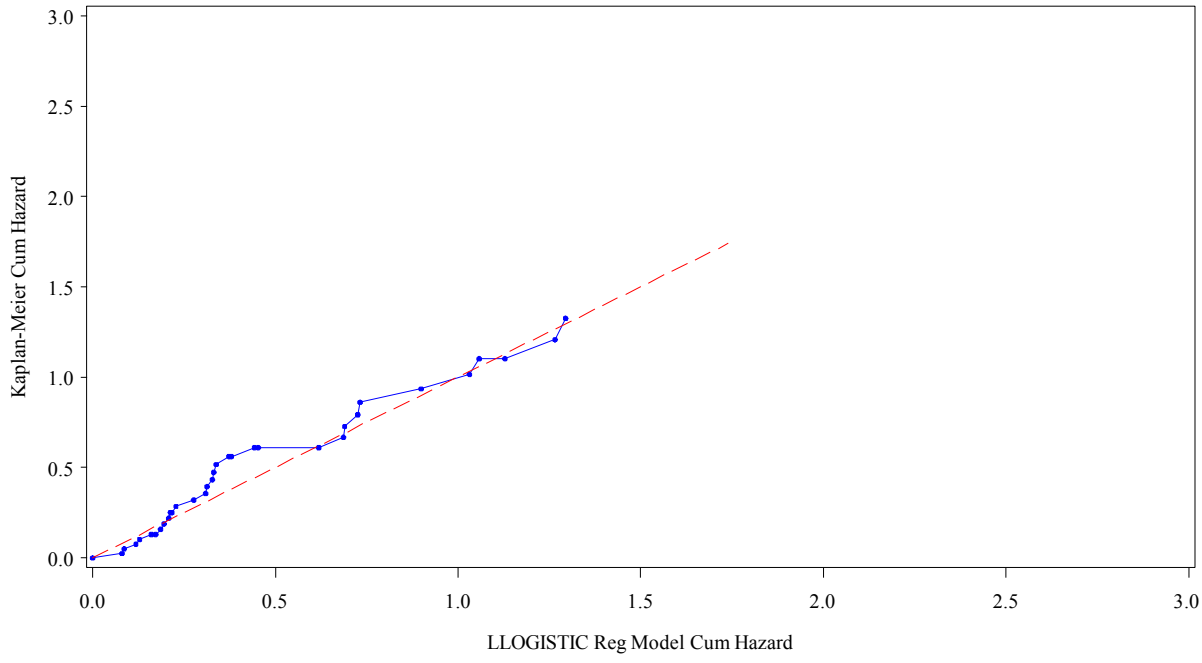
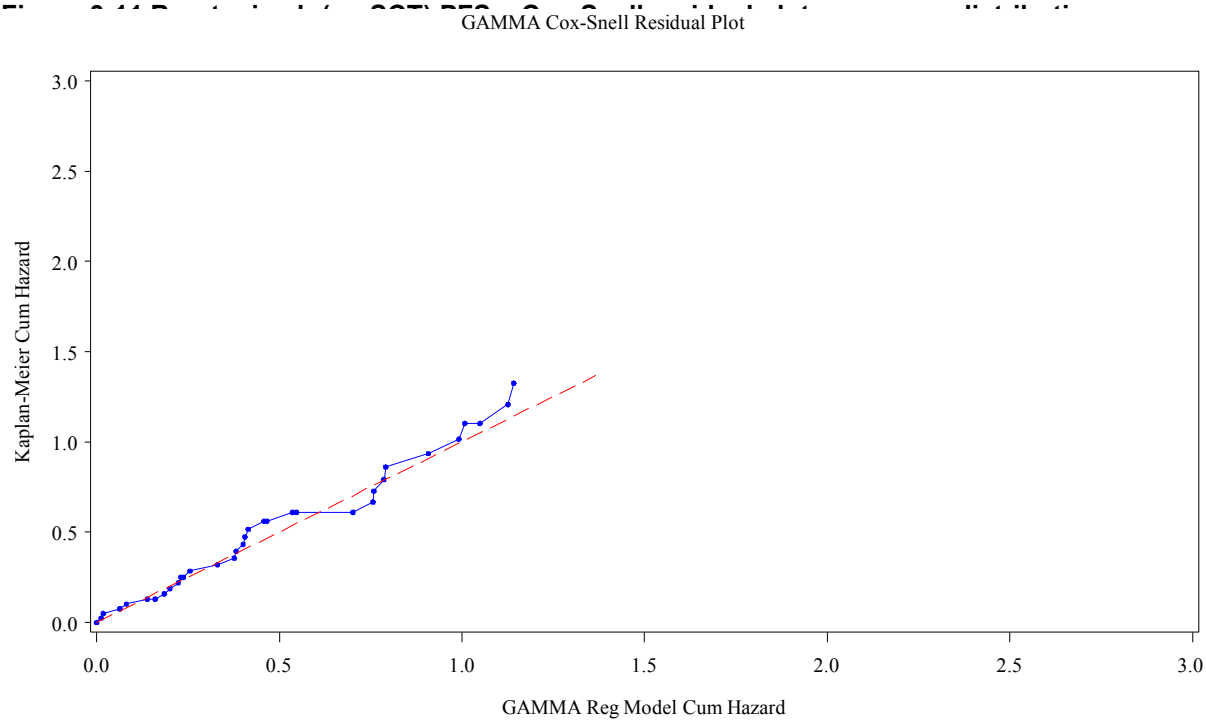


Figure 3-10 Brentuximab (no SCT) PFS – Cox-Snell residual plots – log-logistic distribution





3.3 Brentuximab (no SCT) PFS – Parametric cure model vs standard gamma model fit

Figure 3-12 Within-trial comparison of log-logistic cure model (company base case) and standard (gamma) model for brentuximab vedotin (no SCT) PFS

