NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for relapsed or refractory classical Hodgkin lymphoma [ID972]

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:**
   - Bristol-Myers Squibb Pharmaceuticals Ltd
   - Lymphoma Association
   - The National Cancer Research Institute – Association of Cancer Physicians – Royal College of Physicians – Royal College of Radiologist (joint response)
   - Royal College of Radiologists

   '*No comment' response received from Department of Health*

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

4. **Company new evidence appendix** – submitted by Bristol-Myers Squibb Pharmaceuticals Ltd

5. **Evidence Review Group critique of company new evidence**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab for treating relapsed or refractory classical Hodgkin 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
Bristol-Myers Squibb	**1. Executive summary** This document provides a response to the Appraisal Consultation Document describing the use of nivolumab for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and brentuximab vedotin (BTX). In line with the Appraisal Consultation Document, this response outlines the additional clinical and economic evidence requested by the Appraisal Committee, which can be used to support decision-making. Thus, Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd believes that the recommendations made within the Appraisal Consultation Document are no longer considered valid and suitable; and anticipates that the Appraisal Committee will reconsider their recommendations at the next meeting. Further, BMS would like to highlight that in the absence of appropriate clinical data for the comparator arm, the company submission has applied the best available evidence in the base case analysis, providing a median overall survival (OS) of 19 months. This can be considered an overestimate of survival in clinical practice, as clinician opinion consistently reflects short survival in patients with relapsed or refractory cHL following prior ASCT and BTX. UK-specific data provided in response to the Committee's recommendations support very short survival in this patient population, with few patients expected to survive 24 months. This opinion was supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months. By contrast, the Committee's conclusions on the application of end of life criteria for nivolumab are based on one study where clinical outcomes are driven by use of investigational agents not available to all patients in the UK, rather than the sum of all available evidence. Additionally, BMS considers the Committee's recommendation of including investigational agents as standard of care (SoC) to be inappropriate. The Appraisal Consultation Document does not include clinician comments from the meeting confirming that the use of investigational agents would be minimal (around 5%) and would be limited to patients treated at large treatment centres, implying that those treated in smaller centres would not be able to receive these investigational therapies. This is supported by UK-specific clinical expert opinion, where investigational agent use was estimated to be [redacted]. Further, the Appraisal Committee concluded that the Cheah et al. study overall population would better match the population in the nivolumab studies, as patients in clinical trials tend to be fitter. However, there is no evidence to support this conclusion, and available evidence using baseline characteristics suggests that	Comments noted. The committee considered all the information received from the company as per the process guide (see section 3.7.32-3.7.34 of the NICE guide to the process of technology appraisals). See FAD sections 4.7 and 4.11. Comment noted. See FAD sections 4.23-4.25 Comment noted. See FAD section 4.8.

Consultee	Comment [sic]	Response
	patients in the nivolumab study may be older and have more advanced disease than those in the Cheah et al. study. Based on the final scope for this appraisal and the NICE guide to the methods of technology appraisal, appropriate comparators should represent established NHS practice in England. However, based on the evidence presented at the Appraisal Committee meeting and in this response, the use of investigational agents cannot be considered established NHS practice. Therefore, this recommendation by the Appraisal Committee can be considered inappropriate, particularly when inclusion of these agents results in the conclusion that nivolumab, for the treatment of relapsed or refractory cHL, does not meet end of life criteria. The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after failure of ASCT. However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to support this conclusion. In summary, the availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need. BMS believes that the Committee recommendations do not take into account all relevant evidence, do not accurately reflect clinical and cost-effectiveness conclusions, and do not provide a sound and suitable basis for guidance to the NHS. It is anticipated that further evidence presented in response to the Appraisal Consultation Document will be considered by the Appraisal Committee, and will further demonstrate that nivolumab is cost-effective and is associated with substantial clinical benefit in a population with very short survival and limited treatment options.	Comments noted. See FAD sections 4.23-4.25 The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD section 1.1 and 4.26.
Bristol-Myers Squibb	**2. Evidence requested by the Committee** The Appraisal Committee has recommended that NICE requests from the company for the second appraisal committee meeting revised probabilistic cost-effectiveness analyses comparing nivolumab with standard of care, which incorporate the committee's preferred assumptions regarding method of indirect comparison, costs and utilities. In line with this, a revised base case analysis has been provided in Appendix A, outlining the approach taken with reference to recommendations from the Committee. Further, the Appraisal Committee has recommended that the analyses should also explore the use of UK data for standard of care (for example, from the Haematological Malignancy Research Network) and a range of subsequent allogeneic stem cell transplant (alloSCT) rates for both nivolumab and standard of care that are higher than those used in the Cheah and Perrot studies and are from UK data. In line with this recommendation, BMS has contacted the HMRN to obtain data describing UK clinical practice. Further, BMS has conducted a survey of UK clinicians to elicit opinion on the composition and efficacy of SoC, as well as proportions of patients who would receive alloSCT in clinical practice. This evidence is outlined in Appendix A, along with economic evaluations applying UK-specific data.	Comments noted. The committee considered all the information received from the company as per the process guide (see section 3.7.32-3.7.34 of the NICE guide to the process of technology appraisals). See FAD sections 4.7 and 4.11.

Consultee	Comment [sic]	Response
Bristol-Myers Squibb	**3. Has all relevant evidence been taken into account?** BMS does not believe that the Committee has taken into account all of the relevant evidence, resulting in non-evidence-based recommendations that are not in the patient's interest. Not all clinical and economic evidence was presented in the ERG report and Committee slides, and so was not taken into account when deriving this recommendation.	Comments noted. The committee considered all the information received from the company as per the process guide (see section 3.7.3. of the NICE guide to the process of technology appraisals). Decision-making focussed on the information presented in the base case analysis because this reflected the company's preferred assumptions. Additionally, the committee can only consider evidence and analyses that is within the scope of the appraisal.
	Sources of clinical evidence applied within the economic evaluation and provided within the original submission included: • **Cheah et al., 2016**: data from the overall population and data excluding the efficacy of investigational agents. The naïve comparison was presented to the Committee in the ERG report and Committee slides. Additionally, a matching-adjusted indirect comparison (MAIC) analysis was presented in the submission, and applied in the economic analysis, improving the ICER versus use of the naïve comparison. • **Data from the post-ASCT, post-BTX systematic literature review (SLR)**: the majority of evidence from this SLR described clinical trials of investigational agents, rather than clinical practice. However, data from this SLR was used to inform a naïve indirect comparison and a MAIC, with outputs applied in the economic evaluation as scenario analyses. • **Data from the post-ASCT cohort**: due to the relative lack of data identified within the post-ASCT, post-BTX SLR, the eligibility criteria for the studies was expanded to treatments for relapsed or refractory HL in patients who have previously received prior ASCT (i.e. prior BTX treatment was not a requirement) in an attempt to provide additional supportive data in a patient population whose treatment options and outcomes are subject to considerable uncertainty. Data from this SLR was used to inform a naïve indirect comparison and a MAIC, and outcomes for nivolumab remained superior over published efficacy evidence, despite use in a more treatment-experienced	Comments noted. See FAD section 4.9.

Consultee	Comment [sic]	Response
	population. This evidence was applied in the economic evaluation as scenario analyses supporting the beneficial impact of nivolumab in the wider relapsed or refractory cHL setting. This evidence was not presented to the Committee as the ERG did not consider it to be relevant to the population of interest (post-ASCT, post-BTX HL). This can be considered highly inappropriate in the context of the Committee's conclusions that the published evidence for comparator treatments was limited, and evidence presented did not represent UK practice. It should be noted that additional supportive evidence was provided in the submission but not assessed by the ERG. Since publication of the Appraisal Consultation Document, additional evidence has been sought and further economic evaluations have been undertaken in order to address the Committee's requests. This includes: • Additional evidence from the HMRN describing the treatment pathway and survival for patients with relapsed or refractory cHL following prior ASCT and BTX. • Evidence from a clinician survey describing SoC and outcomes in UK clinical practice for patients with relapsed or refractory cHL following prior ASCT and BTX. • Evidence from UK clinical practice describing survival following alloSCT in UK patients with relapsed or refractory cHL following at least three prior therapies, including ASCT in the majority of cases (62%). • Economic evaluations applying the Committee's preferred assumptions and modelling methods. • Economic evaluations applying efficacy inputs describing UK patients from the UK clinician survey. • Economic evaluations applying a range of alloSCT rates and UK-specific alloSCT survival, in order to describe the impact of increasing alloSCT rates from those applied in the company submission. In summary, the Committee has not reviewed all relevant evidence. In light of the high unmet need in this setting (described in Section 4.7), it is in the patient's best interests for the Committee to review this evidence and reconsider its guidance on the use of nivolumab for the treatment of relapsed or refractory cHL following prior ASCT and BTX.	Comments noted. See FAD 4.7 and 4.11.
Bristol-Myers Squibb	**4. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence** BMS does not believe that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence, as detailed below.	Comment noted. Please see individual responses below.
Bristol-Myers Squibb	**4.1. End of life criteria** There is a distinct paucity of data describing patients with relapsed or refractory cHL following prior ASCT and BTX. This is partly due to the recent availability of BTX and its ongoing NICE appraisal, creating a new clinical pathway and, thus, a new patient population. Further, the low patient numbers and heterogeneous nature of presenting patients result in individualised treatment and variation between clinicians. Additionally, any published evidence is likely to reflect use of clinical trials in this patient population rather than established clinical practice.	Comments noted. See FAD sections 4.23- 4.25.

Consultee	Comment [sic]	Response
	In the absence of definitive data describing the clinical reality of patients, it is essential to consider the views of clinical experts. Clinician opinion consistently reflects short survival in patients with relapsed or refractory cHL following prior ASCT and BTX. The UK-specific data from the HMRN and the clinician survey (both provided in Appendix A) support short survival in this patient population, with few patients estimated to survive 24 months. Further, this is supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.Outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX. Based on this evidence, it is highly unlikely that life expectancy would exceed 24 months in cHL patients who are more treatment-experienced and eligible for nivolumab therapy (i.e. having previously received both ASCT and BTX therapy). Similarly, despite the Committee's reservation about the relevance of the Cheah et al. 2016 population with investigational agents removed, this can also be considered supportive of the views of clinicians, with median survival estimated at 19 months. Further, median OS reduces to 17.9 months following the matching-adjusted indirect comparison process, as detailed in Appendix 3 of the company submission. By contrast, the ERG report life expectancy of 2.9 years in their revised base case. This cannot be considered to reflect current clinical practice, as it is longer than that described by clinical experts and in published literature for a less treatment-experienced, post-ASCT population. Similarly, even the modelled results of the base case analysis in the company submission can be considered to overestimate the life expectancy of patients receiving current clinical practice. Thus, it is anticipated that the Appraisal Committee will reconsider the application of end-of-life criteria to nivolumab use for the treatment of relapsed or refractory cHL following prior ASCT and BTX.	
Bristol-Myers Squibb	**4.2. Clinical effectiveness of nivolumab in this setting** The Committee considered that the evidence for the clinical effectiveness of nivolumab was highly uncertain because the data were immature and from single-arm studies. In addition, the published evidence for comparator treatments was limited, and the evidence presented did not represent UK practice. However, it should be noted that the submission detailed substantial follow-up from relevant studies (CheckMate 205 cohort B: 15.7 months; CheckMate 205 cohort C: 8.9 months; CA209-039: 23.3 months). The data can only be considered immature because of the improvements to survival, since there are fewer events to inform PFS (one-year PFS: [redacted]) and OS (one-year OS: [redacted]) within the available follow-up period. This is of particular relevance in the context of relapsed or refractory cHL following ASCT and BTX, where outcomes are very short. As detailed above, PFS and OS are extremely short in clinical practice for	Comments noted. The committee considered all the information received from the company as per the process guide (see section 3.7.3 of the NICE guide to the process of technology appraisals). Comment noted. See FAD sections 4.5 and 4.10.

Consultee	Comment [sic]	Response
	this patient population; therefore, the relatively few survival events observed following treatment with nivolumab should be considered an indication of the efficacy of nivolumab. Further, it should be noted that several sources of evidence have been identified and presented to the Committee. In addition to the evidence versus the Cheah et al. 2016 publication, a full SLR was undertaken to identify evidence in relapsed or refractory cHL patients following ASCT and BTX, with naive and adjusted indirect treatment comparisons provided in Appendix 3 of the company submission. As evidence from this SLR was primarily derived from clinical trials, the SLR was expanded to include cHL patients following prior ASCT in order to provide supportive evidence in a population where more data exists. Although patients eligible for enrolment into the nivolumab studies would have been more treatment-experienced than those included in the post-ASCT population, both SLRs and ITCs can be considered supportive of a substantial survival advantage for nivolumab. Within the ACD response, two additional sources are detailed describing clinical effectiveness of SoC: the HMRN data and the clinician survey (as detailed in Appendix A). Both outline the poor outcomes in relapsed or refractory cHL following ASCT and BTX. A comparison of survival outcomes for nivolumab versus SOC is provided in Table 1 [*Table provided but not reproduced here*]. As can be seen, PFS outcomes are broadly comparable between sources of evidence, with the exception of the post-ASCT population, which had improved outcomes versus the post-ASCT, post-BTX population. By contrast, nivolumab is associated with substantial PFS benefit, far exceeding all estimates of PFS from clinical experts and the literature. Estimates of OS from the published literature exceed clinical expert expectations, with evidence based on clinical trial data and investigational agent use providing greater estimates of survival. Of interest, estimates of OS from the literature for the post-ASCT, post-BTX population exceed those for the post-ASCT population, which included more studies that could be considered representative of real-world outcomes, and this is likely due to the preponderance of clinical trial data and investigational agent data available in the post-ASCT, post-BTX population. All estimates of OS far exceed those provided by clinicians. However, nivolumab provides substantial OS benefit over all available sources of evidence, as summarised in Table 1 [*Table provided but not reproduced here*]. Further, of the provided sources of evidence, several are directly relevant to current clinical practice in the UK. As can be seen, regardless of data source, there is a substantial benefit in terms of PFS and OS for nivolumab versus standard of care, so that evidence for comparator treatments can be considered exhaustive and representative of UK practice. Table 1: Comparison of outcomes for nivolumab studies and additional evidence sources [*Table provided but not reproduced here*]	Comment noted. Comments noted. See FAD sections 4.7 and 4.23. Comment noted. Comment noted. Comment noted. See FAD section 4.7.

Consultee	Comment [sic]	Response
Bristol-Myers Squibb	**4.3. Relevance to the UK setting** As noted previously in the company submission and this response, there is a distinct paucity of data describing patients with relapsed or refractory cHL following prior ASCT and BTX. This is partly due to the recent availability of BTX, creating a new clinical pathway and thus patient population. Further, the low patient numbers and heterogeneous nature of presenting patients result in individualised treatment and variation between clinicians. Although data from the Cheah et al. 2016 study was based on a US cohort, it can also be considered to adequately represent UK clinical practice based on evidence from the HMRN and two physician surveys conducted by BMS (described in Appendix A). Despite the limitations of available evidence, it can be considered that evidence presented within the submission and this response document is broadly representative of UK clinical practice and outcomes for cHL patients who have relapsed or are refractory following prior ASCT and BTX.	Comments noted. See FAD section 4.7.
Bristol-Myers Squibb	**4.4. Use of investigational agents in UK clinical practice** During the Appraisal Committee meeting, the Appraisal Committee discussed the inclusion of investigational agents as part of SoC, based on the Cheah et al. 2016 population. The Committee considered that the patients in the Cheah et al. study having investigational agents may have differed from people seen in clinical practice more in terms of their fitness to have such treatments rather than the treatments themselves. However, clinical experts present at the Appraisal Committee meeting disagreed with the Committee's suggestion that investigational agent use is commonplace. Clinicians stated that investigational agent use is minimal in this setting (around 5%), and would broadly be confined to large treatment centres, so that patients receiving treatment in smaller centres would not be able to receive these agents. It should be noted that this is supported by evidence from the clinician survey presented in Appendix A. Additionally, the Appraisal Committee suggested that the overall population in the Cheah et al. study, including those having investigational agents, would better match the population in the nivolumab trials because patients in trials tend to be fitter. However, there is no evidence to support this suggestion in the case of the nivolumab studies. On the contrary, patients in the Cheah et al. study tended to be younger, with fewer older patients enrolled, in comparison with the nivolumab studies, and disease stage at study enrolment tended to be better than in the nivolumab studies. Further, the Committee heard that the ERG had contacted the authors of the study, and that only 'a couple' of patients in the study had a PD-1 inhibitor, and therefore the ERG considered that the overall population should be used for comparator data. However, clinicians at the meeting advised that other unlicensed checkpoint inhibitors would be included within investigational agents, including agents targeting CTLA-4 and PD-L1. These agents have similar mechanisms of action to nivolumab, as all utilise pre-existing anti-cancer immune responses to improve patient outcomes; thus, the ERG's argument that the majority of patients did not receive PD-1 inhibitors may be irrelevant.	Comments noted. See FAD sections 4.7 and 4.8.

Consultee	Comment [sic]	Response
	The scope for this appraisal details the following comparators as appropriate: established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine; and best supportive care. Further, the NICE guide to the methods of technology appraisal states several criteria applied when determining appropriate comparators for Technology Appraisal, including consideration of **established** NHS practice in England. However, based on evidence from the clinical experts present at the Appraisal Committee meeting and the clinician survey presented in Appendix A, the investigational agents described by Cheah and colleagues, by definition, do not reflect established practice within the NHS in England. Data pertaining to relevant and established comparator therapies are outlined within other cohorts in this study. It is likely that investigational agents will comprise unlicensed products and those not recommended by NICE, thus limiting the relevance of this category to simulation of clinical practice in the UK. It should also be noted that inclusion of investigational agents into SoC extends the OS beyond which clinical experts consider plausible. Based on data from the HMRN, described in Appendix A, [redacted]. Further, the clinician survey presented in Appendix A details estimated OS of [redacted]. This estimate was supported by clinical experts attending the first Appraisal Committee meeting for the ongoing BTX appraisal [ID722], who suggested that life expectancy without BTX is likely to be less than 24 months. Further, it is supported by the results of the post-ASCT ITC detailed in Table 1 [*Table provided but not reproduced here*], where median OS was estimated as [redacted]. It is extremely implausible that life expectancy would exceed 24 months in cHL patients who are eligible for nivolumab therapy and are more treatment-experienced (i.e. having previously received both ASCT and BTX therapy). The Appraisal Committee has concluded that the overall population of the Cheah et al. study was the most appropriate dataset for standard of care to use in the indirect comparison. However, this is inappropriate when all available evidence is considered, including the view of clinical experts at the Appraisal Committee meeting and the additional evidence presented within this response.	
Bristol-Myers Squibb	**4.5. Alternative OS extrapolation** It was not possible for BMS to check the factual accuracy of all presented data prior to the Appraisal Committee meeting, as an addendum was not made available until immediately prior to the Appraisal Committee meeting. The addendum described economic evaluation where nivolumab OS extrapolation applied the Gompertz parametric fit, resulting in an ICER of £122,825. **4.5.1. Accuracy of analysis** The ERG provided a version of the model to enable verification and it can be confirmed that the correct Gompertz parameters were applied in the model. However, this analysis is misrepresented within the slides presented to the Committee. The ERG addendum clearly states that the ICER produced applies ERG base case assumptions.However, the slides presented to the Committee (and subsequently to the public) provide this analysis amongst scenarios assessed using the base case analysis detailed in the	Comments noted. See FAD section 4.12.

Consultee	Comment [sic]	Response
	company submission of evidence, which implies that the application of these curves increases the ICER from £19,882 to £122,825, which is not the case, as is described in Section 4.5.2. Figure 1: Excerpt from Committee slides [*Figure provided but not reproduced here*] **4.5.2. Application of Gompertz OS extrapolation in company base case** A sensitivity analysis applying the Gompertz curve for nivolumab OS to the base case described in the company submission is provided in Table 2. As can be seen, applying this survival curve for nivolumab has a large reduction on accrual of LYs ([redacted]), QALYs ([redacted]) and costs [redacted]). This impact causes the ICER to increase from £19,882 in the base case analysis to £31,631. The main differences between this analysis and the ERG analysis are derived from application of the Cheah et al. 2016 overall population, and the inappropriate inclusion of alloSCT costs without its associated clinical benefits. When applying base case assumptions as per the ERG, the nivolumab treatment arm accrues total costs of [redacted], which is associated with cost of alloSCT. By comparison, accrual of QALYs ([redacted]) and LYs ([redacted]) in the nivolumab arm is comparable to that in Table 2. Table 2: Impact of applying Gompertz OS extrapolation for nivolumab [*Table provided but not reproduced here*] **4.5.3. Appropriateness of use of Gompertz extrapolations** This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed within the company submission. Parametric extrapolation of survival data from relevant studies was undertaken with reference to the guidance from the NICE Decision Support Unit (DSU) and Bagust and Beale (2014). Parametric survival functions were fitted to the extracted pooled data, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions. These are provided in Figure 2. Goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively). Minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit. On the basis of the AIC and BIC goodness-of-fit statistics, exponential can be selected as the most appropriate parametric fit, followed by lognormal, Weibull and log-logistic. By contrast, using these statistics, Gompertz can be considered one of the least appropriate parametric fits. Figure 2: Parameterisation of overall survival: nivolumab (years 0-5) [*Figure provided but not reproduced here*] Figure 3 [*Figure provided but not reproduced here*] presents the evolution of the hazard profile over time for each parametric extrapolation. As can be seen, the majority of the hazards associated with each extrapolation predict an initial rise in hazard, followed by a gradual decline. This reflects available Kaplan-Meier data, where the majority of events occur in the initial period, and then the risk of death decreases	

Consultee	Comment [sic]	Response
	over time. By contrast, the Gompertz predicts a rapidly accelerating hazard that cannot be supported by available data or clinical rationale. Figure 3: Overall survival: evolutions of hazards – nivolumab combined cohort (n=193) [*Figure provided but not reproduced here*] Finally, the parametric functions and profiles depicted in Figure 3 were assessed by clinical experts during an advisory board meeting. Clinicians noted the paucity of data to inform OS, but considered that PFS and OS hazards would have similar long-term extrapolation (i.e. there would be an initial increase in hazard, followed by a gradual decline in hazard over time). This criteria would exclude the Gompertz and exponential functions. Based on a median follow-up of 11.7 months, three of the models (generalised gamma, generalised F and lognormal) predicted median OS exceeding 100 months (8.3 years), with a fourth (exponential) predicting median OS of 94 months (7.8 years). Additionally, these four parametric functions predict that a proportion of patients remain alive when the parametric functions are extended beyond 60 years. Although this can be considered optimistic, this would provide a level of clinical benefit supported by data from other nivolumab indications. As such, it cannot be considered implausible; however, it was acknowledged that a more conservative approach may be appropriate for the purposes of health technology assessment. As stated in Appendix 6 of the company submission, the Weibull function was determined to be most appropriate based on these criteria. Further, the ERG stated that communication with clinical experts confirmed their agreement to the approach chosen by the company and the ERG considered that the choices made by the company in the base case were the most appropriate extrapolation choices.[15] By contrast, the Gompertz function could be excluded based on all criteria. Further, it should be noted that the predicted survival is implausibly short. As demonstrated in Figure 4, use of the Gompertz function results in OS that falls below that of the OS for SoC based on Cheah et al. 2016 after removal of the impact of investigational agents. Following discussion with clinical experts, this was determined to be implausible, based on clinical experience and the available data for nivolumab. This was confirmed by clinical experts attending the Appraisal Committee meeting. It should be noted that the ERG have not applied the Gompertz function in their base case analysis. Figure 4: Comparison of parametric extrapolation of nivolumab OS versus Cheah 2016 (without investigational agents) OS extrapolation [*Figure provided but not reproduced here*] It should be noted that the lognormal extrapolation can be considered the most appropriate fit, based on goodness-of-fit statistics, visual inspection of the functions and clinical plausibility of the hazard profiles. However, this function was excluded as the predicted OS can be considered optimistic, and a conservative estimate of OS would be more appropriate in the context of health technology assessment. If the lognormal OS function was applied, estimated median OS would increase from 58.2 months (Weibull) to 108.7 months (lognormal). When applied in the economic model, accrual of LYs ([redacted]), QALYs	