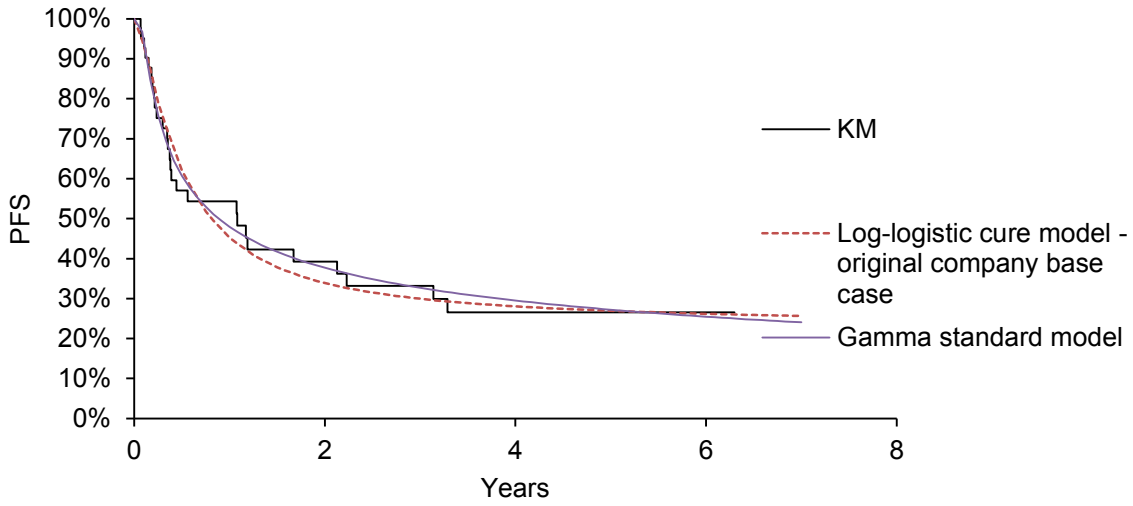
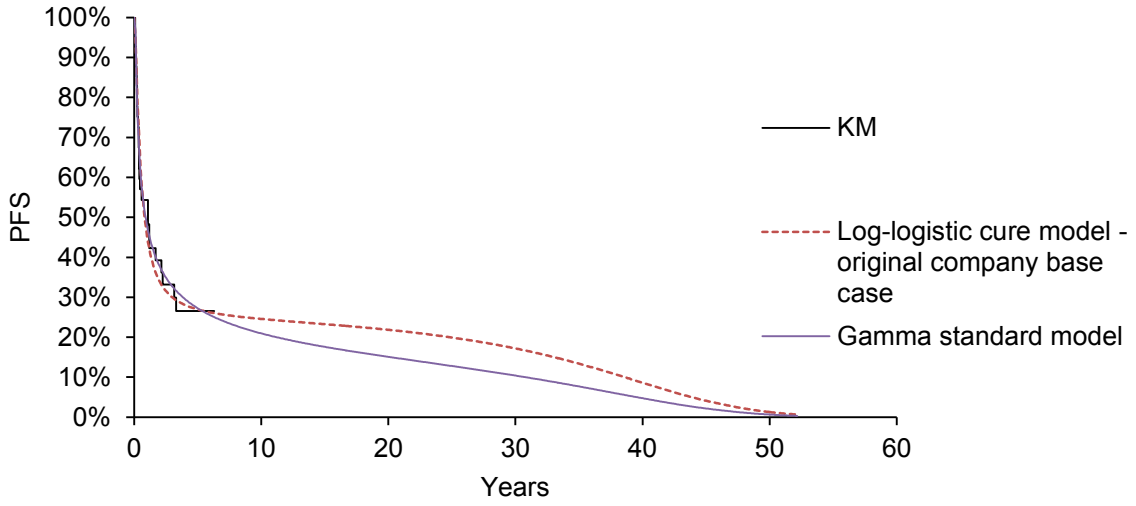
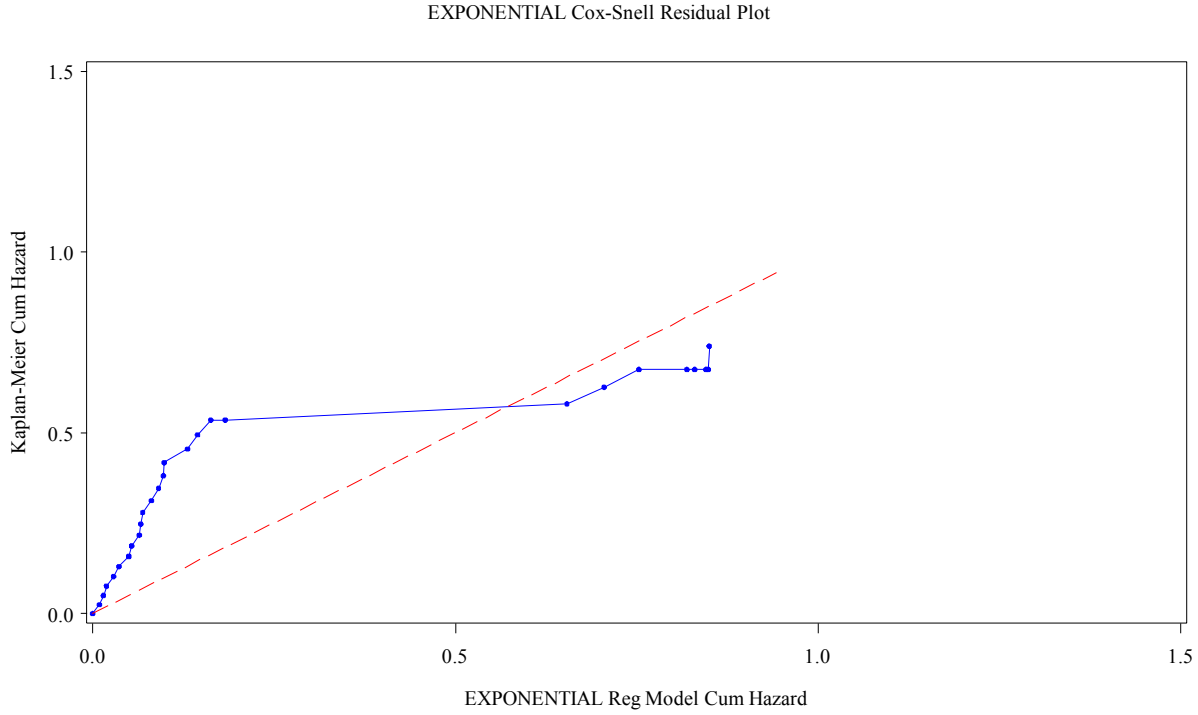


Figure 3-13 Long-term extrapolation comparison of log-logistic cure model (company base case) and standard (gamma) model for brentuximab vedotin (no SCT) PFS