Consultee	Comment [sic]	Response
	([redacted]) and costs [redacted]) increase in the nivolumab arm, resulting in an improved ICER (£11,926). Thus, the presented base case analysis can be considered highly conservative. However, it should be noted that despite use of an implausibly short OS extrapolation, the predicted ICER remained below a £50,000/QALY willingness-to-pay threshold.	
Bristol-Myers Squibb	**4.6. Modelling of alloSCT** Within the Appraisal Consultation Document, the Committee noted that there may be some double-counting because OS extrapolation used in the base case included some patients who had alloSCT. However, alloSCT is associated with short-term mortality and morbidity, but improvements in long-term survival. Thus, patients receiving alloSCT within available data (pooled nivolumab population and Cheah 2016 population) will result in additional death events but have limited impact on long-term extrapolation due to lack of extended follow-up. This was noted within the factual accuracy check on the ERG report. For this reason, censoring patients in the nivolumab pooled population at time of alloSCT improves estimates of long-term OS, as described in Appendix A. Thus, the analysis described in the company submission can be considered conservative.	Comments noted. See FAD section 4.13.
Bristol-Myers Squibb	**4.7. Unmet need in patients with relapsed or refractory classical Hodgkin Lymphoma following ASCT and BTX** As noted within the company submission, outcomes are known to be extremely poor in relapsed or refractory patients who have received both ASCT and BTX. This is reflected in the available published evidence. However, there is a distinct paucity of published data describing the outcomes of patients with relapsed or refractory cHL following prior ASCT and BTX. This is partly due to the recent availability of BTX and its ongoing NICE appraisal, creating a new clinical pathway and, thus, a new patient population. Further, the low patient numbers and heterogeneous nature of presenting patients result in individualised treatment and variation between clinicians. Additionally, any published evidence is likely to reflect use of clinical trials in this patient population rather than established clinical practice. There are few available treatment options in this setting, and those that are available are associated with poor outcomes and tolerability. Based on data from the HMRN, described in Appendix A, [redacted]. Further, the clinician survey described in Appendix A estimated that median OS would be around [redacted]) in this patient population. Further, clinicians predicted that around [redacted] of patients would be alive at 12 months in this setting, and only [redacted] would be alive by 24 months. This is supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.[2] Further, clinicians anticipated that median PFS would also be very short ([redacted]). Thus, there is a high degree of unmet medical need in this patient population. The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after failure of ASCT. However, the Committee	Comments noted. See FAD sections 4.2, 4.25 and 4.26

Consultee	Comment [sic]	Response
	failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to further support this. Further, it should be noted that nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the cHL setting, where a large proportion of cases diagnosed are in elderly patients,who may not be eligible to receive chemotherapies because of their age or comorbidities. This was noted by clinical experts present at the Appraisal Committee meeting, who suggested that elderly patients are more difficult to treat and so may be more likely to receive nivolumab than chemotherapy. However, there may be fewer eligible patients in this population, as the expert also noted that the indication for nivolumab requires prior ASCT, and elderly patients may be less likely to undergo this procedure. The Appraisal Committee also heard from clinical experts that nivolumab had the potential to act as salvage therapy to enable allogeneic stem cell transplant after both ASCT and BTX. HL shows a sharp peak in incidence in people aged 20–24 years, and restricts their ability to study, work or participate in family life, which in turn impacts significantly on quality of life. According to a recent patient group submission to NICE,most people with blood cancer say that they suffer a loss of income and an increased expense as a result of their illness. Further, they may have problems continuing with work or require extended time off due to regular hospital visits and feeling unwell. These effects are not taken into account in the economic model, in line with the NICE reference case. However, the availability of a therapy that can provide a bridge to potentially curative alloSCT may allow patients in this age group to live long and active lives, with significant indirect economic benefits in terms of avoiding lost productivity. In summary, availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need.	Comments noted. Non-health 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 of NICE's 'Guide to the methods of technology appraisal Comment noted. The committee agreed that nivolumab was innovative and promising, but that it had not been presented with any evidence of additional benefits that were not captured in the QALY measure. See FAD section 4.22.
Bristol-Myers Squibb	**5. Are the recommendations sound and a suitable basis for guidance to the NHS?** BMS does not believe that the recommendations can be considered sound and a suitable basis for guidance to the NHS. A thorough discussion of the Appraisal Committee recommendations and Appraisal Consultation Document has been provided above, but in brief:	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD

Consultee	Comment [sic]	Response
	• **Additional evidence**: in line with the Appraisal Consultation Document, this response outlines additional clinical and economic evidence that can be used to support decision-making. Thus, the recommendations made within the Appraisal Consultation Document can no longer be considered valid and suitable, and it is anticipated that the Appraisal Committee will reconsider their recommendations at the next meeting. • **Unmet need**: The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after ASCT fails. However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to support this. • **End of life criteria**: as described in Section 4.1, in the absence of appropriate clinical data, the company submission has applied the best available evidence in the base case analysis, providing a median OS of 19 months. This can be considered an overestimation of survival in clinical practice, based on clinical expert opinion described in Appendix A. This is supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months. The Committee's conclusions on application of end of life criteria are based on one study where clinical outcomes are driven by use of investigational agents that are not available to all patients in the UK, rather than the sum of all available evidence. • **Use of investigational agents**: as detailed in Section 4.4, the Appraisal Consultation Document does not note clinician comments from the meeting that use of investigational agents would be minimal (around 5%) and would be limited to patients treated at large treatment centres, so that those treated in smaller centres would not be able to receive therapies. This is supported by clinical expert opinion elicited in the clinician survey described in Appendix A. Further, the Appraisal Committee concluded that the Cheah study population would better match the population in the nivolumab studies. However, there is no evidence to support this conclusion, and available evidence using baseline characteristics suggests that patients in the nivolumab study may be older and have more advanced disease than those in the Cheah study. Based on the final scope for this appraisal and the NICE guide to the methods of technology appraisal, appropriate comparators should represent established NHS practice in England.However, based on the evidence presented at the meeting and in this response, use of investigational agents cannot be considered established NHS practice.	sections 1.1 and 4.26. The committee considered all the information received from the company as per the process guide (see section 3.7.32 and 3.7.34 of the NICE guide to the process of technology appraisals). Comment noted. See FAD sections 4.2, 4.25 and 4.26. Comments noted. See FAD sections 4.23-4.25. Comment noted. See FAD sections 4.6-4.8 and 4.11.
Bristol-Myers Squibb	**6. 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,**	

Consultee	Comment [sic]	Response
	gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after failure of ASCT. However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to support this. Further, it should be noted that nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the cHL setting, where a large proportion of cases diagnosed are in elderly patients,[8] who may not be eligible to receive chemotherapies because of their age or comorbidities. This was noted by clinical experts present at the appraisal Committee meeting, who suggested that elderly patients are more difficult to treat and so may be more likely to receive nivolumab than chemotherapy. Therefore, it should be noted that elderly patients may be discriminated against by this recommendation due to the potential that there are no other available treatment options. It should also be noted that this recommendation may discriminate against patients treated at smaller centres, which would tend to be located in rural areas. The Appraisal Committee concluded that the overall population of the Cheah study, where efficacy is driven by use of investigational agents, was the most appropriate dataset for standard of care to use in the indirect comparison. This implies that enrolment into clinical trials and the use of investigational agents are considered established care within the NHS in England. However, clinical experts present at the Appraisal Committee meeting disagreed with the Committee's suggestion that investigational agent use is commonplace. Clinicians stated that investigational agent use is minimal in this setting (around 5%), and would broadly be confined to large treatment centres, so that patients receiving treatment in smaller, rural settings would not be able to receive these agents. It should be noted that this is supported by evidence from the clinician survey presented in Appendix A. This additionally raises an important equality issue, in that patients treated at smaller centres would not have access to investigational agents and clinical trials. [*References provided but not reproduced here*]	Comments noted. The recommendations in the FAD have changed. See FAD sections 1.1, 4.26 and the accompanying equality impact assessment. Comments noted. The recommendations in the FAD have changed. See FAD sections 1.1, 4.26 and the accompanying equality impact assessment.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Royal College of Radiologists	**Has all of the relevant evidence been taken into account?** Yes, it has .	Comment noted.
Royal College of Radiologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	Comments noted. The recommendations in the FAD have changed. Nivolumab is now

Nominating organisation	Comment [sic]	Response
	Yes – however there is a need for data which reflects UK practice given the higher rate of allogeneic stem cell transplantation in the UK. This might significantly impact on the cost effectiveness of Nivolumab treatment.	recommended as a treatment option. See FAD sections 1.1 and 4.13-4.15.
Royal College of Radiologists	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Perhaps – with the data presented. Given the higher rates of allogeneic stem cell transplantation in the UK, a better comparison with UK standard of care data would reassure patient and health care professionals alike that the recommendations were valid with respect to UK healthcare and NHS structures. It is likely with a more valid UK comparison, the clinical and cost effectiveness of Nivolumab therapy would be more favourable.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1, 4.7, 4.15 and 4.26.
Royal College of Radiologists	**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 and maternity?** No.	Comment noted.
Lymphoma Association	We are disappointed that NICE is proposing not to recommend nivolumab for routine use on the NHS in England for this group of patients. As we've noted in our submission to the appraisal committee, people with relapsed or refractory Hodgkin lymphoma often have many symptoms, which can be debilitating and distressing. They also know that, despite all the treatment they have been through, their life-expectancy is severely limited. They are faced with a choice between: • treatments that they know have little chance of success (particularly in the long term) but risk them developing significant side effects and/or spending large parts of their remaining life away from family and friends in hospital, or • purely palliative care, which is likely to give them a life-expectancy of a few months only and potentially with a number of symptoms. Nivolumab has the potential to act as salvage therapy to enable an allogeneic stem cell transplant after both autologous stem cell transplant and brentuximab vedotin, a fact that is acknowledged by the committee (ACD, para 4.2). As such a stem cell transplant offers the chance of a cure (estimated by expert clinicians to be of the order of 60% - see also ACD para 4.2), patients will find it hard to understand why they will be denied access to this live-saving treatment. Even those patients who are fit enough and have the possibility of a donor to enable them to undergo an allogeneic	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1 and 4.26. Comment noted.

Nominating organisation	Comment [sic]	Response
	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 or education and make an active contribution to society as well as having a profound positive impact on physical and psychological health. It's not clear that these sorts of issues are factored into NICE's cost-effectiveness and health economic assessments.	Comments noted. Non-health 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 of NICE's 'Guide to the methods of technology appraisal.'
	Many patients with relapsed or refractory Hodgkin lymphoma are young (and are often their prime child-bearing and family years) with potential for a long, healthy and active life if they can undergo transplant. Patients unsuitable for transplant can also benefit from palliative treatment giving significant and prolonged symptom reduction which cannot be achieved with standard chemotherapy options.	Comment noted.
	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. This discriminates against those groups of patients, in this case younger people under the age of 30, who represent one of the peaks of prevalence for Hodgkin lymphoma.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1, 4.22, 4.25 and 4.26.
	We note that the committee concluded that the trial evidence showed that nivolumab is "clinically effective based on the response rates" (ACD para 4.5), although there is a large degree of uncertainty. In our view, given the importance of nivolumab's position in the treatment pathway and the potential for it to meet unmet need (and in some cases save lives), we would urge NICE to be more flexible in its approach to the evidence on clinical effectiveness. Hodgkin lymphoma is a rarer cancer, with the numbers of people affected by relapsed/refractory disease being very low and it would be both difficult and unethical to carry out a randomised controlled trial in this patient population.	Comment noted.

Nominating organisation	Comment [sic]	Response
	We support the call for further evidence, but hope that NICE will treat this further evidence constructively with a view to supporting access to nivolumab on the NHS in England, so that clinicians can begin gathering real world experience and evidence of the treatment. This will be by far the most constructive approach with the most benefit to patients and their families in the immediate future as well as for those in the longer term.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1, 4.25 and 4.26.
Royal College of Physicians	The NCRI-ACP-RP-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 comment. Hodgkin lymphoma which has relapsed after an autograft and after brentuximab is a rare disease with a high area of unmet need. Nivolumab is clearly very effective in this setting. To deny its use to NHS patients in England would be to deprive young patients of an effective treatment which can bridge them to a potentially curative transplant. NHS England and NICE should do everything they can to make this drug available to patients who need it.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1 and 4.26.
Leukaemia CARE	We are writing on behalf of Hodgkin lymphoma patients in response to the recently published ACD for the appraisal of nivolumab – ID 972. We acknowledge that nivolumab has been licensed and is being assessed on limited single-arm data, so this creates uncertainty in the modelling. However, this is because nivolumab represents a step-change in treatment options for patients in this setting. It has received promising innovative medicine (PIM) designation and was made available through the Early Access to Medicines Scheme (EAMS). Now that it is licensed, EAMS has closed to new patients. It is imperative that NICE responds flexibly to data limitations for innovative medicines and reaches a positive decision quickly, to ensure that routine access is available again as soon as possible.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1 and 4.26.
Leukaemia CARE	There is currently no standard of care for patients with relapsed or refractory classical Hodgkin Lymphoma after autologous SCT and treatment with brentuximab vedotin. Patients in this setting currently have less than two years left to live and extremely limited treatment options, most likely chemotherapy, with significant side effects and little prospect of long-term success. As such, nivolumab could alleviate a significant unmet need, having shown high response rates, durable responses and improved quality of life. It could also act as a ‘bridge’ to enable responders to proceed to a potentially curative allogenic SCT.	Comment noted. See FAD sections 4.2, 4.3 and 4.5.

Nominating organisation	Comment [sic]	Response
	We urge you to reconsider this decision and recommend nivolumab for patients with relapsed or refractory classical Hodgkin Lymphoma after autologous SCT and treatment with brentuximab vedotin.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1 and 4.26

Comments received from commentators

Commentator	Comment [sic]	Response

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Healthcare industry (other)		There is a real unmet need in this patient population with few treatment options available to them and this treatment offers significant advancement in the management of the disease and quality of life benefits. We ask that NICE takes a flexible approach when addressing the uncertainty around data and to take into account that the limited data available is due to the innovative nature of the treatment.	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1 and 4.26.
Health professional (within NHS)		Classical Hodgkin lymphoma (cHL) relapsing after autologous stem cell transplant (ASCT) has a dismal prognosis with no standard of care. The current therapeutic goal is to halt disease progression in order to proceed to potentially curative reduced intensity allogeneic stem cell transplant (alloSCT) in the subset of patients who are fit enough to tolerate this procedure. This is on the basis that chemotherapy without consolidation alloSCT is very rarely curative. A recent EMBT study demonstrated the efficacy of alloSCT in 122 patients with post ASCT relapsed cHL. The reported two-year progression-free (PFS) and overall survival (OS) rates were 39.3% and 66% at a median follow-up of 48 months in patients undergoing successful alloSCT using a matched donor (Sarina et al, Blood 2010). Since most deaths following alloSCT occur within the first 2	Comments noted. The recommendations in the FAD have changed. Nivolumab is now recommended as a treatment option. See FAD sections 1.1 and 4.26.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		years of transplant, it is expected that the vast majority of progression-free patients will be cured. Brentuximab vedotin (BV) is licensed for the treatment of post ASCT relapsed cHL and has demonstrated high response rates and associated utility in successfully bridging up to a quarter of patients to alloSCT in the real world UK population (Gibb et al, Haematologica 2011). However, post ASCT patients who do not achieve complete response to BV (i.e. BV failures) have a very poor prognosis with a median PFS < 6 months (Younes et al, JCO 2012). This is not dissimilar to the poor PFS of around 3 months reported for transplant naïve patients who have failed at BV and at least 2 prior lines standard therapy (Eyre et al, personal communication on unpublished UK data, manuscript in progress). Results of the single arm phase II trial of nivolumab in relapsed or refractory HL are unprecedented, especially considering the majority (78% each) had failed prior ASCT and/or prior BV. Nivolumab was well tolerated with mostly low grade and manageable toxicity. An overall response rate of 87% was reported in the subset of patients who had failed both BV and ASCT. Among the 13 responding (complete plus partial response) patients in this subset, 3 patients underwent transplant. Crucially, 6 patients did not undergo consolidation transplant and were in ongoing response with continuing treatment at a median follow-up of 40 weeks. The median survival for all responding patients was not reached (Ansell et al, NEJM, 2015). Results of this landmark study showed for the first time that heavily pre-treated HL patients who have failed best therapy including BV and ASCT, can achieve durable responses without the need for alloSCT. This compares very favourably with a PFS < 6 months reported previously in patient who fail ASCT and BV therapy. This observation of long remissions is supported by our own anecdotal clinical experience of treating patients successfully with nivolumab and other checkpoint inhibitors. Interestingly, this includes some patients achieving durable remissions after 1 or few cycles, which may suggest that this class of agents can 'reset' the immune response such that ongoing treatment after achievement of CR may not be necessary. If durable remissions continue with longer follow-up, nivolumab treatment may be regarded as a transplant sparing agent, substantially reducing the cost and treatment-related morbidity/mortality of treating young patients with relapsed/refractory cHL. There are also emerging data confirming the safety of alloSCT after nivolumab, including our own	Comments noted. Comments noted.

Role*	Section	Comment [sic]	Response
		experience, thus keeping open the option of alloSCT consolidation for the subset of patients who want it and are fit for this conventional approach. There are no randomised studies comparing nivolumab or BV with standard single agent chemotherapy. Anecdotally, few patients who relapse after ASCT are successfully bridged to alloSCT using single agent 'standard' chemotherapy with drugs such as bendamustine, gemcitabine, vinorelbine. Limited published data exist regarding the efficacy of these agents. Little et al reported an ORR of 59% and a median EFS of 8.3 months for single agent vinblastine in a phase 2 trial of 17 post ASCT cHL patients (Little et al, JCO 1998). In a phase 2 trial of 23 patients with relapsed or refractory cHL, of which none had a previous transplant, Santoro et al reported an ORR of 39% and median DOR of 6.7 months for single agent gemcitabine. Moskowitz et al reported an ORR of 53% and median DOR of 5 months for single agent bendamustine in a phase 2 trial of 36 patients with relapsed or refractory cHL of which 75% had relapsed post ASCT (Moskowitz et al, JCO 2013). None of these studies included post BV failure patients, who would be expected to have an inferior response to single agent chemotherapy compared to the patients included in these trials. In summary, results of single agent chemotherapy in BV-naïve mostly ASCT failed cHL patients yields response rates of 39-59% but response duration is short and in the order of 5-8 months. NICE TA 972: nivolumab for treating relapsed or refractory cHL is limited by several evidence gaps, including lack of a randomised comparator, limited comparator single agent chemotherapy data, immature survival data and relatively short follow-up. The available non-randomised comparative evidence for the post ASCT post BV cHL patient population is nevertheless compelling and argues that nivolumab should be made available to patients in England because: • There is no standard of care for patients who relapse post BV and ASCT, and there are no other agents outside of checkpoint inhibitors under investigation in this poor prognostic subset of patients, i.e. no options on the horizon if nivolumab and this class of agents is not available. • The benefits of nivolumab exceed those of comparators: nivolumab produces higher response rates than standard chemotherapy and the difference is expected to be even greater	Comments noted. Comments noted. See FAD section 4.1. Comment noted. See FAD sections 4.9 and 4.10.

Role*	Section	Comment [sic]	Response
		(in favour of nivolumab) when considering that chemotherapy trials were all done in BV naïve patients. • The stopping rule in the pivotal phase 2 trial was to continue until disease progression or complete response or for a maximum of 2 years, which seems reasonable to NHS practice in England. • Relapsed/refractory HL is a rare disease, thus the number of patients in question is small. However, a significant proportion of young patients responding to nivolumab may be cured with subsequent alloSCT enabling them to return to work and contribute to society as a whole. • Nivolumab has the potential to be a transplant sparing therapy with significant cost savings to the NHS and a major safety advantage to patients: nivolumab is the only agent demonstrating durable remissions in the majority of patients with relapsed/refractory cHL without the addition of consolidation alloSCT. Longer follow-up may indicate a transplant-sparing role for nivolumab. • Nivolumab is well tolerated with a manageable toxicity profile	Comment noted. Comment noted. See FAD section 4.2. Comment noted. Comment noted. See FAD section 4.3.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Response to the Appraisal consultation document

Nivolumab (Opdivo®) as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin

Bristol-Myers Squibb Pharmaceuticals Ltd

April 2017

Contents

Abbreviations

AE	Adverse Event
AIC	Akaike Information Criteria
AlloSCT	Allogeneic Stem Cell Transplant
ASCT	Autologous Stem Cell Transplant
BIC	Bayesian Information Criteria
BTX	Brentuximab
cHL	Classical Hodgkin Lymphoma
CR	Complete Response
ERG	External Review Group
HL	Hodgkin Lymphoma
MAIC	Matching-Adjusted Indirect Comparison
OS	Overall Survival
PFS	Progression-free Survival
PR	Partial Response
SD	Stable Disease
SLR	Systematic Literature Review
SoC	Standard of Care

1. Executive summary

This document provides a response to the Appraisal Consultation Document describing the use of nivolumab for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and brentuximab vedotin (BTX).[1] In line with the Appraisal Consultation Document, this response outlines the additional clinical and economic evidence requested by the Appraisal Committee, which can be used to support decision-making. Thus, Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd believes that the recommendations made within the Appraisal Consultation Document are no longer considered valid and suitable; and anticipates that the Appraisal Committee will reconsider their recommendations at the next meeting.

Further, BMS would like to highlight that in the absence of appropriate clinical data for the comparator arm, the company submission has applied the best available evidence in the base case analysis, providing a median overall survival (OS) of 19 months. This can be considered an overestimate of survival in clinical practice, as clinician opinion consistently reflects short survival in patients with relapsed or refractory cHL following prior ASCT and BTX. UK-specific data provided in response to the Committee's recommendations support very short survival in this patient population, with few patients expected to survive 24 months. This opinion was supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.[2] By contrast, the Committee's conclusions on the application of end of life criteria for nivolumab are based on one study where clinical outcomes are driven by use of investigational agents not available to all patients in the UK, rather than the sum of all available evidence.

Additionally, BMS considers the Committee's recommendation of including investigational agents as standard of care (SoC) to be inappropriate. The Appraisal Consultation Document does not include clinician comments from the meeting confirming that the use of investigational agents would be minimal (around 5%) and would be limited to patients treated at large treatment centres, implying that those treated in smaller centres would not be able to receive these investigational therapies. This is supported by UK-specific clinical expert opinion, where investigational agent use was estimated to be [redacted]. Further, the Appraisal Committee concluded that the Cheah et al. study overall population would better match the population in the nivolumab studies, as patients in clinical trials tend to be fitter. However, there is no evidence to support this conclusion, and available evidence using baseline characteristics suggests that patients in the nivolumab study may be older and have more advanced disease than those in the Cheah et al. study. Based on the final scope for this appraisal and the NICE guide to the methods of technology appraisal, appropriate comparators should represent established NHS practice in England.[3,4] However, based on the evidence presented at the Appraisal Committee meeting and in this response, the use of investigational agents cannot be considered established NHS practice. Therefore, this recommendation by the Appraisal Committee can be considered inappropriate, particularly when inclusion of these agents results in the conclusion that nivolumab, for the treatment of relapsed or refractory cHL, does not meet end of life criteria.

The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after failure of ASCT.

However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to support this conclusion.

In summary, the availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need. BMS believes that the Committee recommendations do not take into account all relevant evidence, do not accurately reflect clinical and cost-effectiveness conclusions, and do not provide a sound and suitable basis for guidance to the NHS. It is anticipated that further evidence presented in response to the Appraisal Consultation Document will be considered by the Appraisal Committee, and will further demonstrate that nivolumab is cost-effective and is associated with substantial clinical benefit in a population with very short survival and limited treatment options.

2. Evidence requested by the Committee

The Appraisal Committee has recommended that NICE requests from the company for the second appraisal committee meeting revised probabilistic cost-effectiveness analyses comparing nivolumab with standard of care, which incorporate the committee's preferred assumptions regarding method of indirect comparison, costs and utilities. In line with this, a revised base case analysis has been provided in Appendix A, outlining the approach taken with reference to recommendations from the Committee.

Further, the Appraisal Committee has recommended that the analyses should also explore the use of UK data for standard of care (for example, from the Haematological Malignancy Research Network) and a range of subsequent allogeneic stem cell transplant (alloSCT) rates for both nivolumab and standard of care that are higher than those used in the Cheah and Perrot studies and are from UK data. In line with this recommendation, BMS has contacted the HMRN to obtain data describing UK clinical practice. Further, BMS has conducted a survey of UK clinicians to elicit opinion on the composition and efficacy of SoC, as well as proportions of patients who would receive alloSCT in clinical practice. This evidence is outlined in Appendix A, along with economic evaluations applying UK-specific data.

3. Has all relevant evidence been taken into account?

BMS does not believe that the Committee has taken into account all of the relevant evidence, resulting in non-evidence-based recommendations that are not in the patient's interest. Not all clinical and economic evidence was presented in the ERG report and Committee slides, and so was not taken into account when deriving this recommendation. Sources of clinical evidence applied within the economic evaluation and provided within the original submission included:

- **Cheah et al., 2016**: data from the overall population and data excluding the efficacy of investigational agents. The naïve comparison was presented to the Committee in the ERG report and Committee slides. Additionally, a matching-adjusted indirect comparison (MAIC) analysis was presented in the submission, and applied in the economic analysis, improving the ICER versus use of the naïve comparison.

- **Data from the post-ASCT, post-BTX systematic literature review (SLR)**: the majority of evidence from this SLR described clinical trials of investigational agents, rather than clinical practice. However, data from this SLR was used to inform a naïve indirect comparison and a MAIC, with outputs applied in the economic evaluation as scenario analyses.

- **Data from the post-ASCT cohort**: due to the relative lack of data identified within the post-ASCT, post-BTX SLR, the eligibility criteria for the studies was expanded to treatments for relapsed or refractory HL in patients who have previously received prior ASCT (i.e. prior BTX treatment was not a requirement) in an attempt to provide additional supportive data in a patient population whose treatment options and outcomes are subject to considerable uncertainty. Data from this SLR was used to inform a naïve indirect comparison and a MAIC, and outcomes for nivolumab

remained superior over published efficacy evidence, despite use in a more treatment-experienced population. This evidence was applied in the economic evaluation as scenario analyses supporting the beneficial impact of nivolumab in the wider relapsed or refractory cHL setting. This evidence was not presented to the Committee as the ERG did not consider it to be relevant to the population of interest (post-ASCT, post-BTX HL). This can be considered highly inappropriate in the context of the Committee's conclusions that the published evidence for comparator treatments was limited, and evidence presented did not represent UK practice. It should be noted that additional supportive evidence was provided in the submission but not assessed by the ERG.

Since publication of the Appraisal Consultation Document, additional evidence has been sought and further economic evaluations have been undertaken in order to address the Committee's requests. This includes:

- Additional evidence from the HMRN describing the treatment pathway and survival for patients with relapsed or refractory cHL following prior ASCT and BTX.
- Evidence from a clinician survey describing SoC and outcomes in UK clinical practice for patients with relapsed or refractory cHL following prior ASCT and BTX.
- Evidence from UK clinical practice describing survival following alloSCT in UK patients with relapsed or refractory cHL following at least three prior therapies, including ASCT in the majority of cases (62%).
- Economic evaluations applying the Committee's preferred assumptions and modelling methods.
- Economic evaluations applying efficacy inputs describing UK patients from the UK clinician survey.
- Economic evaluations applying a range of alloSCT rates and UK-specific alloSCT survival, in order to describe the impact of increasing alloSCT rates from those applied in the company submission.

In summary, the Committee has not reviewed all relevant evidence. In light of the high unmet need in this setting (described in Section 4.7), it is in the patient's best interests for the Committee to review this evidence and reconsider its guidance on the use of nivolumab for the treatment of relapsed or refractory cHL following prior ASCT and BTX.

4. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence

BMS does not believe that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence, as detailed below.

4.1 End of life criteria

There is a distinct paucity of data describing patients with relapsed or refractory cHL following prior ASCT and BTX. This is partly due to the recent availability of BTX and its ongoing NICE appraisal, creating a new clinical pathway and, thus, a new patient population. Further, the low patient numbers and heterogeneous nature of presenting patients result in individualised treatment and variation between clinicians. Additionally, any published evidence is likely to reflect use of clinical trials in this patient population rather than established clinical practice.

In the absence of definitive data describing the clinical reality of patients, it is essential to consider the views of clinical experts. Clinician opinion consistently reflects short survival in patients with relapsed or refractory cHL following prior ASCT and BTX. The UK-specific data from the HMRN and the clinician survey (both provided in Appendix A) support short survival in this patient population, with few patients estimated to survive 24 months. Further, this is supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.[2] Outcomes are known to be even poorer in relapsed or refractory patients who have received both ASCT and BTX. Based on this evidence, it is highly unlikely that life expectancy would exceed 24 months in cHL patients who are more treatment-experienced and eligible for nivolumab therapy (i.e. having previously received both ASCT and BTX therapy).

Similarly, despite the Committee's reservation about the relevance of the Cheah et al. 2016 population with investigational agents removed, this can also be considered supportive of the views of clinicians, with median survival estimated at 19 months. Further, median OS reduces to 17.9 months following the matching-adjusted indirect comparison process, as detailed in Appendix 3 of the company submission.

By contrast, the ERG report life expectancy of 2.9 years in their revised base case. This cannot be considered to reflect current clinical practice, as it is longer than that described by clinical experts and in published literature for a less treatment-experienced, post-ASCT population. Similarly, even the modelled results of the base case analysis in the company submission can be considered to overestimate the life expectancy of patients receiving current clinical practice.

Thus, it is anticipated that the Appraisal Committee will reconsider the application of end-of-life criteria to nivolumab use for the treatment of relapsed or refractory cHL following prior ASCT and BTX.

4.2 Clinical effectiveness of nivolumab in this setting

The Committee considered that the evidence for the clinical effectiveness of nivolumab was highly uncertain because the data were immature and from single-arm studies. In addition, the published evidence for comparator treatments was limited, and the evidence presented did not represent UK practice.

However, it should be noted that the submission detailed substantial follow-up from relevant studies (CheckMate 205 cohort B: 15.7 months; CheckMate 205 cohort C: 8.9 months;

CA209-039: 23.3 months). The data can only be considered immature because of the improvements to survival, since there are fewer events to inform PFS (one-year PFS: [redacted]) and OS (one-year OS: [redacted]) within the available follow-up period. This is of particular relevance in the context of relapsed or refractory cHL following ASCT and BTX, where outcomes are very short. As detailed above, PFS and OS are extremely short in clinical practice for this patient population; therefore, the relatively few survival events observed following treatment with nivolumab should be considered an indication of the efficacy of nivolumab.

Further, it should be noted that several sources of evidence have been identified and presented to the Committee. In addition to the evidence versus the Cheah et al. 2016 publication, a full SLR was undertaken to identify evidence in relapsed or refractory cHL patients following ASCT and BTX, with naive and adjusted indirect treatment comparisons provided in Appendix 3 of the company submission. As evidence from this SLR was primarily derived from clinical trials, the SLR was expanded to include cHL patients following prior ASCT in order to provide supportive evidence in a population where more data exists. Although patients eligible for enrolment into the nivolumab studies would have been more treatment-experienced than those included in the post-ASCT population, both SLRs and ITCs can be considered supportive of a substantial survival advantage for nivolumab.

Within the ACD response, two additional sources are detailed describing clinical effectiveness of SoC: the HMRN data and the clinician survey (as detailed in Appendix A). Both outline the poor outcomes in relapsed or refractory cHL following ASCT and BTX.

A comparison of survival outcomes for nivolumab versus SOC is provided in Table 1. As can be seen, PFS outcomes are broadly comparable between sources of evidence, with the exception of the post-ASCT population, which had improved outcomes versus the post-ASCT, post-BTX population. By contrast, nivolumab is associated with substantial PFS benefit, far exceeding all estimates of PFS from clinical experts and the literature.

Estimates of OS from the published literature exceed clinical expert expectations, with evidence based on clinical trial data and investigational agent use providing greater estimates of survival. Of interest, estimates of OS from the literature for the post-ASCT, post-BTX population exceed those for the post-ASCT population, which included more studies that could be considered representative of real-world outcomes, and this is likely due to the preponderance of clinical trial data and investigational agent data available in the post-ASCT, post-BTX population. All estimates of OS far exceed those provided by clinicians. However, nivolumab provides substantial OS benefit over all available sources of evidence, as summarised in Table 1.

Further, of the provided sources of evidence, several are directly relevant to current clinical practice in the UK. As can be seen, regardless of data source, there is a substantial benefit in terms of PFS and OS for nivolumab versus standard of care, so that evidence for comparator treatments can be considered exhaustive and representative of UK practice.

Table 1. Comparison of outcomes for nivolumab studies and additional evidence sources

		PFS		OS	
		Median (months)	One-year survival (%)	Median (months)	One-year survival (%)
Nivolumab overall population		[redacted]	[redacted]	[redacted]	[redacted]
Clinician survey SoC		[redacted]	[redacted]	[redacted]	[redacted]
HMRN SoC		[redacted]	[redacted]	[redacted]	[redacted]
Cheah overall population	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]	[redacted]	[redacted]
Cheah excluding investigational agents	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]	[redacted]	[redacted]
Post-ASCT, post-BTX cHL SLR*	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]	[redacted]	[redacted]
Post-ASCT cHL SLR**	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]	[redacted]	[redacted]

ASCT: autologous stem cell transplant; BTX: brentuximab; cHL: classical Hodgkin lymphoma; HMRN: Haematological Malignancy Research Network; MAIC: matching-adjusted indirect comparison; NA: not available; OS: overall survival; PFS: progression-free survival; SLR: systematic literature review.

[redacted]

4.3 Relevance to the UK setting

As noted previously in the company submission and this response, there is a distinct paucity of data describing patients with relapsed or refractory cHL following prior ASCT and BTX. This is partly due to the recent availability of BTX, creating a new clinical pathway and thus patient population. Further, the low patient numbers and heterogeneous nature of presenting patients result in individualised treatment and variation between clinicians. Although data from the Cheah et al. 2016 study was based on a US cohort, it can also be considered to adequately represent UK clinical practice based on evidence from the HMRN and two physician surveys conducted by BMS (described in Appendix A).

Despite the limitations of available evidence, it can be considered that evidence presented within the submission and this response document is broadly representative of UK clinical practice and outcomes for cHL patients who have relapsed or are refractory following prior ASCT and BTX.

4.4 Use of investigational agents in UK clinical practice

During the Appraisal Committee meeting, the Appraisal Committee discussed the inclusion of investigational agents as part of SoC, based on the Cheah et al. 2016 population. The Committee considered that the patients in the Cheah et al. study having investigational agents may have differed from people seen in clinical practice more in terms of their fitness to have such treatments rather than the treatments themselves. However, clinical experts present at the Appraisal Committee meeting disagreed with the Committee's suggestion that investigational agent use is commonplace. Clinicians stated that investigational agent use is minimal in this setting (around 5%), and would broadly be confined to large treatment centres, so that patients receiving treatment in smaller centres would not be able to receive

these agents. It should be noted that this is supported by evidence from the clinician survey presented in Appendix A.

Additionally, the Appraisal Committee suggested that the overall population in the Cheah et al. study, including those having investigational agents, would better match the population in the nivolumab trials because patients in trials tend to be fitter. However, there is no evidence to support this suggestion in the case of the nivolumab studies. On the contrary, patients in the Cheah et al. study tended to be younger, with fewer older patients enrolled, in comparison with the nivolumab studies, and disease stage at study enrolment tended to be better than in the nivolumab studies.[12]

Further, the Committee heard that the ERG had contacted the authors of the study, and that only 'a couple' of patients in the study had a PD-1 inhibitor, and therefore the ERG considered that the overall population should be used for comparator data. However, clinicians at the meeting advised that other unlicensed checkpoint inhibitors would be included within investigational agents, including agents targeting CTLA-4 and PD-L1. These agents have similar mechanisms of action to nivolumab, as all utilise pre-existing anti-cancer immune responses to improve patient outcomes; thus, the ERG's argument that the majority of patients did not receive PD-1 inhibitors may be irrelevant.

The scope for this appraisal details the following comparators as appropriate: established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine; and best supportive care.[3] Further, the NICE guide to the methods of technology appraisal states several criteria applied when determining appropriate comparators for Technology Appraisal, including consideration of **established** NHS practice in England.[4] However, based on evidence from the clinical experts present at the Appraisal Committee meeting and the clinician survey presented in Appendix A, the investigational agents described by Cheah and colleagues,[12] by definition, do not reflect established practice within the NHS in England. Data pertaining to relevant and established comparator therapies are outlined within other cohorts in this study. It is likely that investigational agents will comprise unlicensed products and those not recommended by NICE, thus limiting the relevance of this category to simulation of clinical practice in the UK.

It should also be noted that inclusion of investigational agents into SoC extends the OS beyond which clinical experts consider plausible. Based on data from the HMRN, described in Appendix A, [redacted]. Further, the clinician survey presented in Appendix A details estimated OS of [redacted]. This estimate was supported by clinical experts attending the first Appraisal Committee meeting for the ongoing BTX appraisal [ID722], who suggested that life expectancy without BTX is likely to be less than 24 months.[14] Further, it is supported by the results of the post-ASCT ITC detailed in Table 1, where median OS was estimated as [redacted]. It is extremely implausible that life expectancy would exceed 24 months in cHL patients who are eligible for nivolumab therapy and are more treatment-experienced (i.e. having previously received both ASCT and BTX therapy).

The Appraisal Committee has concluded that the overall population of the Cheah et al. study was the most appropriate dataset for standard of care to use in the indirect comparison. However, this is inappropriate when all available evidence is considered, including the view

of clinical experts at the Appraisal Committee meeting and the additional evidence presented within this response.

4.5 Alternative OS extrapolation

It was not possible for BMS to check the factual accuracy of all presented data prior to the Appraisal Committee meeting, as an addendum was not made available until immediately prior to the Appraisal Committee meeting. The addendum described economic evaluation where nivolumab OS extrapolation applied the Gompertz parametric fit, resulting in an ICER of £122,825.

4.5.1 Accuracy of analysis

The ERG provided a version of the model to enable verification and it can be confirmed that the correct Gompertz parameters were applied in the model. However, this analysis is misrepresented within the slides presented to the Committee. The ERG addendum clearly states that the ICER produced applies ERG base case assumptions.[15] However, the slides presented to the Committee (and subsequently to the public) provide this analysis amongst scenarios assessed using the base case analysis detailed in the company submission of evidence, which implies that the application of these curves increases the ICER from £19,882 to £122,825, which is not the case, as is described in Section 4.5.2.

Figure 1. Excerpt from Committee slides[16]

ERG's base case (with PAS)
Disaggregated

Assumption	ICER/QALY
Company's base case	£19,882
AlloSCT rates derived from trials	£20,616
SOC survival data; using overall population from Cheah	£22,348
Nivolumab overall survival data; using Gompertz*	£122,825
Pre-progression utilities (nivolumab) CheckMate 205 response-specific	£20,476
Pre-progression utilities (SOC) CheckMate 205 utilities weighted by response	£20,603
Post-progression utilities the same across all interventions	£25,209
alloSCT survival modelling; using original OS treatment curves	£21,517
Post-progression utility for alloSCT; the same across all interventions	£18,174
SOC costs – miniBEAM, dexaBEAM excluded	£20,950
*not in ERG's base case	

4.5.2 Application of Gompertz OS extrapolation in company base case

A sensitivity analysis applying the Gompertz curve for nivolumab OS to the base case described in the company submission is provided in Table 2. As can be seen, applying this survival curve for nivolumab has a large reduction on accrual of LYs (from 5.0 to 3.2),

QALYs [redacted] and costs ([redacted]). This impact causes the ICER to increase from £19,882 in the base case analysis to £31,631.

The main differences between this analysis and the ERG analysis are derived from application of the Cheah et al. 2016 overall population, and the inappropriate inclusion of alloSCT costs without its associated clinical benefits. When applying base case assumptions as per the ERG, the nivolumab treatment arm accrues total costs of [redacted], which is associated with cost of alloSCT. By comparison, accrual of QALYs [redacted] and LYs (3.3 versus 3.2) in the nivolumab arm is comparable to that in Table 2.

Table 2. Impact of applying Gompertz OS extrapolation for nivolumab

	Comparator	Nivolumab	Incremental
Patient-level progression			
Time in pre-progression (years)	**0.405**	[redacted]	[redacted]
- Time in 4th line (years)	0.369	[redacted]	[redacted]
- Time in post 4th line (years)	0.036	[redacted]	[redacted]
Time in post-progression (years)	**1.704**	[redacted]	[redacted]
Patient-level utility breakdown			
Health state utility	**0.956**	[redacted]	[redacted]
- CR	0.048	[redacted]	[redacted]
- PR	0.073	[redacted]	[redacted]
- SD	0.187	[redacted]	[redacted]
- Progressed disease	0.648	[redacted]	[redacted]
AE disutility	**0.020**	**0.003**	**-0.017**
Age based disutility	**0.005**	**0.000**	**-0.005**
Total utilities	**0.932**	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)			
Health state costs	**4,813**	**7,356**	**2,543**
- CR	145	968	823
- PR	218	1,506	1,289
- SD	562	986	424
- Progressed disease	3,888	3,896	8
Treatment costs	**14,420**	[redacted]	[redacted]
- 4th line	10,477	[redacted]	[redacted]
- 5th line	3,943	[redacted]	[redacted]
AE costs	**1,857**	**248**	**-1,609**
Total costs	**21,090**	[redacted]	[redacted]
Patient-level CE results			
Total QALYs	**0.932**	[redacted]	[redacted]
Total LYs	**2.110**	**3.225**	**1.115**
- Median ToT (years)	0.263	0.802	0.539
- Mean ToT (years)	0.369	1.096	0.727
- Median PFS (years)	0.282	1.132	0.851
- Mean PFS (years)	0.405	[redacted]	[redacted]
- Median OS (years)	1.461	3.267	1.806
- Mean OS (years)	2.110	3.225	1.115
Total Costs (£)	**21,090**	[redacted]	[redacted]
ICER (Cost/QALY)			**31,631**

4.5.3 Appropriateness of use of Gompertz extrapolations

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed within the company submission. Parametric extrapolation of survival data from relevant studies was undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[17] and Bagust and Beale (2014).[18]

Parametric survival functions were fitted to the extracted pooled data, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions. These are provided in Figure 2. Goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively). Minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit. On the basis of the AIC and BIC goodness-of-fit statistics, exponential can be selected as the most appropriate parametric fit, followed by lognormal, Weibull and log-logistic. By contrast, using these statistics, Gompertz can be considered one of the least appropriate parametric fits.

Figure 2. Parameterisation of overall survival: nivolumab (years 0-5)

Figure 3 presents the evolution of the hazard profile over time for each parametric extrapolation. As can be seen, the majority of the hazards associated with each extrapolation predict an initial rise in hazard, followed by a gradual decline. This reflects available Kaplan-Meier data, where the majority of events occur in the initial period, and then the risk of death decreases over time. By contrast, the Gompertz predicts a rapidly accelerating hazard that cannot be supported by available data or clinical rationale.

Figure 3. Overall survival: evolutions of hazards - nivolumab combined cohort (n = 193)

Finally, the parametric functions and profiles depicted in Figure 3 were assessed by clinical experts during an advisory board meeting. Clinicians noted the paucity of data to inform OS, but considered that PFS and OS hazards would have similar long-term extrapolation (i.e. there would be an initial increase in hazard, followed by a gradual decline in hazard over time). This criteria would exclude the Gompertz and exponential functions.

Based on a median follow-up of 11.7 months, three of the models (generalised gamma, generalised F and lognormal) predicted median OS exceeding 100 months (8.3 years), with a fourth (exponential) predicting median OS of 94 months (7.8 years). Additionally, these four parametric functions predict that a proportion of patients remain alive when the parametric functions are extended beyond 60 years. Although this can be considered optimistic, this would provide a level of clinical benefit supported by data from other nivolumab indications. As such, it cannot be considered implausible; however, it was acknowledged that a more conservative approach may be appropriate for the purposes of health technology assessment.

As stated in Appendix 6 of the company submission, the Weibull function was determined to be most appropriate based on these criteria. Further, the ERG stated that communication with clinical experts confirmed their agreement to the approach chosen by the company and the ERG considered that the choices made by the company in the base case were the most appropriate extrapolation choices.[15]

By contrast, the Gompertz function could be excluded based on all criteria. Further, it should be noted that the predicted survival is implausibly short. As demonstrated in Figure 4, use of the Gompertz function results in OS that falls below that of the OS for SoC based on Cheah et al. 2016 after removal of the impact of investigational agents. Following discussion with clinical experts, this was determined to be implausible, based on clinical experience and the available data for nivolumab. This was confirmed by clinical experts attending the Appraisal

Committee meeting. It should be noted that the ERG have not applied the Gompertz function in their base case analysis.

Figure 4. Comparison of parametric extrapolation of nivolumab OS versus Cheah 2016 (without investigational agents) OS extrapolation

It should be noted that the lognormal extrapolation can be considered the most appropriate fit, based on goodness-of-fit statistics, visual inspection of the functions and clinical plausibility of the hazard profiles. However, this function was excluded as the predicted OS can be considered optimistic, and a conservative estimate of OS would be more appropriate in the context of health technology assessment. If the lognormal OS function was applied, estimated median OS would increase from 58.2 months (Weibull) to 108.7 months (lognormal). When applied in the economic model, accrual of LYs (5.0 to 9.5 years), QALYs [redacted] and costs ([redacted]) increase in the nivolumab arm, resulting in an improved ICER (£11,926).

Thus, the presented base case analysis can be considered highly conservative. However, it should be noted that despite use of an implausibly short OS extrapolation, the predicted ICER remained below a £50,000/QALY willingness-to-pay threshold.

4.6 Modelling of alloSCT

Within the Appraisal Consultation Document, the Committee noted that there may be some double-counting because OS extrapolation used in the base case included some patients who had alloSCT. However, alloSCT is associated with short-term mortality and morbidity, but improvements in long-term survival. Thus, patients receiving alloSCT within available data (pooled nivolumab population and Cheah 2016 population) will result in additional death events but have limited impact on long-term extrapolation due to lack of extended follow-up. This was noted within the factual accuracy check on the ERG report. For this reason, censoring patients in the nivolumab pooled population at time of alloSCT improves estimates

of long-term OS, as described in Appendix A. Thus, the analysis described in the company submission can be considered conservative.