3.4 Brentuximab (no SCT) OS – Cox-Snell Residual plots

Figure 3-14 Brentuximab (no SCT) OS – Cox-Snell residual plots – exponential distribution



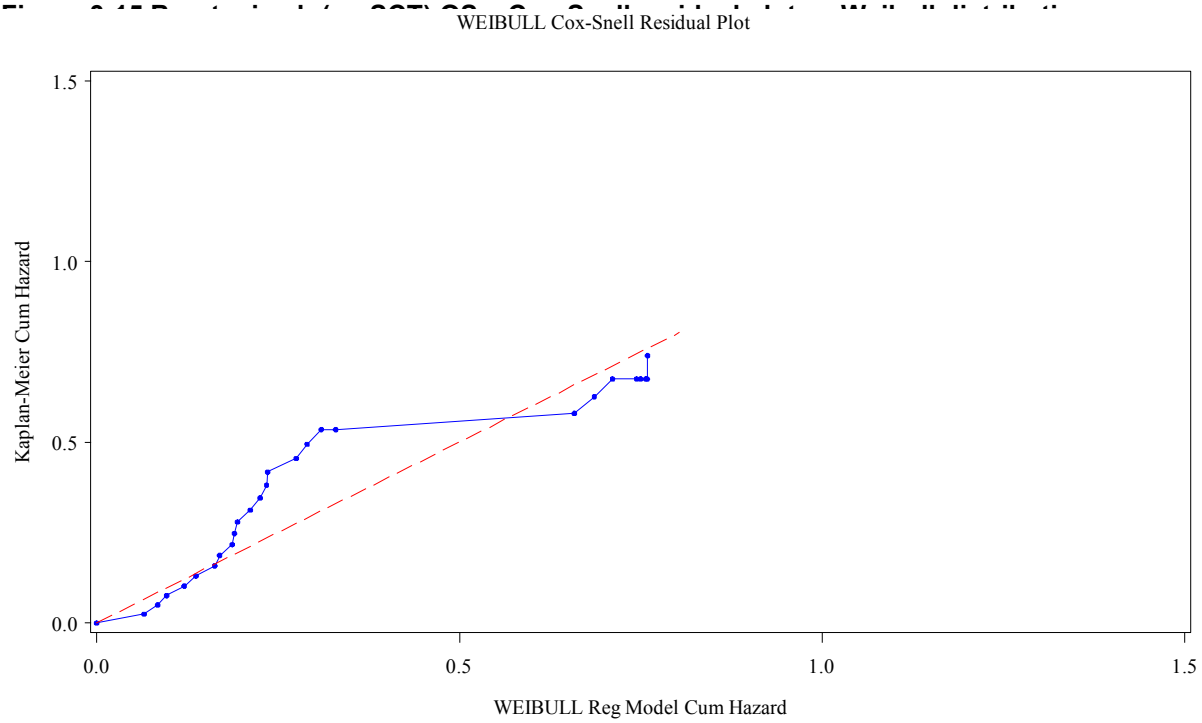
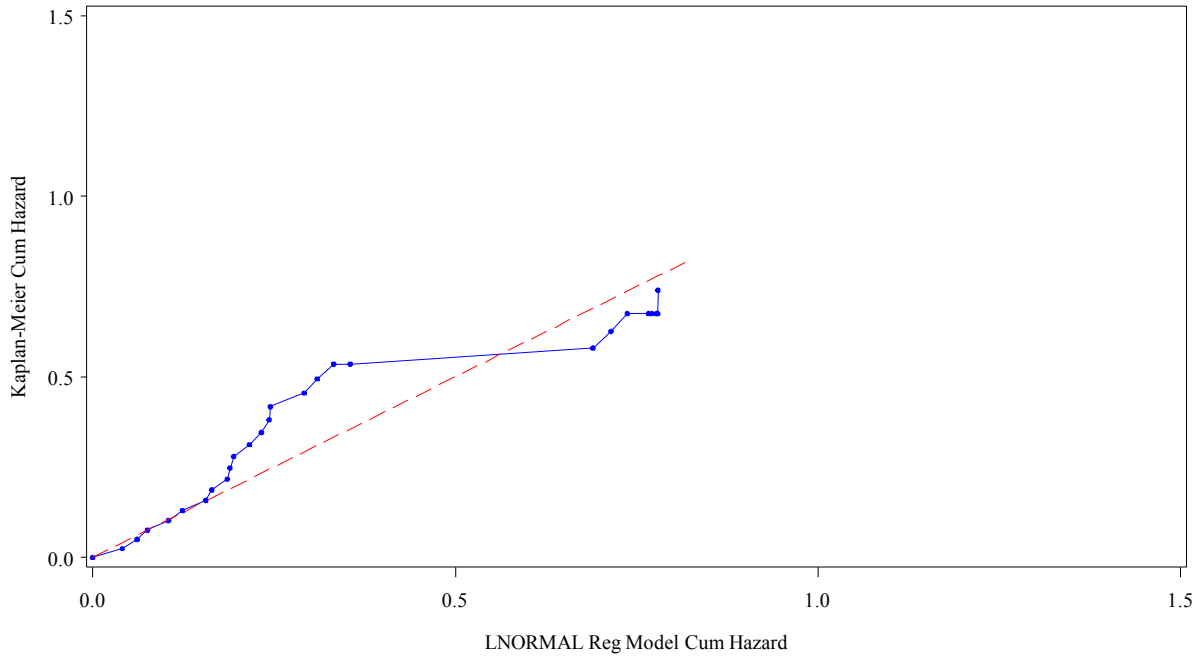


Figure 3-16 Brentuximab (no SCT) OS – Cox-Snell residual plots – lognormal distribution



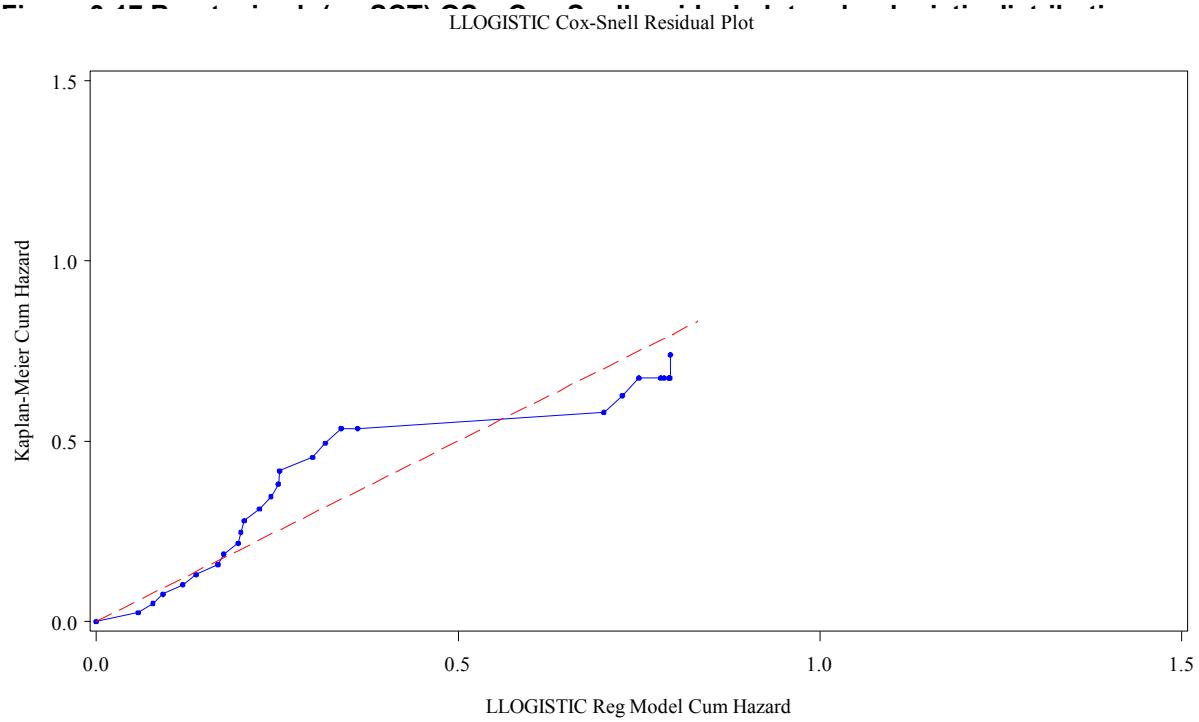
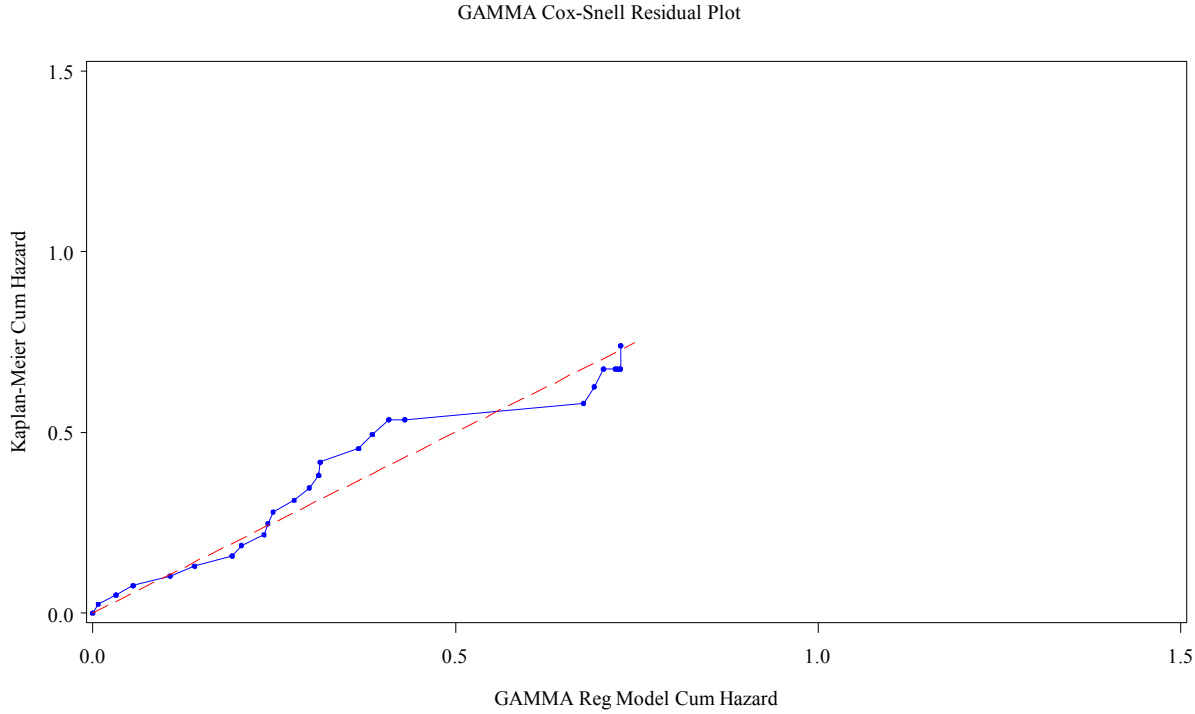


Figure 3-18 Brentuximab (no SCT) OS – Cox-Snell residual plots – gamma distribution



3.5 Brentuximab (no SCT) OS – Parametric cure model vs standard gamma model fit

Figure 3-19 Within-trial comparison of log-logistic cure model (company base case) and standard (gamma) model for brentuximab vedotin (no SCT) OS