4.7 Unmet need in patients with relapsed or refractory classical Hodgkin Lymphoma following ASCT and BTX

As noted within the company submission, outcomes are known to be extremely poor in relapsed or refractory patients who have received both ASCT and BTX. This is reflected in the available published evidence. However, there is a distinct paucity of published data describing the outcomes of patients with relapsed or refractory cHL following prior ASCT and BTX. This is partly due to the recent availability of BTX and its ongoing NICE appraisal, creating a new clinical pathway and, thus, a new patient population. Further, the low patient numbers and heterogeneous nature of presenting patients result in individualised treatment and variation between clinicians. Additionally, any published evidence is likely to reflect use of clinical trials in this patient population rather than established clinical practice.

There are few available treatment options in this setting, and those that are available are associated with poor outcomes and tolerability. Based on data from the HMRN, described in Appendix A, [redacted]. Further, the clinician survey described in Appendix A estimated that median OS would be around [redacted] in this patient population. Further, clinicians predicted that around [redacted] of patients would be alive at 12 months in this setting, and only [redacted] would be alive by 24 months. This is supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.[2] Further, clinicians anticipated that median PFS would also be very short ([redacted]). Thus, there is a high degree of unmet medical need in this patient population.

The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after failure of ASCT. However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to further support this.

Further, it should be noted that nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the cHL setting, where a large proportion of cases diagnosed are in elderly patients,[8] who may not be eligible to receive chemotherapies because of their age or comorbidities. This was noted by clinical experts present at the Appraisal Committee meeting, who suggested that elderly patients are more difficult to treat and so may be more likely to receive nivolumab than chemotherapy. However, there may be fewer eligible patients in this population, as the expert also noted that the indication for nivolumab requires prior ASCT, and elderly patients may be less likely to undergo this procedure.

The Appraisal Committee also heard from clinical experts that nivolumab had the potential to act as salvage therapy to enable allogeneic stem cell transplant after both ASCT and BTX.

HL shows a sharp peak in incidence in people aged 20–24 years[8], and restricts their ability to study, work or participate in family life, which in turn impacts significantly on quality of life. According to a recent patient group submission to NICE,[9] most people with blood cancer say that they suffer a loss of income and an increased expense as a result of their illness. Further, they may have problems continuing with work or require extended time off due to regular hospital visits and feeling unwell. These effects are not taken into account in the economic model, in line with the NICE reference case.[10] However, the availability of a therapy that can provide a bridge to potentially curative alloSCT may allow patients in this age group to live long and active lives, with significant indirect economic benefits in terms of avoiding lost productivity.[11]

In summary, availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need.

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

BMS does not believe that the recommendations can be considered sound and a suitable basis for guidance to the NHS. A thorough discussion of the Appraisal Committee recommendations and Appraisal Consultation Document has been provided above, but in brief:

- **Additional evidence**: in line with the Appraisal Consultation Document, this response outlines additional clinical and economic evidence that can be used to support decision-making. Thus, the recommendations made within the Appraisal Consultation Document can no longer be considered valid and suitable, and it is anticipated that the Appraisal Committee will reconsider their recommendations at the next meeting.

- **Unmet need**: The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after ASCT fails. However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to support this.

- **End of life criteria**: as described in Section 4.1, in the absence of appropriate clinical data, the company submission has applied the best available evidence in the base case analysis, providing a median OS of 19 months. This can be considered an overestimation of survival in clinical practice, based on clinical expert opinion described in Appendix A. This is supported by clinical experts present at the first Appraisal Committee meeting for BTX, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.[2] The Committee's conclusions on application of end of life criteria are based on one study where clinical outcomes are driven by use of investigational agents that are not available to all patients in the UK, rather than the sum of all available evidence.

- **Use of investigational agents**: as detailed in Section 4.4, the Appraisal Consultation Document does not note clinician comments from the meeting that use of investigational agents would be minimal (around 5%) and would be limited to patients treated at large treatment centres, so that those treated in smaller centres would not be able to receive therapies. This is supported by clinical expert opinion elicited in the clinician survey described in Appendix A. Further, the Appraisal Committee concluded that the Cheah study population would better match the population in the nivolumab studies. However, there is no evidence to support this conclusion, and available evidence using baseline characteristics suggests that patients in the nivolumab study may be older and have more advanced disease than those in the Cheah study. Based on the final scope for this appraisal and the NICE guide to the methods of technology appraisal, appropriate comparators should represent established NHS practice in England.[3,4] However, based on the evidence presented at the meeting and in this response, use of investigational agents cannot be considered established NHS practice.

6. 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 and maternity?

The Committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after failure of ASCT. However, the Committee failed to acknowledge that patients who cannot receive nivolumab will have very poor treatment outcomes in clinical practice. Data from the HMRN and the clinician survey provide evidence to support this.

Further, it should be noted that nivolumab provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to limited alternative options, which would manage the patient's illness, but with limited impact on survival. This is of particular importance in the cHL setting, where a large proportion of cases diagnosed are in elderly patients,[8] who may not be eligible to receive chemotherapies because of their age or comorbidities. This was noted by clinical experts present at the appraisal Committee meeting, who suggested that elderly patients are more difficult to treat and so may be more likely to receive nivolumab than chemotherapy. Therefore, it should be noted that elderly patients may be discriminated against by this recommendation due to the potential that there are no other available treatment options.

It should also be noted that this recommendation may discriminate against patients treated at smaller centres, which would tend to be located in rural areas. The Appraisal Committee concluded that the overall population of the Cheah study, where efficacy is driven by use of investigational agents, was the most appropriate dataset for standard of care to use in the indirect comparison. This implies that enrolment into clinical trials and the use of investigational agents are considered established care within the NHS in England. However, clinical experts present at the Appraisal Committee meeting disagreed with the Committee's suggestion that investigational agent use is commonplace. Clinicians stated that investigational agent use is minimal in this setting (around 5%), and would broadly be

confined to large treatment centres, so that patients receiving treatment in smaller, rural settings would not be able to receive these agents. It should be noted that this is supported by evidence from the clinician survey presented in Appendix A. This additionally raises an important equality issue, in that patients treated at smaller centres would not have access to investigational agents and clinical trials.

7. References

1. National Institute for Health and Care Excellence. Appraisal consultation document: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. 2017. Available from: https://www.nice.org.uk/guidance/GID-TA10100/documents/appraisal-consultation-document [accessed 24/03/2017].
2. National Institute for Health and Care Excellence. Appraisal consultation document. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/appraisal-consultation-document [accessed 23/03/2017].
3. National Institute for Health and Care Excellence. Final scope for the appraisal of nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. September 2016.
4. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword [accessed 25 January, 2017].
5. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209205. Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects After Failure of Autologous Stem Cell Transplant (ASCT). 2016.
6. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209039: A Phase 1 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS-936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy. 2016.
7. Lafferty N, Anandram S, Lawes N, et al., editors. Allogeneic Stem Cell Transplantation in Patients with Hodgkin Lymphoma: a Retrospective Single Centre Case Series. British Society for Haemotology 57th Annual Scientific Meeting; 2017; Brighton, UK.
8. Cancer Research UK. Hodgkin lymphoma incidence statistics. 2016. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence#heading-Zero [accessed 16/05/2016].
9. National Institute for Health and Care Excellence. Single Technology Appraisal. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. Committee Papers. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/committee-papers [accessed 03/09/2016].
10. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. Available from: https://www.nice.org.uk/article/pmg9 [accessed 03/06/2016].
11. Bradley CJ, Yabroff KR, Dahman B, et al. Productivity costs of cancer mortality in the United States: 2000-2020. J Natl Cancer Inst. 2008;100(24):1763-70.
12. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016;27(7):1317-23.
13. Bristol-Myers Squibb Company. Understanding treatment patterns and disease management in relapsed/refractory classical Hodgkin lymphoma (HL) patients in the UK, France, Germany and Canada. 2016.
14. National Institute for Health and Care Excellence. Appraisal consultation document: Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/appraisal-consultation-document [accessed 25 January, 2017].

15. National Institute for Health and Care Excellence. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]. Committee Papers. 2017. Available from: https://www.nice.org.uk/guidance/GID-TA10100/documents/committee-papers [accessed 23/03/2017].
16. National Institute for Health and Care Excellence. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]. Public committee slides. 2017. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10100/documents [accessed 23/03/2017].
17. National Institute for Health and Care Excellence Decision Support Unit. Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf [accessed 07/06/2016].
18. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014;34(3):343-51.

PO Box 386, Aylesbury,
Bucks HP20 2GA
Freephone helpline 0808 808 5555
Administration 01296 619400
Fundraising 01296 619419
www.lymphomas.org.uk
information@lymphomas.org.uk

Nivolumab for Hodgkin lymphoma
Appraisal consultation document (March 2017) – Lymphoma Association response – 31 March 2017

We are disappointed that NICE is proposing not to recommend nivolumab for routine use on the NHS in England for this group of patients. As we've noted in our submission to the appraisal committee, people with relapsed or refractory Hodgkin lymphoma often have many symptoms, which can be debilitating and distressing. They also know that, despite all the treatment they have been through, their life-expectancy is severely limited. They are faced with a choice between:

- treatments that they know have little chance of success (particularly in the long term) but risk them developing significant side effects and/or spending large parts of their remaining life away from family and friends in hospital, or
- purely palliative care, which is likely to give them a life-expectancy of a few months only and potentially with a number of symptoms.

Nivolumab has the potential to act as salvage therapy to enable an allogeneic stem cell transplant after both autologous stem cell transplant and brentuximab vedotin, a fact that is acknowledged by the committee (ACD, para 4.2). As such a stem cell transplant offers the chance of a cure (estimated by expert clinicians to be of the order of 60% - see also ACD para 4.2), patients will find it hard to understand why they will be denied access to this live-saving treatment. Even those patients who are fit enough and have the possibility of a donor to enable them to undergo an allogeneic transplant may not be able to do so if their lymphoma cannot be controlled again with effective treatment first.

Achieving cure in these patients can allow them to return to work or education and make an active contribution to society as well as having a profound positive impact on physical and psychological health. It's not clear that these sorts of issues are factored into NICE's cost-effectiveness and health economic assessments.

Many patients with relapsed or refractory Hodgkin lymphoma are young (and are often their prime child-bearing and family years) with potential for a long, healthy and active life if they can undergo transplant. Patients unsuitable for transplant can also benefit from

Lymphoma association

PO Box 386, Aylesbury,
Bucks HP20 2GA
Freephone helpline 0808 808 5555
Administration 01296 619400
Fundraising 01296 619419
www.lymphomas.org.uk
information@lymphomas.org.uk

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. This discriminates against those groups of patients, in this case younger people under the age of 30, who represent one of the peaks of prevalence for Hodgkin lymphoma.

We note that the committee concluded that the trial evidence showed that nivolumab is "clinically effective based on the response rates" (ACD para 4.5), although there is a large degree of uncertainty. In our view, given the importance of nivolumab's position in the treatment pathway and the potential for it to meet unmet need (and in some cases save lives), we would urge NICE to be more flexible in its approach to the evidence on clinical effectiveness. Hodgkin lymphoma is a rarer cancer, with the numbers of people affected by relapsed/refractory disease being very low and it would be both difficult and unethical to carry out a randomised controlled trial in this patient population.

We support the call for further evidence, but hope that NICE will treat this further evidence constructively with a view to supporting access to nivolumab on the NHS in England, so that clinicians can begin gathering real world experience and evidence of the treatment. This will be by far the most constructive approach with the most benefit to patients and their families in the immediate future as well as for those in the longer term.

Yours sincerely

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

From The Registrar
[redacted]

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
tacommc@nice.org.uk

21 March 2017

Dear Stephanie

Re: ACD - Consultees & Commentators: Lymphoma (Hodgkin, classical, relapsed, refractory) - nivolumab [972]

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-RP-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 comment.

Hodgkin lymphoma which has relapsed after an autograft and after brentuximab is a rare disease with a high area of unmet need. Nivolumab is clearly very effective in this setting. To deny its use to NHS patients in England would be to deprive young patients of an effective treatment which can bridge them to a potentially curative transplant. NHS England and NICE should do everything they can to make this drug available to patients who need it.

Yours sincerely
[redacted]

THE ROYAL COLLEGE OF RADIOLOGISTS

Response to:
Single Technology Appraisal (STA)
Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

Has all of the relevant evidence been taken into account?
Yes, it has .

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes – however there is a need for data which reflects UK practice given the higher rate of allogeneic stem cell transplantation in the UK. This might significantly impact on the cost effectiveness of Nivolumab treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Perhaps – with the data presented. Given the higher rates of allogeneic stem cell transplantation in the UK, a better comparison with UK standard of care data would reassure patient and health care professionals alike that the recommendations were valid with respect to UK healthcare and NHS structures. It is likely with a more valid UK comparison, the clinical and cost effectiveness of Nivolumab therapy would be more favourable.

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 and maternity?
No.

The Royal College of Radiologists
April 2017

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

Name	[redacted]
Role	[redacted]
Other role	
Organisation	Leukaemia cancer society
Location	England
Conflict	No
Notes	
Comment on ACD:	
There is a real unmet need in this patient population with few treatment options available to them and this treatment offers significant advancement in the management of the disease and quality of life benefits. We ask that NICE takes a flexible approach when addressing the uncertainty around data and to take into account that the limited data available is due to the innovative nature of the treatment.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Response to the Appraisal consultation document: Appendix

Nivolumab (Opdivo®) as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin

Bristol-Myers Squibb Pharmaceuticals Ltd

April 2017

Contents

List of tables

List of figures

Abbreviations

AE	Adverse Event
AIC	Akaike Information Criteria
AlloSCT	Allogeneic Stem Cell Transplant
ASCT	Autologous Stem Cell Transplant
BIC	Bayesian Information Criteria
BTX	Brentuximab
cHL	Classical Hodgkin Lymphoma
CR	Complete Response
ECOG	Eastern Cooperative Oncology Group
ERG	External Review Group
HL	Hodgkin Lymphoma
ICER	Incremental cost-effectiveness ratio
IRRC	Independent Regulatory Review Committee
LY	Life year
MAIC	Matching-Adjusted Indirect Comparison
NHL	Non-Hodgkin Lymphoma
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PFS	Progression-free Survival
PR	Partial Response
QALY	Quality-adjusted life year
SD	Stable Disease
SoC	Standard of Care

1. Revised base case analysis incorporating the Committee's preferred assumptions

The Appraisal Committee has recommended that NICE request revised probabilistic cost-effectiveness analyses comparing nivolumab with SoC, which incorporate the committee's preferred assumptions regarding method of indirect comparison, costs and utilities.

1.1 Adaptation of base case analysis

1.1.1 Nivolumab OS extrapolation

Within the Appraisal Consultation Document, the Committee noted that there may be some double-counting because overall survival (OS) extrapolation used in the base case included some patients who had allogeneic stem cell transplant (alloSCT; Section 4.14 of the Appraisal Consultation Document[1]). However, alloSCT is associated with short-term mortality and morbidity, but long-term survival is improved. Thus, patients receiving alloSCT within available data (pooled nivolumab population and Cheah et al. 2016 population) will result in additional death events but with limited impact on long-term extrapolation due to lack of extended follow-up. This was noted within the factual accuracy check of the ERG report. Thus, the analysis described in the company submission can be considered conservative. However, in order to address the committee's concerns, it has been necessary to censor OS in patients receiving alloSCT.

As described within the company submission, the original base case analysis uses patient-level data to inform nivolumab progression-free survival (PFS) and OS, derived from Cohort B (n = 80) and Cohort C (n = 98; two patients who had not received brentuximab [BTX] were excluded) of the CheckMate 205 study (total: n = 178) and the patients from CA209-039 who had previously received autologous stem cell transplant (ASCT) and BTX (n = 15). Patients who received alloSCT were censored for PFS and response at the time the patient initiated a preparative regimen for alloSCT; however, OS data were not censored. In order to provide evidence to support decision-making, the revised base case applies nivolumab OS data where patients receiving alloSCT are censored applying the same criteria as applied for PFS.[2,3]

Of the patients included within the pooled nivolumab cohort at that time, alloSCT was received by:

- 7/80 from CheckMate 205 Cohort B
- 8/98 from CheckMate 205 Cohort C
- 3/15 from the post-ASCT, post-BTX subgroup of CA209-039
- 18/193 from the overall pooled nivolumab cohort

Of the 17 OS events in the pooled nivolumab cohort, 4 occurred in patients who had received alloSCT (Cohort B: 0/5 events; Cohort C: 1/8 events; CA209-039: 3/4 events). Thus, this reduces the number of death events in the pooled nivolumab cohort from 17 deaths to 13 deaths.

In line with the methodology detailed in Appendix 6 of the company submission, parametric survival functions were fitted to the extracted pooled data using the R statistics environment, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma

survival distributions. Goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively); minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit.

Figure 1 depicts the impact of censoring OS for patients who receive alloSCT, while Table 1 provides goodness of fit statistics and median survival estimates. As can be seen, predicted survival improves following censoring of patients receiving alloSCT, with the shortest extrapolation predicting median survival of 97.8 months (versus 70.6 months in the base case analysis described in the company submission). In the interests of providing a highly conservative estimate of OS using available data, the Weibull function was applied in the economic model in the revised base case analysis.

Figure 1. Extrapolation of nivolumab OS following censoring of patients who receive alloSCT

Figure 2. Overall survival: log cumulative hazard following censoring of patients who receive alloSCT

Table 1. Goodness of fit statistics and median survival estimates

	OS			
	AIC	BIC	Median (months)	Parameters
Exponential	161.4	164.7	117.3	Lambda: 0.00591
Weibull	163.3	169.8	97.8	Shape: 1.089; Scale: 137.0
Log-logistic	163.2	169.7	123.4	Shape: 1.118; Scale: 123.4
Lognormal	162.1	168.6	212.2	Mu: 5.358; Sigma: 1.948
Gompertz	163.3	169.8	Not reached	Shape: -0.0217; Rate: 0.00682
G Gamma	162.2	171.9	924807.7	Mu: 3.036; Sigma: 3.488; Q: -5.190
AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; OS: overall survival				

1.1.2 Utilities

In line with the Committee's preferred assumptions around utilities (described in Section 4.17 and 4.18 of the Appraisal Consultation Document[1]), response-specific utility values for both arms were derived from nivolumab patient-level data from CheckMate 205.

Table 2. Response-specific utilities applied in revised base case.

	Value*	SE
Complete Remission	[redacted]	[redacted]
Partial Remission	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]
Progressed Disease	[redacted]	[redacted]
* applied in both treatment arms		

1.1.3 SoC costs

SoC costs have been applied as per the ERG costs, in line with the Committee's preferred values (Section 4.16 of the Appraisal Consultation Document[1]). Mini-BEAM and DexaBEAM costs were excluded from the base case analysis, based on clinician opinion obtained by the ERG. However, it is unclear how the ERG inputs were calculated, as it has not been possible to replicate these inputs. In order to address this issue, the monthly cost of SoC excluding mini-BEAM and DexaBEAM have been calculated, with the calculations provided as a separate spreadsheet for the purposes of verification. Updated SoC costs are provided in Table 3 and Table 4.

Table 3. SoC costs excluding mini-BEAM and DexaBeam

Parameter	Submission base case (£)	ERG base case (£)	Revised base case (£)
Month 1	4,729.43	3,710.21	3,957.28
Month 2	4,141.92	3,204.80	3,369.11
Month 3	3,037.50	2,652.61	2,724.88
Month 4	2,251.40	2,251.40	2,256.80
Month 5	2,218.97	2,218.97	2,218.97
Month 6	1,913.31	1,913.32	1,913.31

Month 7	331.52	331.52	331.52
Month 8+	0.00	0	0

Table 4. Intervention and comparator costs: revised base case analysis inputs

	SoC (£)	Nivolumab (£)	
		No PAS	PAS
Month 1	3,957.28	6,497.18	[redacted]
Month 2	3,369.11	6,434.18	[redacted]
Month 3	2,724.88	6,434.18	[redacted]
Month 4	2,256.80	6,434.18	[redacted]
Month 5	2,218.97	6,434.18	[redacted]
Month 6	1,913.31	6,434.18	[redacted]
Month 7	331.52	6,434.18	[redacted]
Month 8+	0	6,434.18	[redacted]
PAS: patient access scheme; SoC: standard of care.			

1.1.4 Source of comparative efficacy data

As described in Section 4.8 of the Appraisal Consultation Document, the Appraisal Committee preferred to use the Cheah et al. 2016 overall population, versus use of the Cheah et al. 2016 population excluding the efficacy of investigational agents.[1] As described in Section 4 of the ACD response, BMS considers this to be inappropriate based on available evidence and clinical expert opinion, for the following reasons:

- **Clinician opinion**: clinicians present at the meeting stated that investigational agent use is minimal in this setting (around 5%), and would broadly be confined to large treatment centres, so that patients receiving treatment in smaller centres would not be able to receive these agents. This was supported by a clinician survey conducted by BMS.

- **Population differences**: the Appraisal Committee suggested that the overall population of the Cheah et al. study, including those having investigational agents, would better match the population in the nivolumab trials because patients in trials tend to be fitter. However, there is no evidence to support this suggestion in the case of the nivolumab studies. On the contrary, patients in the Cheah et al. study tended to be younger, with fewer older patients enrolled, in comparison with the nivolumab studies, and disease stage at study enrolment tended to be better than in the nivolumab studies.[4]

- **Established NHS practice:** The scope for this appraisal details that the comparator should be established clinical management without nivolumab,[5] in line with the NICE guide to the methods of technology appraisal, which states established NHS practice in England should be one of the factors considered when identifying appropriate comparators.[6] However, based on evidence from the clinical experts present at the Appraisal Committee meeting and the clinician survey conducted by BMS, the

investigational agents described by Cheah and colleagues,[4] by definition, do not reflect established practice within the NHS in England.

- **Clinical plausibility**: Inclusion of investigational agents into SoC extends the OS beyond that which clinical experts consider plausible. The clinician survey presented in Section 2.2.1 details estimated OS of [redacted]. This estimate is supported by clinical experts attending the first Appraisal Committee meeting for the ongoing BTX appraisal [ID722], who suggested that life expectancy without BTX is likely to be less than 24 months.[7] Further, it is supported by the results of the post-ASCT ITC detailed in the response to the ACD, where median OS was estimated as [redacted]. It is extremely implausible that life expectancy would exceed 24 months in classical Hodgkin lymphoma (cHL) patients who are eligible for nivolumab therapy and are more treatment-experienced (i.e. having previously received both ASCT and BTX therapy).

Despite this, in order to provide evidence to support decision-making, both populations are assessed in the revised base case analysis.

Table 5. SoC efficacy populations

	CR	PR	Median PFS (months)	Median OS (months)
Cheah overall population	15%	19%	3.5	25.2
Cheah excluding investigational agents	16%	23%	4.3	19.0

CR: complete response; OS: overall survival; PFS: progression-free survival; PR: partial response.

1.1.5 Method of deriving comparative efficacy data

As described in Section 4.9 of the Appraisal Consultation Document, the Appraisal Committee has expressed a preference for the base case analysis to apply outcomes based on the matching-adjusted indirect comparison (MAIC), adjusted using distributions of prognostic factors and effect modifiers.[1] The revised base case analysis applies a MAIC analysis for the nivolumab pooled patient population versus data from the Cheah et al. 2016 study, adjusted on all available baseline characteristics.