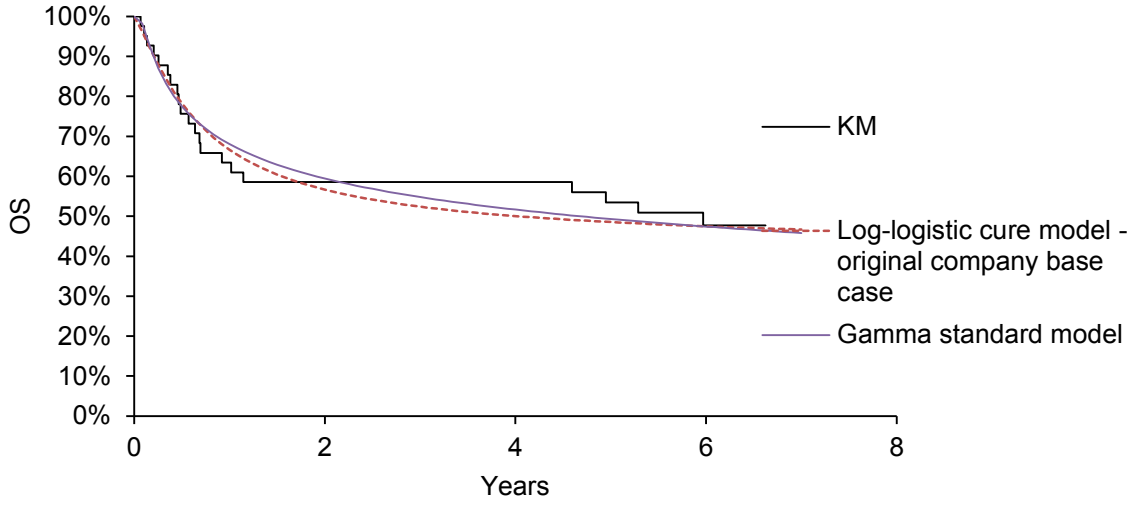
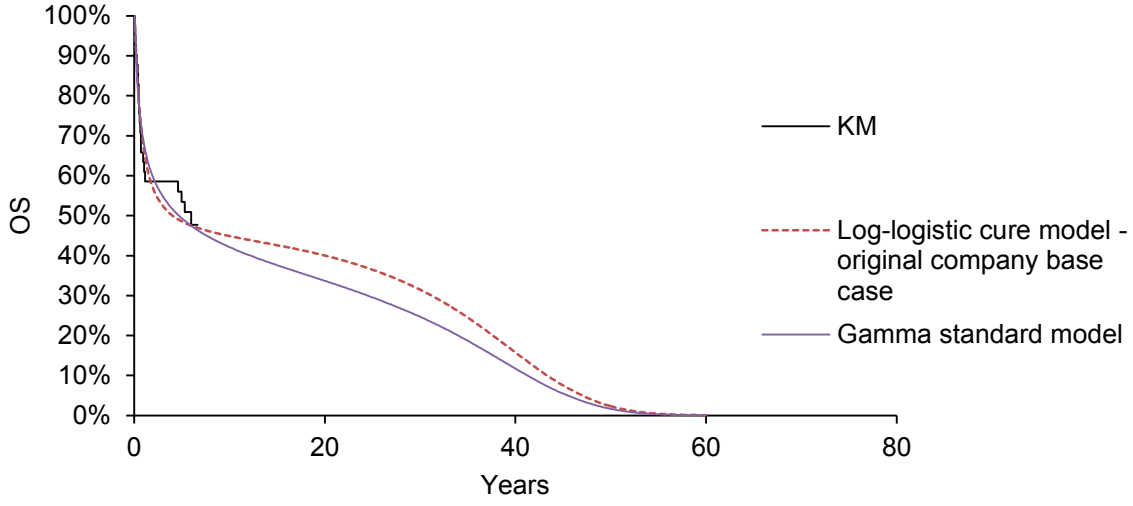


Figure 3-20 Long-term extrapolation comparison of log-logistic cure model (company base case) and standard (gamma) model for brentuximab vedotin (no SCT) OS



Brentuximab vedotin (Adcetris®▼) for treating relapsed or refractory systemic anaplastic large cell lymphoma [ID512]: Appendix 2: End of Life - in response to the ACD (June 2017) for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)
National Institute of Health and Care Excellence

Submitted 5th July 2017

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List of Abbreviations

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

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

1. Introduction

This appendix provides new evidence in response to comments raised in the ACD on the application of the end-of-life (EoL) criteria for brentuximab vedotin for the treatment of R/R sALCL.

The results of the modified economic analysis from Appendix 1 on overall survival outcomes with standard of care and brentuximab vedotin are presented to address the short life expectancy criterion and the extension of life criterion, respectively. In addition, following case precedence, new evidence from the U.K. based Haematological Malignancy Research Network (HMRN) on the observed survival of R/R sALCL patients in a real-world UK setting is presented to support the short life expectancy criterion.

2. End of life

In line with the supplementary guidance provided by NICE (2009), Takeda believe that brentuximab vedotin for the treatment of R/R sALCL fulfils the criteria for an end-of-life (EoL) medicine.

sALCL is an ultra-orphan disease with fewer than 100 patients[1, 2] diagnosed each year in England and Wales. Approximately 50% of patients diagnosed will either relapse or be refractory following front line therapy and for these patients their prognosis is poor. Prior to the availability of brentuximab vedotin only a small proportion could be salvaged with conventional chemotherapy (+/- stem cell transplant) and go on to experience long term survival.

2.1.1 Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The health economic model (base case) estimates that the median OS for standard care (chemotherapy) in this setting is only 1.26 years (15.18 months) if an SCT rate of 14% (7% ASCT and 7% Allo SCT) is assumed. That is, half of all R/R sALCL patients would have died within 1.26 years.

At 2 years, the majority (approximately 63%) of patients treated with chemotherapy (+/- SCT) are expected to have died. The cohort of patients (37%) still alive at 2 years are likely to experience long term survival and potentially cure. It is this small cohort that drives up the mean survival such that it extends beyond 24 months in the model (due to the lifetime time horizon of the model). However, it is clear that for the majority of patients their survival will be less than 24 months.

Please note that the above analysis is based on the PTCL cohort from Mak et al. 2013 with a PS of <2 which was used to inform the health economic model. The model is able to explore the impact of using the ALCL Kaplan-Meier data to inform PFS and OS for chemotherapy (no SCT). Use of the PS<2 data was preferred to the ALCL data due to increased patient numbers (N=47 vs 17), and the ability to control for heterogeneity between SG35-0004 and Mak et al (2013) in terms of performance status. The Mak et al publication notes that the median OS for the R/R sALCL cohort specifically is only 3.0 months, which shows that this particular sub-group of patients (i.e. the group covered by the Marketing Authorisation for brentuximab vedotin) has a significantly worse survival than the broader group from Mak et al which was used for the health economic modelling.[3]

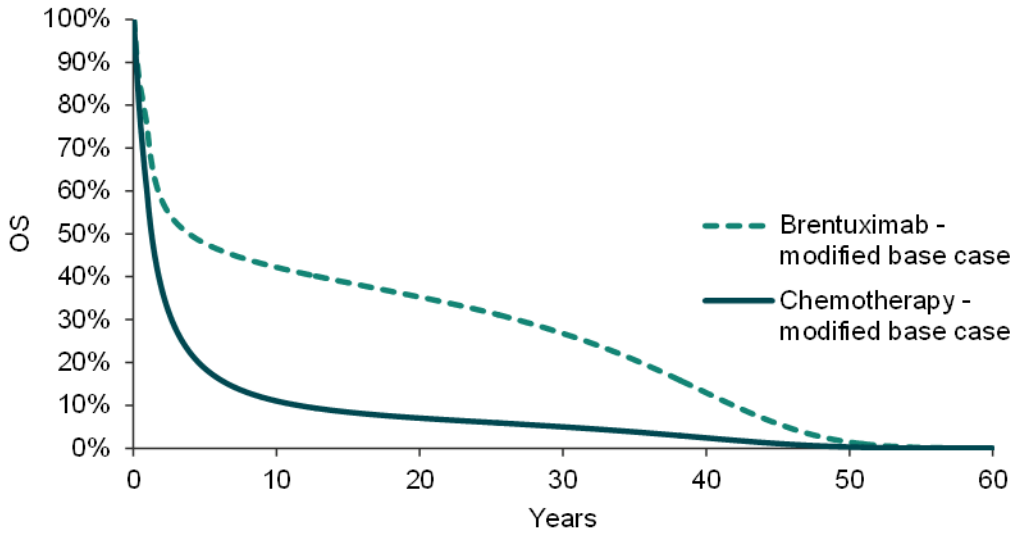
Table 2.1: Cost-effectiveness model estimates of survival, chemotherapy cohorts (PTCL PS<2)

Breakdown of Comparator group	Mean survival (years)	Median survival (years)	Proportion
Chemotherapy (no SCT)	2.79	1.11	86%
Chemotherapy + ASCT	13.70	4.39	7%
Chemotherapy + AlloSCT	9.97	1.88	7%

Table 2.2: Cost-effectiveness model estimates of survival, chemotherapy (PTCL PS <2)

Comparator	Mean survival (years)	Median survival (years)	% of patients alive at 24 months
Chemotherapy (All patients)	3.98	1.26	37%

Figure 2-1: Modelled overall survival by treatment arm sALCL



Despite the limitations described above, by any reasonable interpretation of the clinical meaning of "normally less than 24 months", we believe the model generally supports that the first end-of-life criterion is met. This is further supported by feedback Takeda has received from a large number of UK based clinical experts that, without brentuximab vedotin, R/R sALCL patients would have an average life expectancy of less than 6 months and that only a small minority would survive for 2 years and beyond.

While the ACD states that *"the committee's preference is for mean values for overall survival"* (rather than median) when deciding whether this criterion is met, we would like to make a number of relevant points.[4]

1. The EoL guidance does not state that mean OS must be used and we would suggest that the phrase "normally less than 24 months" is open to interpretation.
2. Having reviewed a large number of EoL decisions by NICE, there seems to be some variability in how this criterion is applied by different committees – some committees seem to accept median OS (rather than mean OS) more readily than others. For an example, precedence for the use of median OS to support the short life expectancy (< 24 months) criterion has been demonstrated in the appraisal of lenalidomide for the treatment of multiple myeloma (TA171).[5]
3. Takeda has consulted fifteen UK clinical experts on this question and all consider that the median provides a much better estimate than the mean of what the prognosis is for the average patient. All clinical experts consulted believe that the median OS provides a better estimate than the mean OS of whether or not survival is "normally less than 24 months", particularly in a very rare condition like R/R sALCL

where a small number of patients surviving an unusually long time can skew the mean quite dramatically. For this reason, it is standard practice in haematology/oncology to report OS as the median rather than the mean.

Takeda also note that in the recent NICE appraisal of nivolumab for R/R Hodgkin lymphoma (R/R HL; ID972, end of life was granted. Furthermore, within ID972, data from the UK based Haematological Malignancy Research Network (HMRN) was used to support the application of end-of-life for nivolumab.[6] Takeda has contacted the HMRN and obtained similar outcome date for patients with R/R sALCL in the UK. This data has not yet been published by HMRN and is provided here strictly on an Academic in Confidence (AIC) basis. The HMRN data for R/R sALCL patients is summarised in Table 2.3 and Figure 2-2 below and clearly shows that both the mean OS and median OS are less than 24 months (years and (respectively).[7] We would note that the median OS reported in the HMRN data Canadian data from Mak et al. Hence, this real-world data from the UK also provides further evidence that the first criterion of short life expectancy is met for R/R sALCL.

Table 2.3: HMRN data for RR sALCL [7]

*End of first line treatment if refractory or relapse date.

Figure 2-2: Overall survival from end of first line treatment (if refractory) or relapse date [7]

A final point relates to the consistency of NICE's decision-making in respect of the EoL criteria. As noted above, nivolumab for R/R HL (TA972) was recently granted EoL status. There are a number of aspects of the nivolumab EoL decision that Takeda believes are similar to, and highly relevant for, the committee's deliberations in respect of the EoL status of brentuximab vedotin for R/R sALCL:

1. The FAD for nivolumab states in Section 4.23 that *"The committee noted that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months"*. Furthermore *"the committee acknowledged that nivolumab did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply. It therefore agreed that on balance nivolumab met the criterion for short life expectancy, and that it would take this into account in its decision-making.*" We would expect that the committee would be minded to apply similar pragmatism and flexibility in respect of its EoL decision-making for brentuximab vedotin in R/R sALCL.

2. The committee accepted *"data from the HMRN provided by the company in response to consultation which showed shorter survival"* and therefore suggested that the modelling may have been optimistic in respect of the comparator treatment arm. As in point 1 above, we would expect that the committee would be minded to apply similar pragmatism and flexibility in respect of its EoL decision-making for brentuximab vedotin in R/R sALCL.

Furthermore, every clinical expert we have spoken with has confirmed that R/R sALCL has a more aggressive disease trajectory than R/R HL, even at its end stage. Hence, given that the short life expectancy criterion has been deemed to be met in the case of nivolumab for R/R HL then logically it is reasonable to conclude that it should also be met for brentuximab vedotin in R/R sALCL.