1.1.5.1 Comparison versus Cheah 2016 data

1.1.5.1.1 Baseline characteristics

As described in Appendix 3 of the company submission, patient-level data were pooled for the relevant patients in the nivolumab studies (CheckMate 205 [cohorts B+C] and CA209-039). Complete baseline characteristics were not available for every patient in the nivolumab cohort; in the case of a missing value, the mean cohort value was used.

Baseline characteristics after matching to the Cheah et al. (2016) data are presented in Table 6. As can be observed, more female patients and fewer older patients were enrolled in Cheah et al. (2016) versus the nivolumab studies.

Table 6. Matching of baseline characteristics between nivolumab and Cheah (2016) data[8]

Baseline characteristics	Nivolumab cohort		Cheah et al. 2016
	Before matching	After matching	
Effective study size	[redacted]	[redacted]	NA
Female	[redacted]	[redacted]	47.0%
Median age (years)	[redacted]	[redacted]	32.0
Age > 45	[redacted]	[redacted]	14.0%
Disease stage 1*	[redacted]	[redacted]	2.4%
Disease stage 2*	[redacted]	[redacted]	29.8%
Disease stage 3*	[redacted]	[redacted]	21.4%
Disease stage 4*	[redacted]	[redacted]	NA
B-symptoms	[redacted]	[redacted]	8.1%
Haemoglobin < 10^5 g/l	[redacted]	[redacted]	35.0%
Lymphocytes < 0.6 x10^9/l	[redacted]	[redacted]	41.0%
White cell count > 15 x10^9/l	[redacted]	[redacted]	5.0%
Albumin < 40g/l	[redacted]	[redacted]	28.0%
Any extranodal site	[redacted]	[redacted]	35.0%
ECOG ≥ 1	[redacted]	[redacted]	59.0%
Max tumour diameter ≥ 4cm	[redacted]	[redacted]	26.0%
Median prior lines	[redacted]	[redacted]	3

ECOG: Eastern Cooperative Oncology Group performance score; NA: not applicable.
* Disease classification methods not specified in Cheah (2016). Assumed equivalent to methods applied in nivolumab studies, or equivalent prognosis between staging methods.

1.1.5.1.2 Outcomes

Results for the adjusted risk ratios for complete response (CR) and partial response (PR) for nivolumab versus alternative treatment options can be found in Table 7. Table 8 contains the adjusted time to median survival (PFS and OS). After adjusting for cross-trial differences, CR, PR, median PFS and median OS were found to be considerably improved over alternative treatment options available, based on the results of the Cheah et al. (2016) study.

Table 7. Adjusted relative risk of response for nivolumab versus alternative treatment options (Cheah 2016)[8]

	Nivolumab cohort	Cheah (2016)*	Relative risk
CR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]

CR: complete response; PR: partial response
* Includes investigational agents

Table 8. Adjusted time to median survival between nivolumab and alternative treatment options (Cheah 2016)[8]

	Nivolumab cohort	Cheah (2016)*	Acceleration factor
Median PFS (months)	[redacted]	[redacted]	[redacted]
Median OS (months)	[redacted]	[redacted]	[redacted]

OS: overall survival; PFS: progression-free survival.
* Includes investigational agents

1.1.5.2 Cheah 2016 excluding investigational agents

As previously described, investigational agents within Cheah et al. (2016)[8] were highly beneficial in terms of increased median OS. However, these therapies are of limited relevance to established clinical practice for treatment of relapsed or refractory cHL.

In order to provide an assessment of the efficacy of SoC in clinical practice, an additional analysis was performed using Cheah et al. 2016 data excluding the impact of investigational agents. Baseline characteristics for the investigational agent subgroup were not available separately, and there were no external patient level data to inform multiple imputation. As such, it was assumed that the baseline characteristics for patients receiving investigational agents were equivalent to those for the overall population; however, the resulting relative efficacy was calculated against the non-investigational agent outcome data.

Results were supportive of the main analysis, in that after adjusting for cross-trial differences, nivolumab was found to be associated with superior rates of CR, PR and improved median PFS and median OS than alternative treatment options, based on the results of the Cheah et al. study.

Table 9. Adjusted relative risk of response between nivolumab and alternative treatment options (Cheah 2016), investigational agents removed

	Nivolumab cohort	Cheah (2016)*	Relative risk/Acceleration factor
CR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
Median PFS (months)	[redacted]	[redacted]	[redacted]
Median OS (months)	[redacted]	[redacted]	[redacted]

CR: complete response; OS: overall survival; PFS: progression-free survival; PR: partial response.
* Excludes investigational agents
Survival outcomes based on parameterisation of available data
Relative risk indicates the proportional improvement in response of nivolumab over the comparator response rate.
Acceleration indicates the factor by which progression towards the endpoint occurs in the comparator compared to nivolumab.

1.1.5.3 Efficacy inputs applied in economic analysis

An overview of efficacy inputs applied in the revised base case analysis are provided in Table 10.

Table 10. Overview of efficacy inputs for revised base case analysis

		Nivolumab cohort	Cheah (2016) overall population	Cheah (2016) excluding investigational agents
CR		[redacted]	[redacted]	[redacted]
PR		[redacted]	[redacted]	[redacted]
PFS	Exponential rate	[redacted]	[redacted]	[redacted]
	Median (months)	[redacted]	[redacted]	[redacted]
OS	Exponential rate	[redacted]	[redacted]	[redacted]
	Median (months)	[redacted]	[redacted]	[redacted]

CR: complete response; OS: overall survival; PFS: progression-free survival; PR: partial response.

1.1.5.4 Allogeneic stem cell transplant use

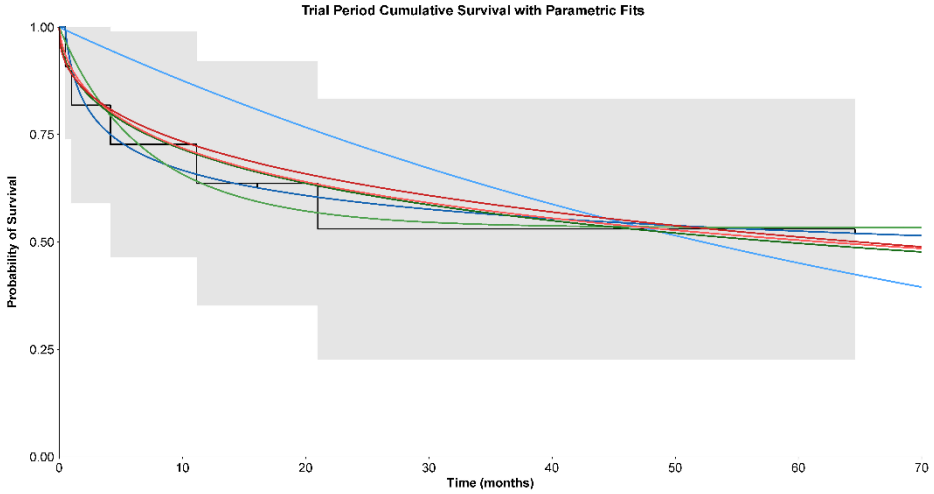
1.1.5.4.1 UK-specific post-alloSCT survival

In order to obtain data in the UK setting, PFS and OS curves were derived from a UK retrospective case series reporting alloSCT in patients with HL following at least three prior therapies.[11] These data reflect the high initial mortality in patients with alloSCT, with extended long-term survival. This source was applied as it is UK-specific, and there was limited time available to assess use of alloSCT survival data described in Sections 3.1 and 3.2. It should be noted that these data reflect a slightly lower OS and PFS at one year than can be expected based on the survival following PD-1 inhibitor use, reported in Sections 3.1 and 3.2, and so use of this data can be considered conservative. Further, these data are reflective of UK clinical practice, and reflect patient selection and the preparative regimens applied in UK clinical practice.

Kaplan-Meier data describing PFS and OS for these patients were digitised, and parametric survival functions were fitted to the extracted data using the R statistics environment. As previously, goodness-of-fit was evaluated using AIC and BIC, visual assessment of parametric fit and the clinical plausibility of the long-term extrapolation.

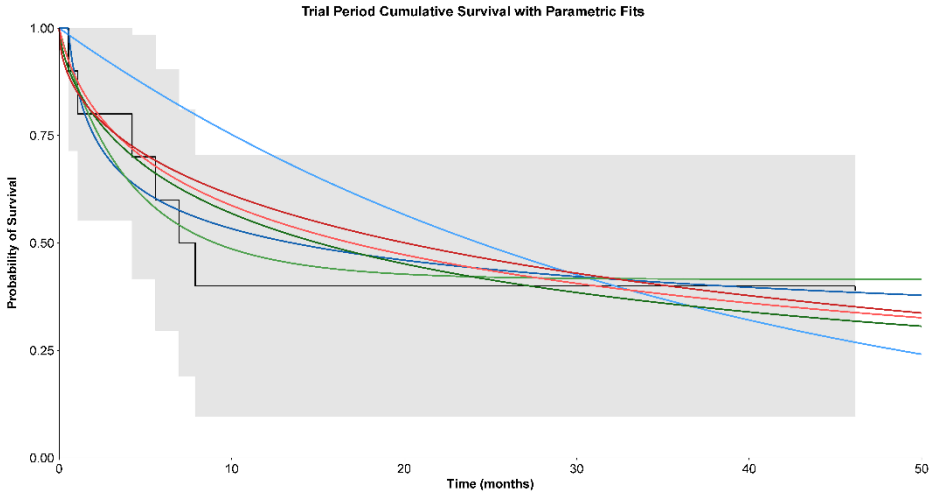
Figure 3 and Figure 4 depict parametric extrapolation of OS and PFS, respectively. Based on AIC and BIC, Gompertz can be considered the most appropriate fit for both PFS and OS; further, this parametric extrapolation reflected the initial steep hazard, followed by a subsequent decline in hazard.

Figure 3. UK-specific post-alloSCT survival: disease-specific overall survival



Distribution	AIC	BIC	Median Survival	Parameters
Exponential	55.22	55.62	52.2	λ=0.013
Generalised gamma	48.63	49.83	86.9	μ=−0.677 σ=0.247 Q=−30.372
Gompertz	49.04	49.84	Inf	θ=−0.110 λ=0.069
Log−logistic	50.60	51.39	58.6	β=0.522 α=58.610
Log−normal	50.10	50.90	62.1	μ=4.129 σ=3.159
Weibull	51.12	51.91	64.9	k=0.431 θ=151.960

Figure 4. UK-specific post-alloSCT survival: progression-free survival



Distribution	AIC	BIC	Median Survival	Parameters
Exponential	56.72	57.02	24.4	λ=0.028
Generalised gamma	49.95	50.85	13.5	μ=−0.601 σ=0.192 Q=−24.397
Gompertz	47.72	48.33	9.0	θ=−0.172 λ=0.151
Log−logistic	52.07	52.68	15.0	β=0.680 α=15.025
Log−normal	51.63	52.23	17.0	μ=2.831 σ=2.395
Weibull	53.35	53.95	20.1	k=0.494 θ=42.155

1.1.5.4.2 Proportion of patients receiving alloSCT

The proportion of patients receiving alloSCT in the revised base case analysis has been derived in line with the ERG's preferred approach, whereby the proportion of patients has been derived from the pooled nivolumab population (40 out of 193 patients) and from the Cheah 2016 study (14 out of 79 patients). The rates applied are irrespective of response achieved, and describe the proportion of patients who are alive and progression-free, receiving alloSCT in the model at six months.

As noted by clinical experts during the Appraisal Committee meeting, these rates may provide an underestimate of alloSCT use in UK clinical practice and as such further scenario analyses using UK-specific rates (based on the outputs of the clinician survey) have been explored in Section 2.3.

Table 11. Proportion of patients receiving alloSCT in revised base case analysis

	Nivolumab pooled population		Cheah 2016	
	Mean value	SE	Mean value	SE
CR	[redacted]	[redacted]	17.7%	4.3%
PR	[redacted]	[redacted]	17.7%	4.3%
SD	[redacted]	[redacted]	17.7%	4.3%

1.1.5.4.3 Cost and utility following alloSCT

Two alternative costs of alloSCT were applied as described in Section 5.8.3.2 of the company submission. Similarly, utility values were applied as described in the company submission.

Table 12. Cost of alloSCT

Scenario	Initial cost		Ongoing monthly cost	
	Value	SE	Value	SE
Scenario 1: Costs from NHS reference costs[15]	33,072.38	3,185.38	91.69	16.49
Scenario 2: Costs derived from Radford 2013[16]	110,374.00	23,763.30	91.69	16.49

Table 13. Utility of alloSCT

Health state following alloSCT	Utility	
	Value	SE
Pre-progression	0.856	0.0532
Post-progression	As in Table 2	

1.2 Revised base case analysis results

1.2.1 Revised base case analysis including alloSCT

1.2.1.1 Deterministic base case analysis results including alloSCT

Deterministic base case analysis results (with PAS) are provided in Table 14 (overall population) and Table 15 (excluding the impact of investigational agents).

Use of alloSCT has a larger impact in the nivolumab arm, as more patients receive alloSCT in the nivolumab arm than the SoC arm. This is partly due to the higher response rate in the nivolumab arm. However, this is also because PFS and OS are shorter in the SoC arm, so that fewer patients are alive and in pre-progression at six months, lowering the eligible patient population.

As described in Section 1.1.1, censoring OS at alloSCT results in extended survival in the nivolumab arm, while inclusion of the long-term benefits of alloSCT results in short-term mortality but improves survival over the time horizon. This has a large impact on the analysis, increasing mean LYs from 5.0 in the original base case analysis to 8.2 LYs in the revised base case analysis. This results in increased disease management costs, as well as increased cost of initial treatment and subsequent treatment, so that total costs were increased versus the original base case ([redacted] in scenario 1 and [redacted] in scenario 2 versus [redacted]).

Despite inclusion of alloSCT, use of MAIC values slightly reduced OS in the SoC treatment arm (overall population: 2.6 LYs versus 3.0 LYs; excluding investigational agents: 2.1 LYs versus 2.1 LYs). However, mean PFS was improved in both populations (0.46 years in the overall population and 0.53 years when excluding investigational agents versus 0.40 years) due to availability of alloSCT, so that accumulation of pre-progression utilities and costs (including treatment costs and adverse event [AE] costs) are slightly increased.

This revised base case analysis reflects use of alloSCT, applied in line with the Committee's preferred assumptions. However, UK-specific use of alloSCT is reflected in the analyses presented in Section 2.3. In comparison with the ERG revised base case analysis, this has reduced the relative costs of subsequent therapy (including alloSCT) due to increased proportion of patients receiving alloSCT in the SoC arms. As the ERG do not model the survival benefit associated with alloSCT, there is relatively little impact on predicted survival beyond that described above.

These changes have a large impact on the predicted cost-effectiveness of nivolumab. The incremental cost-effectiveness ratio (ICER) in the revised base case analysis is £13,352 in scenario 1 and £15,181 in scenario 2 for the Cheah et al. overall population, versus £22,855 in the original analysis and £36,525 in the ERG base case analysis. Similarly, the ICER in the Cheah et al. excluding investigational agents analysis is £13,069 in scenario 1 and £14,741 in scenario 2, reduced from a base case ICER of £19,882.

Table 14. Revised base case analysis (with PAS) including alloSCT: Cheah 2016 overall population

	Original Cheah overall analysis			ERG base case			AlloSCT scenario 1			AlloSCT scenario 2		
	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental
Patient-level progression												
Time in pre-progression (years)	0.283	[redacted]	[redacted]	0.317	[redacted]	[redacted]	0.464	[redacted]	[redacted]	0.464	[redacted]	[redacted]
- Time in 4th line (years)	0.271	[redacted]	[redacted]	0.265	[redacted]	[redacted]	0.291	[redacted]	[redacted]	0.291	[redacted]	[redacted]
- Time in post 4th line (years)	0.013	[redacted]	[redacted]	0.052	[redacted]	[redacted]	0.173	[redacted]	[redacted]	0.173	[redacted]	[redacted]
Time in post-progression (years)	2.687	[redacted]	[redacted]	2.616	[redacted]	[redacted]	2.135	[redacted]	[redacted]	2.135	[redacted]	[redacted]
Patient-level utility breakdown												
Health state utility	1.235	[redacted]	[redacted]	2.133	[redacted]	[redacted]	1.255	[redacted]	[redacted]	1.255	[redacted]	[redacted]
- CR	0.033	[redacted]	[redacted]	0.041	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]	[redacted]
- PR	0.041	[redacted]	[redacted]	0.062	[redacted]	[redacted]	0.134	[redacted]	[redacted]	0.134	[redacted]	[redacted]
- SD	0.141	[redacted]	[redacted]	0.159	[redacted]	[redacted]	0.197	[redacted]	[redacted]	0.197	[redacted]	[redacted]
- Progressed disease	1.021	[redacted]	[redacted]	1.871	[redacted]	[redacted]	0.870	[redacted]	[redacted]	0.870	[redacted]	[redacted]
AE disutility	0.012	0.003	-0.009	0.014	0.002	-0.012	0.016	0.002	-0.013	0.016	0.002	-0.013
Age based disutility	0.019	0.057	0.037	0.017	0.06	0.043	0.028	0.287	0.259	0.028	0.287	0.259
Total utilities	1.204	[redacted]	[redacted]	2.102	[redacted]	[redacted]	1.212	[redacted]	[redacted]	1.212	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)												
Health state costs	6,775	11,434	4,659	6,691	11,639	4,948	5,928	18,757	12,829	5,928	18,757	12,829
- CR	98	1,065	967	113	1,075	962	144	1,430	1,287	144	1,430	1,287
- PR	123	1,657	1,534	170	1,672	1,502	367	2,225	1,858	367	2,225	1,858
- SD	425	1,085	660	440	1,095	655	548	1,457	909	548	1,457	909
- Progressed disease	6,129	7,627	1,498	5,968	7,797	1,830	4,870	13,646	8,776	4,870	13,646	8,776
Treatment costs	11,199	[redacted]	[redacted]	15,020	[redacted]	[redacted]	13,723	[redacted]	[redacted]	16,278	[redacted]	[redacted]
- 4th line	6,995	[redacted]	[redacted]	7,723	[redacted]	[redacted]	8,423	[redacted]	[redacted]	8,423	[redacted]	[redacted]
- 5th line	4,205	4,676	472	7,297	20,572	13,275	5,300	10,023	4,723	7,855	21,104	13,249
AE costs	1,014	257	-757	1,333	223	-1,110	1,462	231	-1,230	1,462	231	-1,230
Total costs	18,988	[redacted]	[redacted]	23,043	[redacted]	[redacted]	21,113	[redacted]	[redacted]	23,668	[redacted]	[redacted]
Patient-level CE results												
Total QALYs	1.204	[redacted]	[redacted]	2.102	[redacted]	[redacted]	1.212	[redacted]	[redacted]	1.212	[redacted]	[redacted]
Total LYs	2.97	5.013	2.043	2.933	5.103	2.169	2.599	8.224	5.625	2.599	8.224	5.625
- Median ToT (years)	0.218	0.801	0.583	0.195	0.585	0.39	0.215	0.587	0.372	0.215	0.587	0.372
- Median PFS (years)	0.224	1.128	0.904	0.203	1.155	0.953	0.225	1.031	0.806	0.225	1.031	0.806
- Median OS (years)	1.996	4.042	2.047	2.032	4.12	2.089	1.618	5.459	3.841	1.618	5.459	3.841
Total Costs (£)	18,988	[redacted]	[redacted]	23,043	[redacted]	[redacted]	21,113	[redacted]	[redacted]	23,668	[redacted]	[redacted]
ICER (Cost/QALY)	**22,855**			**36,525**			**13,352**			**15,181**		

Table 15. Revised base case analysis (with PAS) including alloSCT: Cheah 2016 excluding impact of investigational agents

	Original base case analysis			AlloSCT scenario 1			AlloSCT scenario 2		
	Comparator	**Nivolumab**	**Incremental**	**Comparator**	**Nivolumab**	**Incremental**	**Comparator**	**Nivolumab**	**Incremental**
Patient-level progression									
Time in pre-progression (years)	0.405	[redacted]	[redacted]	0.532	[redacted]	[redacted]	0.532	[redacted]	[redacted]
- Time in 4th line (years)	0.369	[redacted]	[redacted]	0.322	[redacted]	[redacted]	0.322	[redacted]	[redacted]
- Time in post 4th line (years)	0.036	[redacted]	[redacted]	0.210	[redacted]	[redacted]	0.210	[redacted]	[redacted]
Time in post-progression (years)	1.704	[redacted]	[redacted]	1.598	[redacted]	[redacted]	1.598	[redacted]	[redacted]
Patient-level utility breakdown									
Health state utility	0.956	[redacted]	[redacted]	1.119	[redacted]	[redacted]	1.119	[redacted]	[redacted]
- CR	0.048	[redacted]	[redacted]	0.062	[redacted]	[redacted]	0.062	[redacted]	[redacted]
- PR	0.073	[redacted]	[redacted]	0.154	[redacted]	[redacted]	0.154	[redacted]	[redacted]
- SD	0.187	[redacted]	[redacted]	0.226	[redacted]	[redacted]	0.226	[redacted]	[redacted]
- Progressed disease	0.648	[redacted]	[redacted]	0.677	[redacted]	[redacted]	0.677	[redacted]	[redacted]
AE disutility	0.02	0.003	-0.017	0.017	0.002	-0.015	0.017	0.002	-0.015
Age based disutility	0.005	0.057	0.052	0.027	0.287	0.260	0.027	0.287	0.260
Total utilities	0.932	[redacted]	[redacted]	1.074	[redacted]	[redacted]	1.074	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)									
Health state costs	4,813	11,434	6,621	4,857	18,757	13,900	4,857	18,757	13,900
- CR	145	1,065	920	165	1,430	1,266	165	1,430	1,266
- PR	218	1,657	1,439	420	2,225	1,805	420	2,225	1,805
- SD	562	1,085	523	628	1,457	829	628	1,457	829
- Progressed disease	3,888	7,627	3,739	3,644	13,646	10,001	3,644	13,646	10,001
Treatment costs	14,420	[redacted]	[redacted]	14,158	[redacted]	[redacted]	17,216	[redacted]	[redacted]
- 4th line	10,477	[redacted]	[redacted]	8,873	[redacted]	[redacted]	8,873	[redacted]	[redacted]
- 5th line	3,943	4,676	733	5,285	10,023	4,738	8,342	21,104	12,761
AE costs	1,857	257	-1,600	1,620	231	-1,388	1,620	231	-1,388
Total costs	21,090	[redacted]	[redacted]	20,635	[redacted]	[redacted]	23,692	[redacted]	[redacted]
Patient-level CE results									
Total QALYs	0.932	[redacted]	[redacted]	1.074	[redacted]	[redacted]	1.074	[redacted]	[redacted]
Total LYs	2.11	5.013	2.903	2.129	8.224	6.094	2.129	8.224	6.094
- Median ToT (years)	0.263	0.801	0.538	0.239	0.587	0.348	0.239	0.587	0.348
- Median PFS (years)	0.282	1.128	0.847	0.252	1.031	0.779	0.252	1.031	0.779
- Median OS (years)	1.461	4.042	2.581	1.250	5.459	4.209	1.250	5.459	4.209
Total Costs (£)	21,090	[redacted]	[redacted]	20,635	[redacted]	[redacted]	23,692	[redacted]	[redacted]
ICER (Cost/QALY)	**19,882**			**13,069**			**14,741**		

1.2.2.2 Probabilistic base case analysis including alloSCT

A probabilistic sensitivity analysis (PSA) was undertaken around the revised base case analysis, using the methods outlined in the company submission. Several inputs are derived from sources where it has not been possible to ascertain SEs. To assess uncertainty around these inputs, a SE of 10% has been assumed.

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in

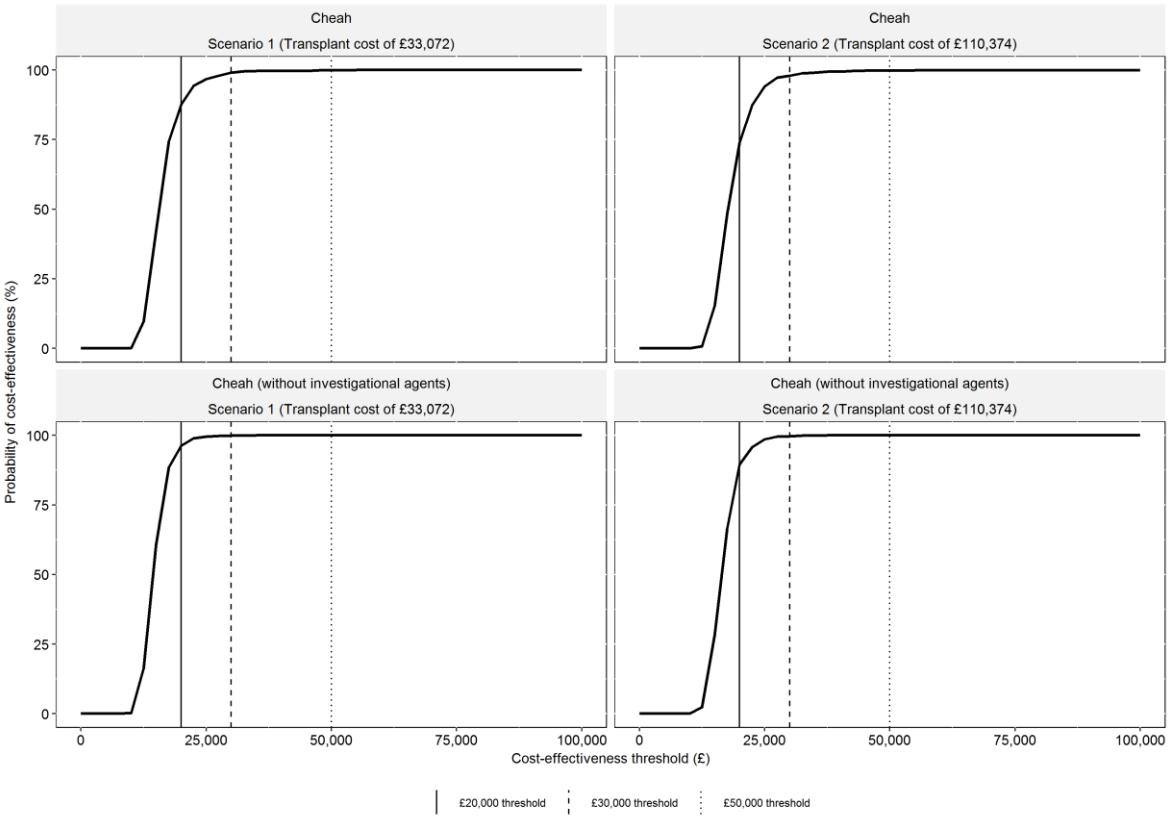


Figure 6 and cost-effectiveness acceptability curves (CEACs) are presented in Figure 5, while a summary of the results is provided in

***[redacted]

Table 16. Applying the Cheah et al. overall population, the probability that nivolumab is cost-effective versus SoC is 99.0% at a willingness-to-pay (WTP) threshold of £30,000 per quality-adjusted life year (QALY) in scenario 1 and 98.0% in scenario 2, increasing to 99.9% and 99.8%, respectively, at a £50,000/QALY threshold. When applying data excluding the impact of investigational agents, the probability that nivolumab is cost-effective versus SoC increases to 99.9% in scenario 1 and 99.7% in scenario 2 at a WTP threshold of £30,000/QALY, or 100% across scenarios at a £50,000/QALY threshold.

Over the course of the four PSAs, nivolumab was always predicted to be clinically beneficial versus SoC, with incremental QALYs ranging from [redacted] Accrual of costs was

reassuringly stable, resulting in incremental costs of [redacted]

Table 16. Revised base case analysis (with PAS) including alloSCT: probabilistic results

	Cheah overall population		Cheah excluding investigational agents	
	Scenario 1	**Scenario 2**	**Scenario 1**	**Scenario 2**
ICER (£/QALY)	£15,652	£17,826	£14,493	£16,385
Probability cost-effective at threshold:				
£20,000/QALY	87.6%	73.9%	96.3%	89.5%
£30,000/QALY	99.0%	98.0%	99.9%	99.7%
£50,000/QALY	99.9%	99.8%	100%	100%
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.				

Figure 5. Revised base case analysis (with PAS) excluding alloSCT: cost-effectiveness acceptability curve

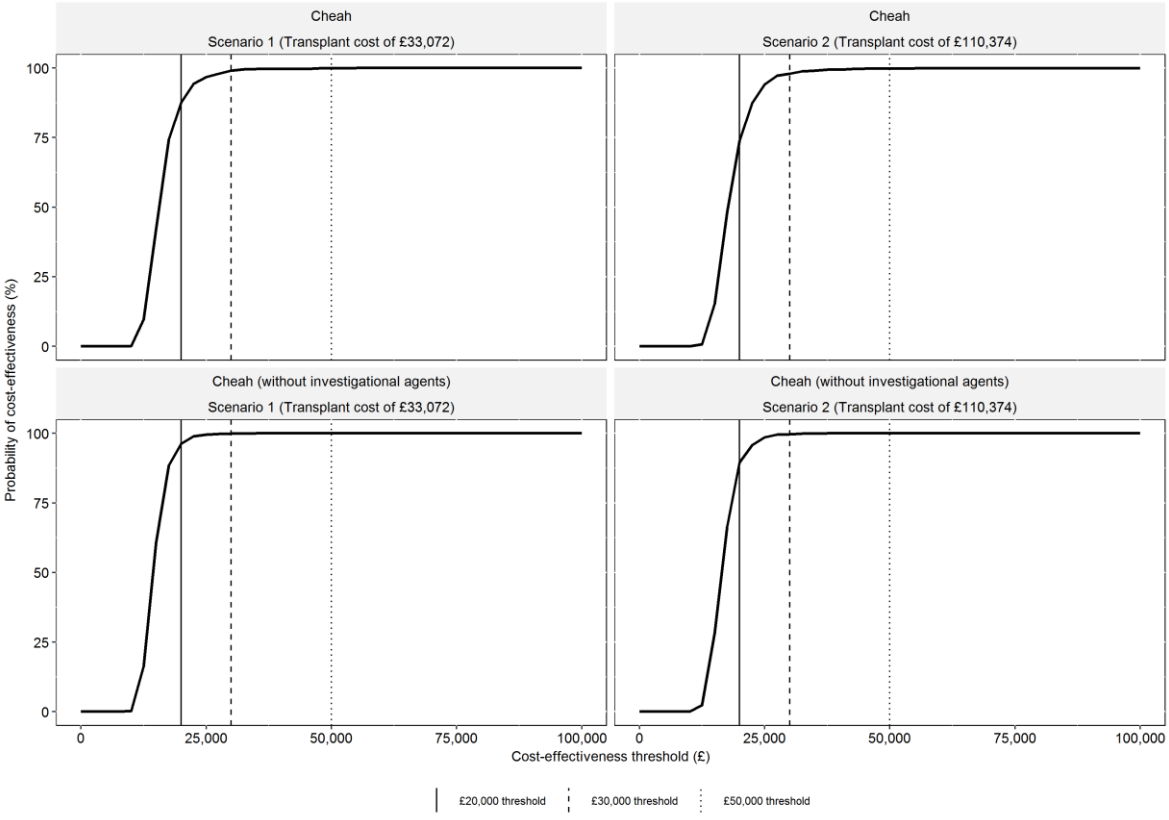


Figure 6. Revised base case analysis (with PAS) excluding alloSCT: cost-effectiveness scatterplot

1.2.2 Revised base case analysis without alloSCT

1.2.2.1 Deterministic base case analysis results without alloSCT

In order to comply with the scope of this appraisal, deterministic base case analysis results excluding the benefits of alloSCT are provided in Table 17 (overall population) and Table 18 (excluding the impact of investigational agents).

As described in Section 1.1.1, censoring OS at alloSCT results in extended survival in the nivolumab arm, and this has a large impact on the analysis, increasing mean LYs from 5.0 in the original base case analysis to 7.9 LYs in the revised base case analysis. This results in increased disease management costs, as well as increased cost of initial treatment, so that total costs were increased versus the original base case ([redacted] versus [redacted]).

Similarly, use of MAIC values reduced OS in the SoC treatment arm (overall population: 2.4 LYs versus 3.0 LYs; excluding investigational agents: 1.8 LYs versus 2.1 LYs). However, mean PFS was slightly improved in the overall population (0.28 years versus 0.32 years) due to the use of alternative parametric extrapolation curves (lognormal versus exponential), so that accumulation of pre-progression utilities and costs (including treatment costs and adverse event [AE] costs) are slightly increased. By contrast, in the Cheah excluding investigational agents analysis, mean PFS was decreased by use of MAIC-derived inputs (0.40 years versus 0.37 years), resulting in lower costs in the pre-progression state.

This revised base case analysis does not reflect use of alloSCT. Use of alloSCT is reflected in the analyses presented in Section 1.2.1. In comparison with the ERG revised base case analysis, this has reduced the costs of subsequent therapy due to lack of alloSCT costs (overall population: [redacted]). As the ERG do not model the survival benefit associated with alloSCT, there is relatively little impact on predicted survival beyond that described above.

These changes have a large impact on the predicted cost-effectiveness of nivolumab. The incremental cost-effectiveness ratio (ICER) in the revised base case analysis is £14,365 in the Cheah et al. overall population, versus £22,855 in the original analysis and £36,525 in the ERG base case analysis. Similarly, the ICER in the Cheah et al. excluding investigational agents analysis is £13,998, reduced from a base case ICER of £19,882.

Table 17. Revised base case analysis (with PAS) without alloSCT: Cheah 2016 overall population

	Original analysis			ERG base case			Revised base case analysis		
	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental
Patient-level progression									
Time in pre-progression (years)	0.283	[redacted]	[redacted]	0.317	[redacted]	[redacted]	0.323	[redacted]	[redacted]
- Time in 4th line (years)	0.271	[redacted]	[redacted]	0.265	[redacted]	[redacted]	0.302	[redacted]	[redacted]
- Time in post 4th line (years)	0.013	[redacted]	[redacted]	0.052	[redacted]	[redacted]	0.022	[redacted]	[redacted]
Time in post-progression (years)	2.687	[redacted]	[redacted]	2.616	[redacted]	[redacted]	2.028	[redacted]	[redacted]
Patient-level utility breakdown									
Health state utility	1.235	[redacted]	[redacted]	2.133	[redacted]	[redacted]	1.035	[redacted]	[redacted]
- CR	0.033	[redacted]	[redacted]	0.041	[redacted]	[redacted]	0.042	[redacted]	[redacted]
- PR	0.041	[redacted]	[redacted]	0.062	[redacted]	[redacted]	0.051	[redacted]	[redacted]
- SD	0.141	[redacted]	[redacted]	0.159	[redacted]	[redacted]	0.171	[redacted]	[redacted]
- Progressed disease	1.021	[redacted]	[redacted]	1.871	[redacted]	[redacted]	0.771	[redacted]	[redacted]
AE disutility	0.012	0.003	-0.009	0.014	0.002	-0.012	0.016	0.003	-0.013
Age based disutility	0.019	0.057	0.037	0.017	0.060	0.043	0.007	0.231	0.224
Total utilities	1.204	[redacted]	[redacted]	2.102	[redacted]	[redacted]	1.011	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)									
Health state costs	6,775	11,434	4,659	6,691	11,639	4,948	5,363	18,098	12,735
- CR	98	1,065	967	113	1,075	962	112	1,173	1,061
- PR	123	1,657	1,534	170	1,672	1,502	140	1,825	1,685
- SD	425	1,085	660	440	1,095	655	485	1,195	710
- Progressed disease	6,129	7,627	1,498	5,968	7,797	1,830	4,625	13,904	9,279
Treatment costs	11,199	[redacted]	[redacted]	15,020	[redacted]	[redacted]	12,540	[redacted]	[redacted]
- 4th line	6,995	[redacted]	[redacted]	7,723	[redacted]	[redacted]	8,433	[redacted]	[redacted]
- 5th line	4,205	4,676	472	7,297	20,572	13,275	4,107	4,953	846
AE costs	1,014	257	-757	1,333	223	-1,110	1,517	268	-1,249
Total costs	18,988	[redacted]	[redacted]	23,043	[redacted]	[redacted]	19,420	[redacted]	[redacted]

	Original analysis			ERG base case			Revised base case analysis		
	Comparator	**Nivolumab**	**Incremental**	**Comparator**	**Nivolumab**	**Incremental**	**Comparator**	**Nivolumab**	**Incremental**
Patient-level CE results									
Total QALYs	1.204	[redacted]	[redacted]	2.102	[redacted]	[redacted]	1.011	[redacted]	[redacted]
Total LYs	2.970	5.013	2.043	2.933	5.103	2.169	2.351	7.935	5.583
- Median ToT (years)	0.218	0.801	0.583	0.195	0.585	0.390	0.215	0.809	0.594
- Mean ToT (years)	0.271	1.134	0.864	0.265	0.984	0.719	0.302	1.182	0.881
- Median PFS (years)	0.224	1.128	0.904	0.203	1.155	0.953	0.225	1.160	0.935
- Mean PFS (years)	0.283	[redacted]	[redacted]	0.317	[redacted]	[redacted]	0.323	[redacted]	[redacted]
- Median OS (years)	1.996	4.042	2.047	2.032	4.120	2.089	1.628	5.806	4.177
- Mean OS (years)	2.970	5.013	2.043	2.933	5.103	2.169	2.351	7.935	5.583
Total Costs (£)	18,988	[redacted]	[redacted]	23,043	[redacted]	[redacted]	19,420	[redacted]	[redacted]
ICER (Cost/QALY)	**22,855**			**36,525**			**14,365**		

Table 18. Revised base case analysis (with PAS) without alloSCT: Cheah 2016 excluding impact of investigational agents

	Original base case analysis			Revised base case analysis		
	Comparator	**Nivolumab**	**Incremental**	**Comparator**	**Nivolumab**	**Incremental**
Patient-level progression						
Time in pre-progression (years)	0.405	[redacted]	[redacted]	0.365	[redacted]	[redacted]
- Time in 4th line (years)	0.369	[redacted]	[redacted]	0.336	[redacted]	[redacted]
- Time in post 4th line (years)	0.036	[redacted]	[redacted]	0.029	[redacted]	[redacted]
Time in post-progression (years)	1.704	[redacted]	[redacted]	1.446	[redacted]	[redacted]
Patient-level utility breakdown						
Health state utility	0.956	[redacted]	[redacted]	0.848	[redacted]	[redacted]
- CR	0.048	[redacted]	[redacted]	0.048	[redacted]	[redacted]
- PR	0.073	[redacted]	[redacted]	0.073	[redacted]	[redacted]
- SD	0.187	[redacted]	[redacted]	0.177	[redacted]	[redacted]
- Progressed disease	0.648	[redacted]	[redacted]	0.550	[redacted]	[redacted]
AE disutility	0.020	0.003	-0.017	0.018	0.003	-0.015
Age based disutility	0.005	0.057	0.052	0.002	0.231	0.229
Total utilities	0.932	[redacted]	[redacted]	0.828	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)						
Health state costs	4,813	11,434	6,621	4,132	18,098	13,966
- CR	145	1,065	920	129	1,173	1,044
- PR	218	1,657	1,439	202	1,825	1,624
- SD	562	1,085	523	502	1,195	693
- Progressed disease	3,888	7,627	3,739	3,299	13,904	10,605
Treatment costs	14,420	[redacted]	[redacted]	12,733	[redacted]	[redacted]
- 4th line	10,477	[redacted]	[redacted]	8,887	[redacted]	[redacted]
- 5th line	3,943	4,676	733	3,847	4,953	1,107
AE costs	1,857	257	-1,600	1,692	268	-1,425
Total costs	21,090	[redacted]	[redacted]	18,558	[redacted]	[redacted]

Patient-level CE results						
Total QALYs	0.932	[redacted]	[redacted]	0.828	[redacted]	[redacted]
Total LYs	2.110	5.013	2.903	1.812	7.935	6.123
- Median ToT (years)	0.263	0.801	0.538	0.239	0.809	0.570
- Mean ToT (years)	0.369	1.134	0.765	0.336	1.182	0.846
- Median PFS (years)	0.282	1.128	0.847	0.252	1.160	0.908
- Mean PFS (years)	0.405	[redacted]	[redacted]	0.365	[redacted]	[redacted]
- Median OS (years)	1.461	4.042	2.581	1.254	5.806	4.552
- Mean OS (years)	2.110	5.013	2.903	1.812	7.935	6.123
Total Costs (£)	21,090	[redacted]	[redacted]	18,558	[redacted]	[redacted]
ICER (Cost/QALY)	**19,882**			**13,998**		

1.2.2.2 Probabilistic base case analysis without alloSCT

A PSA was undertaken around the revised base case analysis, using the methods outlined in the company submission. Several inputs are derived from sources where it has not been possible to ascertain SEs. To assess uncertainty around these inputs, a SE of 10% has been assumed.

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in

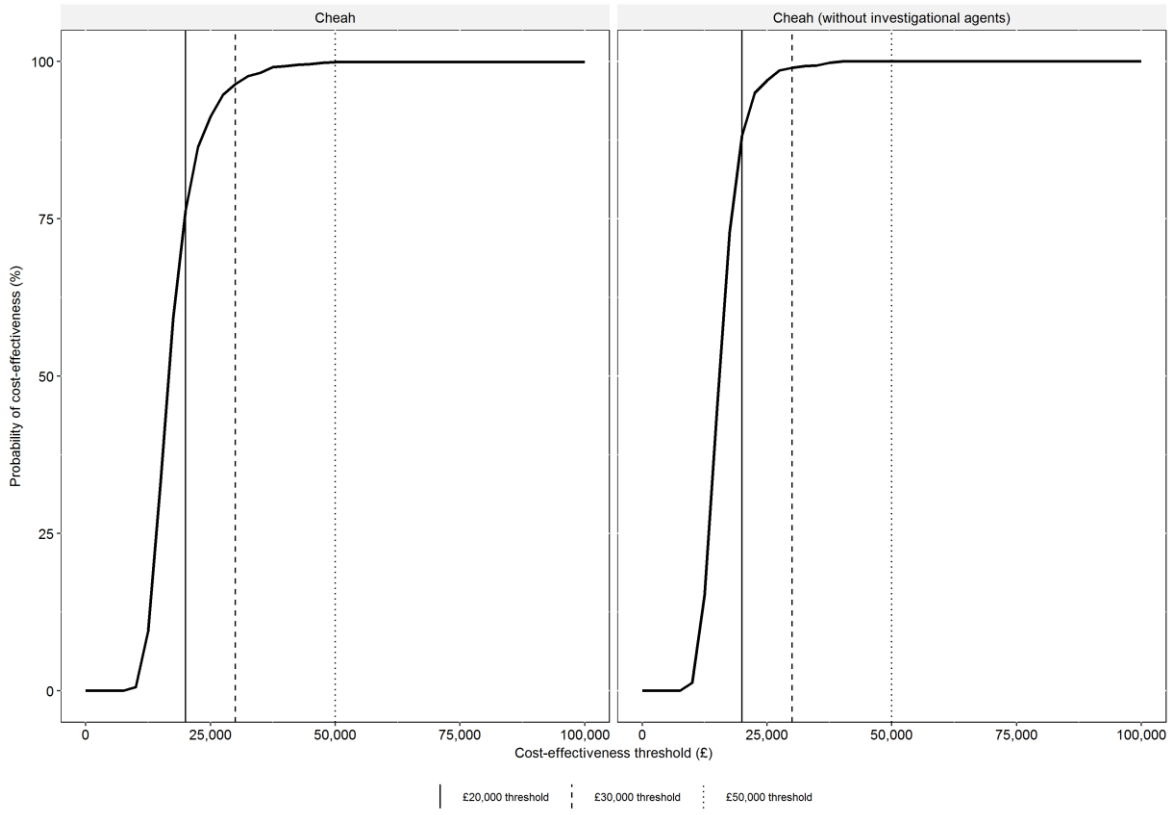


Figure 8 and CEACs are presented in Figure 7, while a summary of the results is provided in ***[redacted]

Table 19. Applying the Cheah overall population, the probability that nivolumab is cost-effective versus SoC is 96.4% at a WTP threshold of £30,000, increasing to 99.9% at a £50,000 threshold. When applying data excluding the impact of investigational agents, the probability that nivolumab is cost-effective versus SoC increases to 99.0% at a WTP threshold of £30,000, or 100% at a £50,000 threshold.

Over the course of the two PSAs, nivolumab was always predicted to be clinically beneficial versus SoC, with incremental QALYs ranging from [redacted]. Accrual of costs was reassuringly stable, resulting in incremental costs of [redacted]

Table 19. Revised base case analysis (with PAS) excluding alloSCT: probabilistic results

	Cheah overall population	Cheah excluding investigational agents
ICER (£/QALY)	£16,785	£15,461
Probability cost-effective at threshold:		
£20,000/QALY	76.3%	88.2%
£30,000/QALY	96.4%	99.0%
£50,000/QALY	99.9%	100%
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.		