2.1.2 Criterion 2: There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

Regarding the second end-of-life criterion of an extension to life that is normally at least an additional 3 months, we would note that the updated health economic model using the committee's preferred assumptions estimates an increase in *median* OS of 2.61 years (31.28 months) and in *mean* OS of 10.3 years (123.58 months) with brentuximab vedotin in the base case. Hence, the criterion for extension to life is easily met and indeed is very significantly exceeded. As discussed in Section **Error! Reference source not found.**, this difference between mean and median survival is likely driven by a proportion of patients who experience long term survival and potentially cure causing the mean to be skewed. The full results of the updated health economic analysis are presented in Appendix 1.

Therefore, overall, we believe there is compelling evidence (supported by both real world data from the UK and also UK clinical expert opinion) that brentuximab vedotin for R/R sALCL meets the end-of-life criteria.

Notwithstanding the end-of-life consideration, we believe that brentuximab vedotin (with PAS) has already been shown to be cost effective for R/R sALCL, even at the standard NICE cost-effectiveness threshold of £30,000/QALY.

3. References

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Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma

ERG critique of the revised economic analysis submitted by the company in response to the ACD

Produced by Aberdeen HTA Group

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This report provides the ERG's commentary and critique of revised economic evidence submitted by the company (Takeda UK Ltd) on 06/07/2017 as document: ID512 brentuximab Takeda ACD Response v0.2 050717 SY [ACIC]. The revised model and results are discussed briefly in the following pages. This commentary should be read in conjunction with the company ACD response and associated appendices.

Summary of the revised modelling submitted by the company

The appraisal consultation document (ACD) produced by National Institute for Health and Care Excellence (NICE) for brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma (sALCL), set out draft recommendations on its use:

"The committee is minded not to recommend brentuximab vedotin, within its marketing authorisation, for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults.

The committee recommends that NICE requests a revised probabilistic cost-effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and should:

- *Use data from Mak et al. (2013) for extrapolating both progression-free and overall survival for chemotherapy.*
- *Explore a number of parametric models for extrapolating progression free and overall survival for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate.*
- *Include a range of excess mortality rates higher than those used in the company's base-case analyses. The range should come from published literature identified through a systematic literature review rather than clinical expert opinion."* [1]

In response to the ACD, the company have submitted a revised model and accompanying report. As stated by the company, the revised model incorporates the following changes:

- *"Use of data from Mak et al. (2013) for extrapolating both progression-free survival (PFS) and overall survival (OS) for chemotherapy*
- *Exploration of a number of parametric models for extrapolating PFS and OS for brentuximab vedotin and chemotherapy, including those already considered in the original submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate*
- *Exploration of a range of excess mortality rates, based on published literature, higher than those used in the base-case analyses. The modified based case assumptions for excess mortality, as identified through a targeted literature review, are an increase of 100% for brentuximab vedotin or chemotherapy without a subsequent transplant, 200% following autologous stem cell transplant and 300% following allogeneic stem cell transplant."* [2]

The ERG have reviewed the submitted documentation and model and are content that the company have addressed all of the requested analyses from the ACD. The ERG has replicated the company's analyses contributing to the modified base case. The ERG are satisfied that the analyses are reflective of the ACD requirements and that these have been correctly implemented in the company's submitted model.

The modelling of alternative standard parametric survival distributions for progression free survival (PFS) and overall survival (OS), for brentuximab vedotin and chemotherapy, has been adequately described and the approach to selection of the preferred distributions has been justified. With the modified approach, the company select the generalised gamma distribution for both PFS and OS for brentuximab vedotin. For chemotherapy, the company have used the data from Mak et al.[3] (PTCL patients with performance status < 2) for both PFS and OS as requested. Standard lognormal distributions are selected in the company's modified base case for both PFS and OS for chemotherapy. The model now also allows for extrapolations of PFS and OS for brentuximab vedotin (no SCT) using standard Weibull, exponential, log-logistic and lognormal distributions as well as the original mixture cure models presented in the original company submission. The model allows for the same range of standard parametric models, as well as a Gompertz distribution, for extrapolation of PFS and OS with chemotherapy (no SCT). The fitted distributions for PFS for chemotherapy and brentuximab vedotin, compared with the observed Kaplan Maier data, can be observed in figures 1.2, 1.3, 1.6 and 1.7 of appendix one of the company response to the ACD. For OS, figures 1.10, 1.11 and 1.14 of the company's appendix one show the fitted curves versus observed data.

Further to the above changes, the company have applied revised excess mortality rates over and above general population mortality. As indicated above, the general population mortality rate is now increased by 100% for brentuximab vedotin or chemotherapy without a subsequent transplant, by 200% following autologous stem cell transplant and by 300% following allogeneic stem cell transplant. These have been informed by review of available literature as detailed in the company's response to the ACD. The ERG are satisfied that these excess rates are justified by available literature, rather than based on expert option.

Company revised cost-effectiveness results

Based on the described changes, the company report a modified base case ICER (with approved patient access scheme), including all of the committee's preferred assumptions, of £18,324/QALY. An updated probabilistic analysis generates an ICER £20,399, with the probability of brentuximab vedotin being cost-effective at £20,000, £30,000 and £50,000 per QALY being equal to 52%, 77% and 97% respectively.

The company have provided a large range of deterministic sensitivity and scenario analyses around each point in the ACD. Furthermore, the company has presented a set of deterministic sensitivity analyses around the modified base case ICER (see section 1.2.4 of appendix 1 of the company's response to ACD). However the set of analyses around the modified base case does not fully explore the uncertainty associated with alternative standard parametric survival curves combined with the revised excess mortality assumptions.

ERG further exploratory analyses

The ERG considers that the committee may be interested in a more complete exploration of the uncertainty surrounding the selection of alternative standard parametric survival models in combination with the revised excess mortality rates applied in the model. The ERG have therefore presented a small number of further analyses where alternative parametric curves are applied to the brentuximab vedotin (no SCT) or chemotherapy (no SCT) cohorts, with the revised excess mortality rates also incorporated. Please note, these are for illustrative purposes and the ERG would like to re-iterate that it considers the choice of standard parametric models by the company to be appropriate and in line with NICE DSU recommendations[4].