Figure 7. Revised base case analysis (with PAS) excluding alloSCT: cost-effectiveness acceptability curve

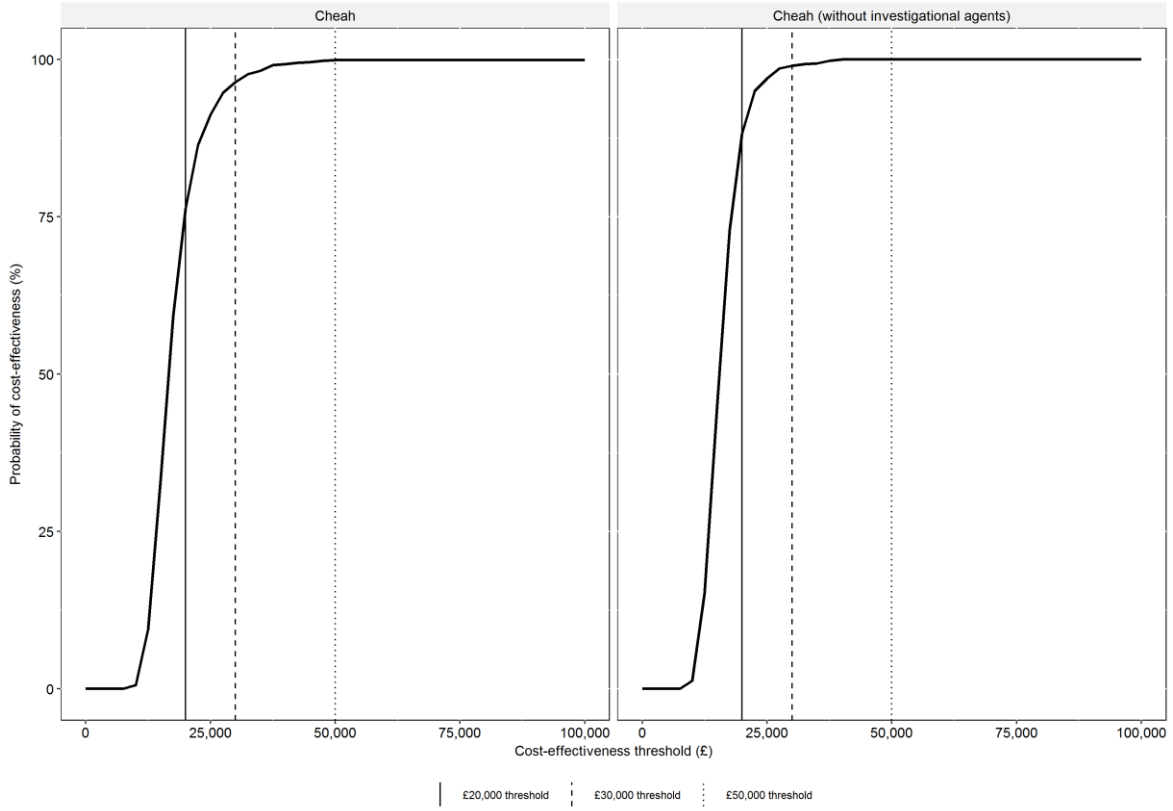


Figure 8. Revised base case analysis (with PAS) excluding alloSCT: cost-effectiveness scatterplot

2. UK data sources

2.1 HMRN

The Appraisal Committee has recommended that analyses should also explore the use of UK data for standard of care (for example, from the Haematological Malignancy Research Network [HMRN]). Prior to submitting to NICE, BMS contacted the HMRN to identify any suitable data, but data was not yet available. In response to the Appraisal Committee's request, BMS contacted the HMRN again in order to assess any progress in availability of data. In response, the HMRN presented a provisional analysis of available cHL patients, presented as Appendix B.[9]

The provisional analysis assessed [redacted] patients who were newly diagnosed with cHL between [redacted]. Complete follow-up ([redacted]) is available for [redacted] of these patients, [redacted]. In newly diagnosed cHL patients, the [redacted], and the [redacted], in line with previous estimates. However, [redacted]. Of these patients, [redacted]. Figure 9 indicates the treatment pathways for patients [redacted]. Median survival from [redacted], as depicted in Figure 10.

Table 20. Patients assessed by HMRN analysis in provisional analysis

	N
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Of the [redacted]. Of the three patients who [redacted], therapy can be considered [redacted]:
[redacted]

Figure 9. HMRN provisional analysis: treatment pathways for cHL patients receiving brentuximab

Figure 10. HMRN provisional analysis: overall survival from initiation of BTX in patients who received prior ASCT

2.2 Clinician survey

As data from the HMRN was limited, BMS was mindful of the request from the Appraisal Committee and elicited the opinions of UK clinicians, with the aim of better understanding treatment pathways in cHL patients in the UK and provide evidence to support additional analyses in line the Appraisal Committee request. BMS conducted a survey with UK physicians ( ) who actively treat relapsed or refractory cHL patients who have previously received ASCT and BTX.

2.2.1 Survey results

The clinician survey demonstrated that there are very few patients in this setting, and treatment patterns are highly individualised and heterogeneous between clinicians.

In terms of composition of SoC, results from the survey show that the . It should be noted that . This supports the views of clinicians at the Appraisal Committee meeting that use of investigational agents would be minimal outside of large treatment centres, leading to disparity of access across the UK. Despite this, composition of other therapies can be considered to that applied in the base case analysis provided in the company submission, indicating that this analysis has direct relevance to the UK setting.

In terms of efficacy, it may be that PFS is slightly using the Cheah et al. 2016 (excluding investigational agents) data (3.6 months versus), while OS is slightly

[redacted] (19.0 months versus [redacted]). Further, clinicians predicted that around [redacted].
This is supported by clinical experts present at the first Appraisal Committee meeting for brentuximab, where survival in relapsed or refractory cHL following ASCT was considered to be less than 24 months.[10]

Further, clinicians predicted that around [redacted].
This is supported by evidence from patients who received PD-1 inhibitors prior to alloSCT (described in Sections 3.1 and 3.2). However, this is [redacted] than described by a UK retrospective case series reporting alloSCT in patients with Hodgkin lymphoma (HL) following at least three prior therapies.[11]

Table 21. Survey of eight UK-based clinicians

[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]

2.2.2 Scenario analysis

In order to address the Appraisal Committee request for analyses exploring the use of UK data, a scenario analysis has been undertaken applying data from this clinician survey. SoC PFS and OS has been derived from median survival provided by clinicians, with utility for SoC derived from the response rates estimated by clinicians. Further, cost of SoC has been derived from the composition suggested by clinicians. All other model inputs are as described in the revised base case analysis.

2.2.2.1 Scenario inputs

2.2.2.1.1 Efficacy of Standard of Care

Efficacy inputs for SoC were derived from the mean response rates reported in the clinician survey. OS and PFS for PFS was similarly derived from the average median survival reported by clinicians. Given the available data, a conservative approach was taken and an exponential curve was fitted to the available median survival, in line with the Bagust and Beale (2014)[12] rationale that an exponential distribution should be considered the default parametric function for long-term survival projection.

Model inputs applied for the clinician survey scenario analysis are presented in Table 22.

Table 22. Overview of efficacy inputs for clinician survey scenario analysis

		Nivolumab cohort	SoC from clinician survey
CR		[redacted]	[redacted]
PR		[redacted]	[redacted]
PFS	Exponential rate	[redacted]	[redacted]
	Median (months)	[redacted]	[redacted]
OS	Exponential rate	[redacted]	[redacted]
	Median (months)	[redacted]	[redacted]
CR: complete response; OS: overall survival; PFS: progression-free survival; PR: partial response; SoC: standard of care.			

2.2.2.1.2 Utility of Standard of Care

In line with the Committee's preferred assumptions around utilities (described in Section 4.17 and 4.18 of the Appraisal Consultation Document[1]), response-specific utility values for both arms were derived from nivolumab patient-level data from CheckMate 205.

Table 23. Response-specific utilities applied in revised base case

	Utility*
Complete Remission	[redacted]
Partial Remission	[redacted]
Stable Disease	[redacted]
Progressed Disease	[redacted]
* applied in both treatment arms	

2.2.2.1.3 Cost of Standard of Care

The composition of SoC was derived applying the reported composition from the clinician survey:

[redacted]

Chemotherapy costs were calculated using the same methods as reported in the company submission, excluding Mini-BEAM and DexaBEAM, in line with the Committee's preferred assumptions. Cost of radiotherapy and palliative care was calculated using NHS Reference Costs 2015-2016.[13]

Table 24. Calculation of radiotherapy costs

Cost	Currency description	Unit cost (£)	Activity cost (£)	Use	Total (£)
Initial cost	SC45Z: Preparation for Simple Radiotherapy with Imaging and Dosimetry	357.01	463.24	75%	347.43
	SC22Z: Deliver a Fraction of Treatment on a Megavoltage Machine	106.24			
	SC45Z: Preparation for Simple Radiotherapy with Imaging and Dosimetry	357.01	489.95	25%	
	SC23Z: Deliver a Fraction of Complex Treatment on a Megavoltage Machine	132.94			
Subsequent costs	SC22Z: Deliver a Fraction of Treatment on a Megavoltage Machine	106.24		75%	122.49
	SC23Z: Deliver a Fraction of Complex Treatment on a Megavoltage Machine	132.94		25%	

Radiotherapy resource use derived from ongoing BTX appraisal[14]
Resource cost from NHS Reference Costs 2015-2016.[13]
Assumed monthly for 12 cycles.

Table 25. Calculation of palliative care costs

Currency	Currency Description	Activity	Unit Cost (£)
SD01A	Inpatient Specialist Palliative Care, 19 years and over	129,869	395.84
SD02A	Inpatient Specialist Palliative Care, Same Day, 19 years and over	32,220	107.84
SD03A	Hospital Specialist Palliative Care Support, 19 years and over	449,808	100.19
SD04A	Medical Specialist Palliative Care Attendance, 19 years and over	75,969	138.45
SD05A	Non-Medical Specialist Palliative Care Attendance, 19 years and over	152,557	75.94
Weighted average			145.23

Resource cost from NHS Reference Costs 2015-2016.[13]
Assumed monthly until progression

Table 26. Therapy costs per cycle

	Cost per cycle	Dosing instructions	Cycle length	Number of cycles
ICE	£1,993.51	every 14 d for two cycles	14	2
IVE	£2,833.51	21 day cycle; 2 cycles	21	2
MINE	£1,683.20	every 28 days; 2 courses	28	2
IVOx	£3,128.47	21 day cycle - 3 cycles	21	3
IGEV	£3,703.72	21 day cycle - 4 cycles	21	4
GEM-P	£2,198.83	28 day cycle; three cycles	28	3
GDP	£1,484.32	21 days; 2 cycles	21	2
GVD	£3,020.85	21 days; 2 cycles	21	2
ESHAP	£1,056.87	every 21-28 d for 4 cycles	28	4
ASHAP	£1,058.87	Assumed 28 day cycle; 3 cycles	28	3
DHAP	£1,204.27	every 21 days for two cycles	21	2
DHAOx	£2,004.77	21 day cycle; 4 cycles	21	4
Bendamustine	£2,096.91	every 28d for 6 cycles	28	6
ChIVPP	£1,082.93	cycle length: 4 weeks; 6 cycles	28	6
GEM-Ox	£2,567.33	14 days; 7 cycles	14	7
BEACOPP	£1,109.59	21 days; 6 cycles	21	6
Gemcitabine	£2,014.33	28 days; 6 cycles	28	6
Palliative care	£145.23	Monthly; ongoing palliative therapy	monthly	-
Radiotherapy	£469.92 initial cost, followed by £106.24	Monthly, for 12 cycles	monthly	12

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BEACOPP: Cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisolone, vincristine, bleomycin; ChIVPP: chlorambucil, vinblastine, procarbazine, prednisolone; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; GEM-Ox: gemcitabine and oxaliplatin; GEM-P: gemcitabine, cisplatin, methylprednisolone; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IVE: ifosfamide, epirubicin, etoposide; IVOx: ifosfamide, etoposide, oxaliplatin; MINE: mitoxantrone, ifosfamide, vinorelbine, etoposide.

Table 27. Cost of SoC applied in clinician survey scenario

	Gem	Bend	Platinum	Alkylator	Radio	Palliative	ChlVPP	Overall
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Bend: bendamustine; ChlVPP: chlorambucil, vinblastine, procarbazine, prednisolone; Gem: gemcitabine-based therapy; Radio: radiotherapy.

2.2.2.2 Scenario analysis results

Deterministic base case analysis results are provided in Table 28. As described for the revised base case analysis, censoring OS at alloSCT results in extended survival in the nivolumab arm, and this is reflected in this scenario analysis.

Similar to the revised base case analysis, survival for patients receiving SoC was estimated to be lower than that derived from Cheah 2016, resulting in shorter OS (1.7 LYs from this scenario analysis versus 2.1 LYs in the overall population and 1.8 LYs in the analysis excluding the impact of investigational agents). However, median PFS was estimated to be longer by clinicians as opposed to Cheah 2016, resulting in longer PFS and longer time on treatment, so that accumulation of pre-progression utilities is slightly increased.

SoC treatment costs were derived from the composition specified by clinicians, and this was lower than that applied in the revised base case analysis, due to increased use of palliative care and radiotherapy. When applied in this scenario, treatment costs are significantly reduced versus the revised base case analysis, and this reduction outweighs the longer time on treatment due to improved PFS.

Overall, these changes have a minimal impact on the predicted cost-effectiveness of nivolumab. The ICER in the revised base case analysis is £14,365 in the Cheah et al. overall population and £13,998 when the impact of investigational agents is excluded. By contrast, the ICER in this scenario increases to £14,677, due to the slightly increased utility and reduced treatment costs in the SoC arm.

Table 28. Scenario analysis results (with PAS): clinician survey

	Comparator	Nivolumab	Incremental
Patient-level progression			
Time in pre-progression (years)	**0.510**	[redacted]	[redacted]
- Time in 4th line (years)	0.451	[redacted]	[redacted]
- Time in post 4th line (years)	0.059	[redacted]	[redacted]
Time in post-progression (years)	**1.205**	[redacted]	[redacted]
Patient-level utility breakdown			
Health state utility	**0.874**	[redacted]	[redacted]
- CR	0.059	[redacted]	[redacted]
- PR	0.145	[redacted]	[redacted]
- SD	0.212	[redacted]	[redacted]
- Progressed disease	0.458	[redacted]	[redacted]
AE disutility	**0.024**	**0.003**	**-0.021**
Age based disutility	**0.002**	**0.231**	**0.229**
Total utilities	**0.848**	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)			
Health state costs	**3,912**	**18,098**	**14,187**
- CR	158	1,173	1,016
- PR	403	1,825	1,423
- SD	602	1,195	593
- Progressed disease	2,749	13,904	11,155
Treatment costs	**9,395**	[redacted]	[redacted]
- 4th line	5,826	[redacted]	[redacted]
- 5th line	3,569	4,953	1,384
AE costs	**2,267**	**268**	**-1,999**
Total costs	**15,573**	[redacted]	[redacted]
Patient-level CE results			
Total QALYs	**0.848**	[redacted]	[redacted]
Total LYs	**1.715**	**7.935**	**6.220**
- Median ToT (years)	0.321	0.809	0.488
- Mean ToT (years)	0.451	1.182	0.731
- Median PFS (years)	0.353	1.160	0.806
- Mean PFS (years)	0.510	[redacted]	[redacted]
- Median OS (years)	1.187	5.806	4.618
- Mean OS (years)	1.715	7.935	6.220
Total Costs (£)	**15,573**	[redacted]	[redacted]
ICER (Cost/QALY)			[redacted]

2.3 Allogeneic stem cell transplantation

The Appraisal Committee has recommended that analyses should be conducted applying a range of alloSCT rates for nivolumab and SoC, and these should be derived from UK data. Using the scenario analysis described in Section 1.2.1 (revised base case analysis) and Section 2.2.2 (UK clinician survey scenario analysis), a range of scenario analyses were conducted (these applied the updated PFS and OS curves derived from a UK retrospective case series reporting alloSCT in patients with HL following at least three prior therapies).[11] In order to explore alloSCT rates relevant to the UK population, rates were applied from the clinician survey detailed in Section 2.2.1.

2.3.1 Scenario analysis

2.3.1.1 UK-specific post-alloSCT survival

In order to obtain data in the UK setting, PFS and OS curves were derived from a UK retrospective case series reporting alloSCT in patients with HL following at least three prior therapies,[11] as described in Section 1.1.5.4.1. These data reflect the high initial mortality in patients with alloSCT, with extended long-term survival. This source was applied as it is UK-specific, and there was limited time available to assess use of alloSCT survival data described in Sections 3.1 and 3.2. It should be noted that these data reflect a slightly lower OS and PFS at one year than can be expected based on the survival following PD-1 inhibitor use, reported in Sections 3.1 and 3.2, and so this use of this data can be considered conservative. Further, these data are reflective of UK clinical practice, and reflect patient selection and the preparative regimens applied in UK clinical practice.

Kaplan-Meier data describing PFS and OS for these patients were digitised, and parametric survival functions were fitted to the extracted data using the R statistics environment. Gompertz was considered the most appropriate fit for both PFS and OS; further, this parametric extrapolation reflected the initial steep hazard, followed by a subsequent decline in hazard.

2.3.1.2 Proportion of patients receiving alloSCT

In order to explore alloSCT rates relevant to the UK population, rates were applied from the clinician survey detailed in Section 2.2.2. Applying these rates, a proportion of patients who are alive and progression-free at six months received alloSCT based on level of response, regardless of treatment arm.

Table 29. Proportion of patients receiving alloSCT at six months

Response	Proportion receiving alloSCT
CR	[redacted]
PR	[redacted]
SD	[redacted]
AlloSCT: allogeneic stem cell transplant; CR: complete response; PR: partial response: SD: stable disease.	

2.3.1.3 Cost and utility of alloSCT

Two alternative costs of alloSCT were applied as described in Section 5.8.3.2 of the company submission, and in Section 1.1.5.4.3 of this appendix.

2.3.1.4 Additional alloSCT scenarios

In order to ensure that alternative estimates of alloSCT are assessed in line with the Committee's recommendations, an additional scenario analysis was also undertaken based on the UK clinician survey analysis, assessing the impact of assuming rates of alloSCT by 10% increments, regardless of response.

2.3.2 Scenario analysis results

Results from this analysis are provided in

Table 30. As can be expected, survival is increased in both treatment arms, with slightly shorter time receiving initial treatment and longer time receiving subsequent treatment. In line with this, cost of initial treatment is decreased, while cost of subsequent treatment is increased.

As previously stated, use of alloSCT has a larger impact in the nivolumab arm, as more patients receive alloSCT in the nivolumab arm than the SoC arm. This is partly due to the higher response rate in the nivolumab arm. However, this is also because PFS and OS are shorter in the SoC arm, so that fewer patients are alive and in pre-progression at six months, lowering the eligible patient population.

Overall, these changes have a relatively small impact on the predicted cost-effectiveness of nivolumab. In scenario 1, where lower initial costs of alloSCT are applied, the ICER is reduced to £12,148 in the UK-specific scenario, £11,388 in the Cheah overall population and £11,216 if the effects on investigational agents are excluded from Cheah 2016; similarly, in scenario 2, the ICER increases to £16,607, £16,770 and £16,236, respectively. Although the ICER is increased in scenario 2, addition of alloSCT to nivolumab can still be considered highly cost-effective. Further, as can be seen in Figure 11, scenario 2 remains cost-effective at a willingness-to-pay threshold even when alloSCT use is increased to 100%.

Figure 11. Scenario analysis: impact of increasing alloSCT use in UK-specific scenario

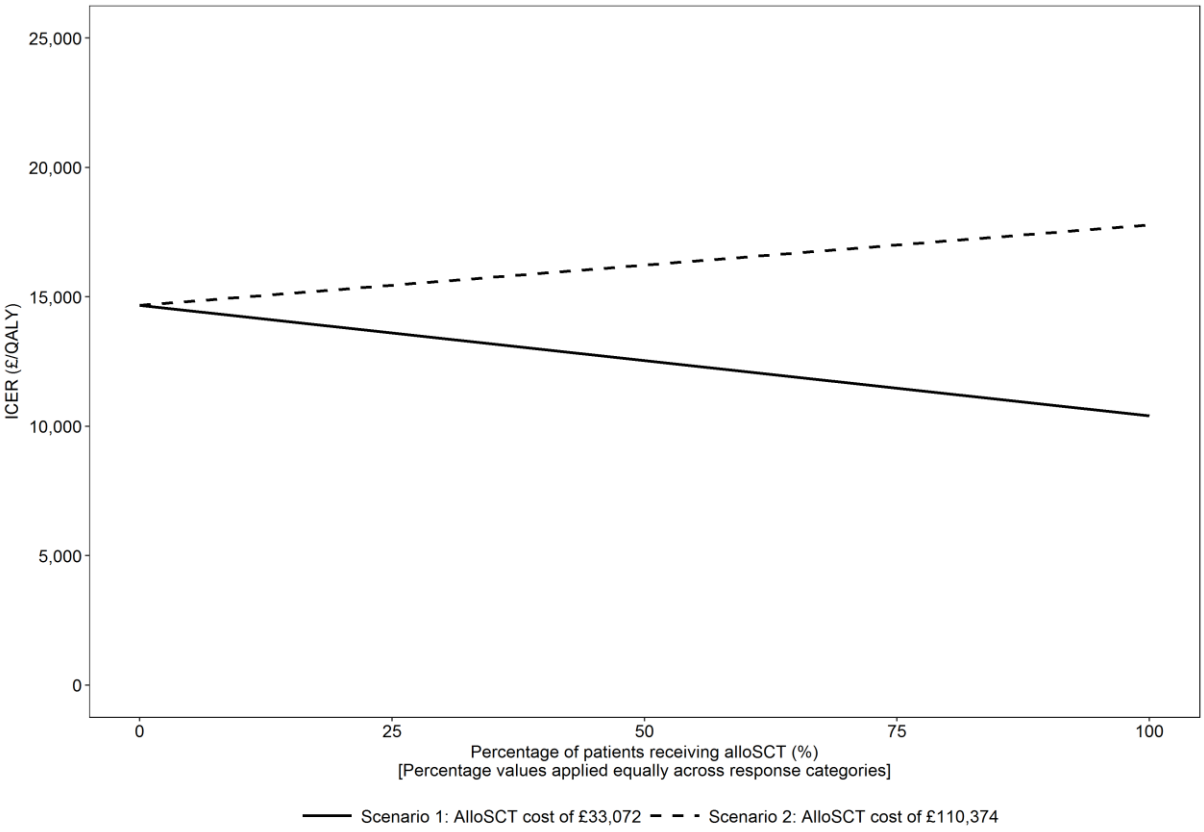


Table 30. Scenario analysis: impact of alloSCT on UK-specific scenario

	Scenario 1			Scenario 2		
	Comparator	**Nivolumab**	**Incremental**	**Comparator**	**Nivolumab**	**Incremental**
Patient-level progression						
Time in pre-progression (years)	1.200	[redacted]	[redacted]	1.200	[redacted]	[redacted]
- Time in 4th line (years)	0.370	[redacted]	[redacted]	0.370	[redacted]	[redacted]
- Time in post 4th line (years)	0.830	[redacted]	[redacted]	0.830	[redacted]	[redacted]
Time in post-progression (years)	1.895	[redacted]	[redacted]	1.895	[redacted]	[redacted]
Patient-level utility breakdown						
Health state utility	2.029	[redacted]	[redacted]	2.029	[redacted]	[redacted]
- CR	0.182	[redacted]	[redacted]	0.182	[redacted]	[redacted]
- PR	0.418	[redacted]	[redacted]	0.418	[redacted]	[redacted]
- SD	0.410	[redacted]	[redacted]	0.410	[redacted]	[redacted]
- Progressed disease	1.020	[redacted]	[redacted]	1.020	[redacted]	[redacted]
AE disutility	0.020	0.002	-0.018	0.020	0.002	-0.018
Age based disutility	0.109	0.397	0.288	0.109	0.397	0.288
Total utilities	1.900	[redacted]	[redacted]	1.900	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)						
Health state costs	7,059	20,041	12,982	7,059	20,041	12,982
- CR	486	2,152	1,666	486	2,152	1,666
- PR	1,124	3,136	2,012	1,124	3,136	2,012
- SD	1,125	1,612	486	1,125	1,612	486
- Progressed disease	4,323	13,141	8,818	4,323	13,141	8,818
Treatment costs	15,600	[redacted]	[redacted]	28,718	[redacted]	[redacted]
- 4th line	5,814	[redacted]	[redacted]	5,814	[redacted]	[redacted]
- 5th line	9,785	19,901	10,116	22,904	52,569	29,665
AE costs	1,862	160	-1,701	1,862	160	-1,701
Total costs	24,521	[redacted]	[redacted]	37,639	[redacted]	[redacted]
Patient-level CE results						
Total QALYs	1.900	[redacted]	[redacted]	1.900	[redacted]	[redacted]
Total LYs	3.095	8.787	5.692	3.095	8.787	5.692
- Median ToT (years)	0.321	0.460	0.139	0.321	0.460	0.139
- Mean ToT (years)	0.370	0.708	0.338	0.370	0.708	0.338
- Median PFS (years)	0.353	0.826	0.473	0.353	0.826	0.473
- Mean PFS (years)	1.200	[redacted]	[redacted]	1.200	[redacted]	[redacted]
- Median OS (years)	1.177	4.502	3.326	1.177	4.502	3.326
- Mean OS (years)	3.095	8.787	5.692	3.095	8.787	5.692
Total Costs (£)	24,521	[redacted]	[redacted]	37,639	[redacted]	[redacted]
ICER (Cost/QALY)	**12,148**			**16,607**		