The ERG further notes that the ACD documentation states that the committee discussed the number of treatment cycles on brentuximab vedotin, and noted that:

"The clinical expert highlighted that real world evidence from the Cancer Drugs Fund suggests that the median number of cycles for brentuximab vedotin is 5 to 6 and that this estimate includes people who go on to have stem cell transplant and those who do not."[1]

And that:

"… the summary of product characteristics for brentuximab vedotin states that it should be used for a minimum of 8 cycles up to a maximum of 16 cycles in patients whose disease is stable."[1]

The ERG's clinical expert noted that the most likely dosage would be between 5 and 6 cycles, in line with the opinion of the committee. From a modelling perspective, the ERG prefer the use of the trial data for brentuximab vedotin acquisition and administration costs, as doing so aligns directly with the effectiveness data included in the model. However, to inform any potential uncertainties that the committee may have around brentuximab vedotin costs, the ERG have conducted three analyses varying the number of treatment cycles using the company's modified base case. Table 1 reports the impact of all further analyses undertaken by the ERG on the modified base case ICER.

Table 1: Additional sensitivity analyses around the company's modified base case:

Modification	Intervention	Lys	QALYs	Costs	Inc. costs	Inc. QALYs	ICER (per QALY)
Original company base case	Chemotherapy	3.35	[redacted]	[redacted]	-	-	£12,873
	Brentuximab vedotin	9.53	[redacted]	[redacted]	[redacted]	[redacted]	
Company modified base case	Chemotherapy	3.09	[redacted]	[redacted]	-	-	£18,324
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	
Excess mortality rates (increase to 500% in both BV and chemo, no SCT)	Chemotherapy	2.99	[redacted]	[redacted]	-	-	£22,193
	Brentuximab vedotin	6.92	[redacted]	[redacted]	[redacted]	[redacted]	
Reducing number of cycles on BV (all cohorts) to 5 (clinical opinion)	Chemotherapy	3.09	[redacted]	[redacted]	-	-	£11,048
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	
Increasing number of cycles on BV (all cohorts) to 16 (on maximum dose in SPC)	Chemotherapy	3.09	[redacted]	[redacted]			£35,848
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	
Increasing number of cycles on BV (No SCT cohort only) to 16 (on maximum dose in SPC)	Chemotherapy	3.09	[redacted]	[redacted]			£31,136
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	
Analyses surrounding standard parametric models for brentuximab vedotin (PFS and OS)							
Weibull for PFS and OS (Brentuximab)	Chemotherapy	3.09	[redacted]	[redacted]			£25,353

	Brentuximab vedotin	7.12	[redacted]	[redacted]	[redacted]	[redacted]	
Exponential for PFS and OS (Brentuximab) – *most pessimistic for BV*	Chemotherapy	3.09	[redacted]	[redacted]			£32,801
	Brentuximab vedotin	6.12	[redacted]	[redacted]	[redacted]	[redacted]	
Log Normal for PFS and OS (Brentuximab)	Chemotherapy	3.09	[redacted]	[redacted]			£24,064
	Brentuximab vedotin	7.32	[redacted]	[redacted]	[redacted]	[redacted]	
Mixture cure models *(log logistic for both PFS and OS)*	Chemotherapy	3.09	[redacted]	[redacted]			£16,253
	Brentuximab vedotin	8.44	[redacted]	[redacted]	[redacted]	[redacted]	
Analyses surrounding standard parametric models for chemotherapy (PFS and OS)							
Weibull for PFS and OS (Chemo)	Chemotherapy	3.22	[redacted]	[redacted]			£18,475
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	
Exponential for PFS and OS (Chemo) *(most optimistic for chemo)*	Chemotherapy	3.41	[redacted]	[redacted]			£19,108
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	
Gamma for PFS and OS (Chemo)	Chemotherapy	3.18	[redacted]	[redacted]			£18,537
	Brentuximab vedotin	8.02	[redacted]	[redacted]	[redacted]	[redacted]	

BV: Brentuximab Vedotin; Chemo: Chemotherapy; ICER: Incremental Cost-effectiveness ratio; OS: Overall survival; PFS: Progression Free Survives; QALY: Quality-adjusted Life Year; SCT: Stem-cell transplant; SPC: Statement of Product Characteristics;

ERG commentary on the company's application for End of Life consideration

Appendix 2 of the company response to the ACD outlines further justification for end of life criteria to apply to the appraisal of brentuximab vedotin. The ERG has reviewed the company's submission for End of Life (EoL) consideration and makes the following observations:

1. On the grounds that patients with sALCL have less than two years left to live on standard care (chemotherapy +/-SCT), the ERG notes that the median OS projected by the company model meets this criterion, but projected mean overall survival for the whole chemotherapy cohort does not (mean OS = 3.98 years). A difference between mean and median is inevitable given that a small proportion of survivors on chemotherapy will go on to have extended remission, driving up the mean OS.

   The company put forward several arguments for considering median OS when applying the end of life criteria (see pages 8 to 10 of appendix 2 of the company ACD response). Among these they note that the median OS has been previously accepted for applying EoL criteria in a number of other NICE TAs (e.g. lenalidomide for the treatment of multiple myeloma (TA171).[5] They also make reference to the fact that flexibility has been applied when considering EoL status in previous TAs, and provide an example from section 4.23 of the FAD for nivolumab (see page 10 of appendix two to the company response to ACD).

   The ERG note that the company have also obtained and reported additional data from the UK based Haematological Malignancy Research Network (HMRN) which provides additional evidence supporting the end of life application, where both mean and median survival are less than 2 years (see Table 2.3 and Figure 2.2 in appendix 2 of the company response to ACD). It is not clear from the data reported why the OS is lower in this cohort when compared against the model projections, but it may be due to a number of factors including patient characteristics and/or differences in SCT rates and their associated efficacy following chemotherapy.

2. The ERG note that the company's application for EoL consideration easily meets NICE's guidelines on the grounds that the treatment under consideration offers an extension to life over standard care, with modelled additional overall survival well in excess of the 3 month threshold.

The ERG are confident that the numbers used to support the EoL application are correct and based on the modelled data for the modified base case ICER with one exception. In section 2.1.2 of the

company's response to the ACD, it is noted that the economic model "*using the committee's preferred assumptions"* estimates a mean increase in OS of 10.3 years. The ERG have attempted to replicate this number in the company submitted model and were unable to do so. The ERG believe that the correct increase in mean OS is 8.3 years. However, the ERG note that in either case, the additional OS is well in excess of the 3 month threshold for consideration as an EoL treatment.

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