Table 31. Scenario analysis: impact of UK-specific alloSCT uptake on revised base case analysis

	Cheah						Cheah no inv					
	Scenario 1			Scenario 2			Scenario 1			Scenario 2		
	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental
Patient-level progression												
Time in pre-progression (years)	0.731	[redacted]	[redacted]	0.731	[redacted]	[redacted]	0.848	[redacted]	[redacted]	0.848	[redacted]	[redacted]
- Time in 4th line (years)	0.270	[redacted]	[redacted]	0.270	[redacted]	[redacted]	0.295	[redacted]	[redacted]	0.295	[redacted]	[redacted]
- Time in post 4th line (years)	0.461	[redacted]	[redacted]	0.461	[redacted]	[redacted]	0.553	[redacted]	[redacted]	0.553	[redacted]	[redacted]
Time in post-progression (years)	2.339	[redacted]	[redacted]	2.339	[redacted]	[redacted]	1.885	[redacted]	[redacted]	1.885	[redacted]	[redacted]
Patient-level utility breakdown												
Health state utility	1.672	[redacted]	[redacted]	1.672	[redacted]	[redacted]	1.632	[redacted]	[redacted]	1.632	[redacted]	[redacted]
- CR	0.110	[redacted]	[redacted]	0.110	[redacted]	[redacted]	0.129	[redacted]	[redacted]	0.129	[redacted]	[redacted]
- PR	0.253	[redacted]	[redacted]	0.253	[redacted]	[redacted]	0.295	[redacted]	[redacted]	0.295	[redacted]	[redacted]
- SD	0.251	[redacted]	[redacted]	0.251	[redacted]	[redacted]	0.290	[redacted]	[redacted]	0.290	[redacted]	[redacted]
- Progressed disease	1.058	[redacted]	[redacted]	1.058	[redacted]	[redacted]	0.919	[redacted]	[redacted]	0.919	[redacted]	[redacted]
AE disutility	0.014	0.002	-0.013	0.014	0.002	-0.013	0.016	0.002	-0.014	0.016	0.002	-0.014
Age based disutility	0.067	0.397	0.330	0.067	0.397	0.330	0.075	0.397	0.322	0.075	0.397	0.322
Total utilities	1.591	[redacted]	[redacted]	1.591	[redacted]	[redacted]	1.541	[redacted]	[redacted]	1.541	[redacted]	[redacted]
Patient-level cost breakdown (All figures in £)												
Health state costs	7,001	20,041	13,040	7,001	20,041	13,040	6,233	20,041	13,808	6,233	20,041	13,808
- CR	294	2,152	1,858	294	2,152	1,858	343	2,152	1,809	343	2,152	1,809
- PR	682	3,136	2,454	682	3,136	2,454	793	3,136	2,343	793	3,136	2,343
- SD	691	1,612	920	691	1,612	920	798	1,612	814	798	1,612	814
- Progressed disease	5,334	13,141	7,807	5,334	13,141	7,807	4,299	13,141	8,842	4,299	13,141	8,842
Treatment costs	15,968	[redacted]	[redacted]	23,374	[redacted]	[redacted]	16,864	[redacted]	[redacted]	25,726	[redacted]	[redacted]
- 4th line	8,402	[redacted]	[redacted]	8,402	[redacted]	[redacted]	8,849	[redacted]	[redacted]	8,849	[redacted]	[redacted]
- 5th line	7,566	19,901	12,335	14,972	52,569	37,597	8,015	19,901	11,886	16,878	52,569	35,691
AE costs	1,357	160	-1,197	1,357	160	-1,197	1,482	160	-1,321	1,482	160	-1,321
Total costs	24,326	[redacted]	[redacted]	31,732	[redacted]	[redacted]	24,578	[redacted]	[redacted]	33,441	[redacted]	[redacted]
Patient-level CE results												

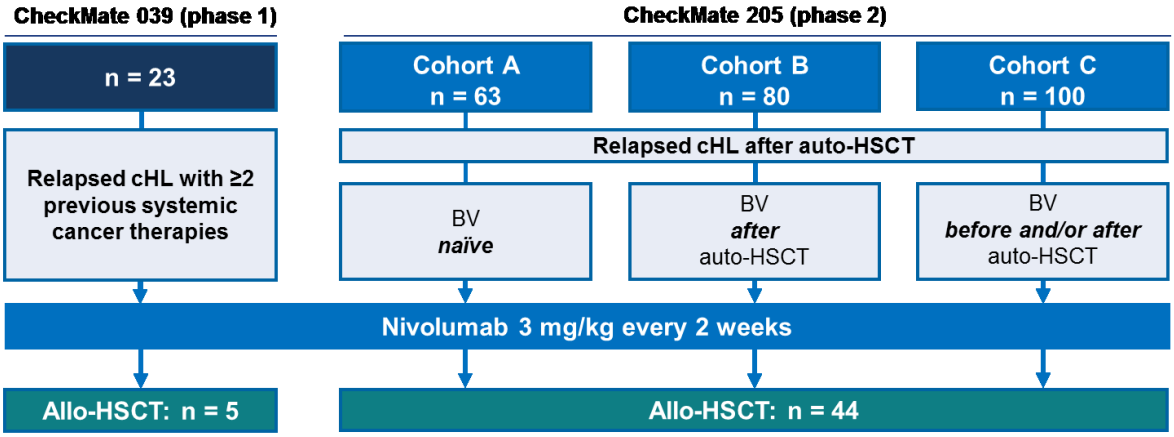
	Cheah						Cheah no inv					
	Scenario 1			Scenario 2			Scenario 1			Scenario 2		
	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental	Comparator	Nivolumab	Incremental
Total QALYs	1.591	[redacted]	[redacted]	1.591	[redacted]	[redacted]	1.541	[redacted]	[redacted]	1.541	[redacted]	[redacted]
Total LYs	3.070	8.787	5.717	3.070	8.787	5.717	2.733	8.787	6.054	2.733	8.787	6.054
- Median ToT (years)	0.215	0.460	0.245	0.215	0.460	0.245	0.239	0.460	0.221	0.239	0.460	0.221
- Mean ToT (years)	0.270	0.708	0.438	0.270	0.708	0.438	0.295	0.708	0.413	0.295	0.708	0.413
- Median PFS (years)	0.225	0.826	0.601	0.225	0.826	0.601	0.252	0.826	0.574	0.252	0.826	0.574
- Mean PFS (years)	0.731	[redacted]	[redacted]	0.731	[redacted]	[redacted]	0.848	[redacted]	[redacted]	0.848	[redacted]	[redacted]
- Median OS (years)	1.599	4.502	2.903	1.599	4.502	2.903	1.243	4.502	3.259	1.243	4.502	3.259
- Mean OS (years)	3.070	8.787	5.717	3.070	8.787	5.717	2.733	8.787	6.054	2.733	8.787	6.054
Total Costs (£)	24,326	[redacted]	[redacted]	31,732	[redacted]	[redacted]	24,578	[redacted]	[redacted]	33,441	[redacted]	[redacted]
ICER (Cost/QALY)	**11,388**			**16,770**			**11,216**			**16,236**		

3. Additional evidence

3.1 AlloSCT in patients receiving nivolumab

As described in Section 4.13.4.1 of the company submission, patients enrolled in the nivolumab studies (CA205-039 and CheckMate 205) could receive alloSCT following nivolumab therapy. An overview of patients receiving alloSCT is provided in Figure 12. Outcomes following alloSCT were collected prospectively in CheckMate 205 and retrospectively in CheckMate 039.[17]

Figure 12. Nivolumab-treated clinical trial patients receiving alloSCT[17]



Evidence has been presented recently (43rd Annual Meeting of the European Society for Blood and Marrow Transplantation, 27th- 29thMarch 2017) describing outcomes for the 49 patients who received alloSCT following receipt of nivolumab in the clinical trial setting[17] (Table 32). Of these, 55% were male and 48 (98%) had previously prior ASCT; the median number of therapies prior to nivolumab was 4. As described in Table 33, the majority of these patients (69.4%) had achieved a CR or PR to nivolumab; however, 27% had received a subsequent therapy after nivolumab and before alloSCT.[17]

Median follow-up was 5.6 months, but ranged between 0 months and 19.0 months, with 49% of patients followed up for at least 6 months and 20% followed up for at least a year. During this time, median OS has not yet been reached. However, of the 49 patients who received alloSCT, 11 have subsequently died; 9 of these patients were classed as transplant-related mortality, while 2 were due to disease progression. Further, 25 patients (51%) experienced acute graft versus host disease (GVHD), of which 13 patients (27%) were classed as Grade 3-4.[17]

Table 32. Overview of nivolumab-treated patients who received alloSCT[17]

Characteristic	Value
N	49
Age, median (min–max) years	31 (18–61)
Male, n (%)	27 (55)
No. of therapies prior to nivolumab, median (min–max)	4 (2–9)
Prior ASCT, n (%)	48 (98)

ASCT: autologous stem cell transplant

Table 33. Characteristics of nivolumab-treated patients who received alloSCT[17]

	Total	CheckMate 039	CheckMate 205
N	49	5	44
Nivolumab doses received, median (min–max)	13 (3–38)	9 (6–13)	13 (3–38)
Best overall response to nivolumab[a]			
CR	8	1	7
PR	26	2	24
SD	11	1	10
PD	4	1	3
Patients who discontinued nivolumab due to disease progression	11 (22%)	1	10
Patients who received therapeutic intervention after nivolumab and before alloSCT	13 (27%)	1	12
Time from last nivolumab dose to alloSCT, median (min–max) months	1.5 (0.4–13.5)	1.4 (0.4–3.1)	1.6 (0.5–13.5)
Disease status at alloSCT[b]			
CR	-	Not collected	21 (48%)
PR	-		19 (43%)
NA/UTD	-		4 (9%)
Follow-up,[c] median (min–max) months	5.6 (0.0–19.0)	11 (3.5–17.0)	5.5 (0.0–19.0)
Patients followed to at least:			
100 days	37 (76%)	5	32
6 months	24 (49%)	3	21
1 year	10 (20%)	2	8

AlloSCT: allogeneic stem cell transplant; CR: complete response; IRRC: Independent Regulatory Review Committee; NA: not available; PD: progressed disease; PR: partial response; SD: stable disease; UTD: unable to determine.
[a]IRRC-assessed; [b]Investigator-assessed; [c]Time from alloSCT to last known date alive

Figure 13. Transplant-related mortality and disease progression in nivolumab-treated patients following progression[17]

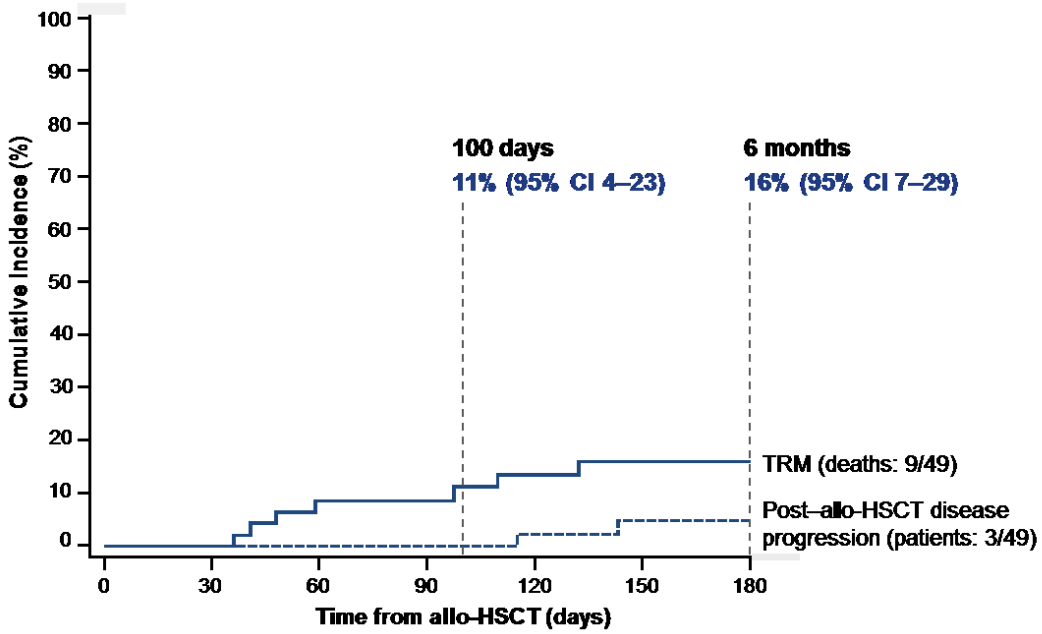
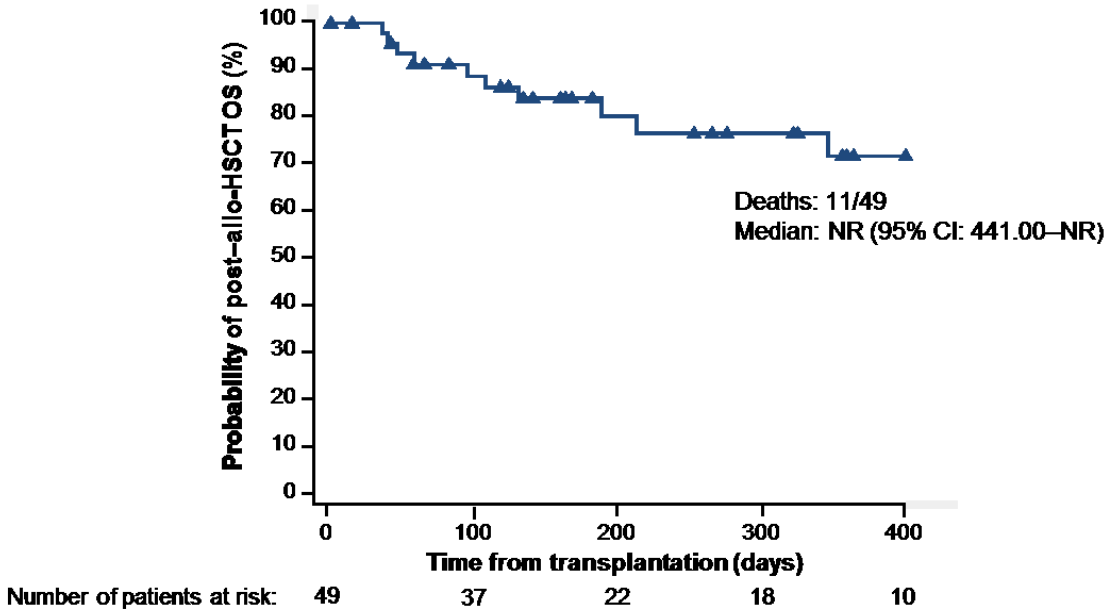


Figure 14. Overall survival in nivolumab-treated patients following progression[17]



3.2 AlloSCT in patients receiving PD-1 inhibitors

In addition to the evidence outlined in Section 3.1, an international retrospective analysis has been conducted assessing the outcomes of patients receiving alloSCT following use of PD-1 inhibitors.[18] As described in Table 34, the study included 39 patients who received nivolumab (72%; 28/39) or pembrolizumab (28%; 11/39) for the treatment of HL or non-Hodgkin lymphoma (NHL) between July 2013 and March 2016 and subsequently underwent alloSCT. A total of 31 patients (79%; 31/39) were transplanted for cHL, while the remainder

were transplanted due to NHL. The median follow-up was 12 months (range 2-33). At one year following alloSCT, OS and PFS were high, at 89% and 76% respectively. [18]

Table 34. Baseline characteristics from Merryman 2017[18]

	Patients (n = 39)
Age at transplant, years (median, range)	34 (21-67)
Number of systemic treatments (median, range)	4 (2-8)
Number of cycles of PD-1 inhibitor (median, range)	8 (3-7)
PD-1 inhibitor received	
Nivolumab	28 (72%)
Pembrolizumab	11 (28%)
Best response to PD-1 inhibitor	
CR	14 (36%)
PR	10 (26%)
SD	7 (18%)
PD	8 (21%)
Patients receiving salvage therapy between PD-1 inhibitor and alloSCT	19 (49%)

Table 35. Outcomes at one-year[18]

Outcome	Overall (n = 39)	HL subgroup (n = 31)
OS, % (95% CI)	89% (74-96)	90% (71-97)
PFS, % (95% CI)	76% (56-87)	74% (50-88)
Incidence of relapse, % (95% CI)	14% (4-29)	16% (3-36)
Non-relapse mortality, % (95% CI)	11% (3-23)	10% (3-25)

3.3 International, multicentre, cross-sectional survey of relapsed or refractory HL treatment pathways

BMS has also undertaken a multicentre, cross-sectional survey of relapsed or refractory cHL patients receiving third- or fourth-line treatment. The study was conducted in [redacted] and consisted of [redacted]. [redacted]. A total of [redacted] UK physicians participated in this study with data on [redacted] extracted.[13]

As shown in Figure 15, for UK patients who received BTX in the third-line setting, the main fourth-line treatment was [redacted], reflecting the heterogeneity of treatment pathways in this population. It should be noted that a [redacted] of patients received [redacted] in this setting, reflecting the paucity of options and the need for efficacious treatments. This composition of

chemotherapy can be considered [redacted] with that described by Cheah (2016) and that evidenced by UK clinicians in the survey described in Section 2.2.2.

Figure 15. Chemotherapy regimens received by UK cHL patients in the fourth-line setting followed by brentuximab in the third-line setting[13]

It is acknowledged that this study has some limitations.

[redacted] This may not be reflected in the patient group depicted in Figure 15.

4. References

1. National Institute for Health and Care Excellence. Appraisal consultation document: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. 2017. Available from: https://www.nice.org.uk/guidance/GID-TA10100/documents/appraisal-consultation-document [accessed 24/03/2017].
2. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209205. Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects After Failure of Autologous Stem Cell Transplant (ASCT). 2016.
3. Bristol-Myers Squibb Pharmaceuticals Ltd. Interim Clinical Study Report for Study CA209039: A Phase 1 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS-936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy. 2016.
4. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016;27(7):1317-23.
5. National Institute for Health and Care Excellence. Final scope for the appraisal of nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. September 2016.
6. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword [accessed 25 January, 2017].
7. National Institute for Health and Care Excellence. Appraisal consultation document: Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/appraisal-consultation-document [accessed 25 January, 2017].
8. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016.
9. Haematological Malignancy Research Network. HMRN-Classical Hodgkin Lymphoma (provisional analysis). 2017.
10. National Institute for Health and Care Excellence. Appraisal consultation document. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/appraisal-consultation-document [accessed 23/03/2017].
11. Lafferty N, Anandram S, Lawes N, et al., editors. Allogeneic Stem Cell Transplantation in Patients with Hodgkin Lymphoma: a Retrospective Single Centre Case Series. British Society for Haemotology 57th Annual Scientific Meeting; 2017; Brighton, UK.
12. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014;34(3):343-51.
13. Department of Health. NHS reference costs 2015 to 2016. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [accessed 30/03/2017].
14. National Institute for Health and Care Excellence. Single Technology Appraisal. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. Committee Papers. 2016. Available from: https://www.nice.org.uk/guidance/GID-TAG467/documents/committee-papers [accessed 03/09/2016].

15. Department of Health. NHS reference costs 2014 to 2015. 2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 [accessed 07/09/2016].
16. Radford J, Johnson R, McKay P, et al. Treatment pathways and resource use associated with the management of recurrent Hodgkin lymphoma after autologous stem cell transplantation. Haematologica. 2013.
17. Carlo-Stella C, Collins GP, Armand P, et al., editors. Allogeneic Hematopoietic Stem Cell Transplantation Outcomes After Nivolumab Monotherapy for Relapsed/Refractory Hodgkin Lymphoma (CheckMate 039 and CheckMate 205). The 43rd Annual Meeting of the European Society for Blood and Marrow Transplantation; 2017; Marseille, France.
18. Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. Blood. 2017;129(10):1380-8.

Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

Evidence Review Group (ERG) commentary on company additional analyses

April 11 2017

Produced by	Southampton Health Technology Assessments Centre (SHTAC) University of Southampton First Floor, Epsilon House Enterprise Road, Southampton Science Park Southampton SO16 7NS
Authors	Mr Micah Rose, Research Fellow (Health economics), Dr Keith Cooper, Senior Research Fellow (Health economics) Dr Joanna Picot, Senior Research Fellow, SHTAC

ERG commentary on company additional analyses

Following the first Appraisal Committee meeting and preliminary decision for the STA of nivolumab for treating relapsed or refractory classical Hodgkin lymphoma, NICE provided the opportunity for the company to comment on the Appraisal Consultation Document (ACD) and requested from the company revised probabilistic cost-effectiveness analyses. The revised cost-effectiveness analyses were to compare nivolumab with standard of care (SoC), incorporating the committee's preferred assumptions regarding the method of indirect comparison, costs and utilities. The use of UK data for standard of care and allogeneic stem cell transplant (alloSCT) rates were also to be explored. The company responded with a 'Response to the Appraisal consultation document' and a separate 'Appendix' to this document. An updated executable version of the company model was not initially submitted but this was obtained on request. The 'Response to the Appraisal consultation document' focuses on responding to the four questions posed at the start of the ACD (Has all of the relevant evidence been taken into account?: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Are the recommendations sound and a suitable basis for guidance to the NHS?; 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 and maternity?) and the 'Response to the Appraisal consultation document: Appendix' contains:

1. The company's revised base case analysis incorporating the Committee's preferred assumptions
2. UK data sources
3. Additional evidence
4. References

At the request of NICE, the ERG has assessed the company's revised base case analysis incorporating the Committee's preferred assumptions and the additional scenario analyses submitted.

The Committee's preferred assumptions for the cost-effectiveness analysis are summarised in Table 1.

Table 1 Summary of the Committee's preferred assumptions from the ACD

ACD section	Summary of preferred assumptions	ERG confirmation of analysis
4.7 Indirect treatment comparison	Provide analyses that explore the use of data available from the UK (for example, from the Haematological Malignancy Research Network) to assess the clinical effectiveness of nivolumab compared with standard of care in the UK	UK specific post-alloSCT survival based on a study of 13 patients, most of whom (12/13) had nodular sclerosing HL not classical Hodgkin's lymphoma. Similarly only 62% (8/13) had prior autoSCT and we don't know whether any received prior brentuximab. Data from HMRN was explored, but [redacted] patients had received both an ASCT and brentuximab vedotin (and [redacted] received brentuximab vedotin as the immediate subsequent treatment following ASCT). Overall [redacted] of [redacted] patients with relapse had an alloSCT [redacted]
4.8 Indirect treatment comparison	Use the overall population of the Cheah study for standard of care in the indirect comparison.	The company used a MAIC with the overall Cheah population adjusted for on all available baseline characteristics (Appendix 1.1.5). We note that limitations of the MAIC noted in the ERG report remain.
4.9 Indirect treatment comparison	Use the matched-adjusted indirect comparison or an alternative indirect comparison method to take account of different distributions of prognostic factors and effect modifiers in the base-case analysis.	
4.12 Modelling survival data	Use results of the matched-adjusted indirect treatment comparison in the base-case analysis because it accounts for differences in the baseline characteristics of the patients in the trials	
4.15 Subsequent alloSCT	Use a range of subsequent allogeneic stem cell transplant rates for both nivolumab and standard of care that are higher than those used in the Cheah and Perrot studies and which are derived from UK data to more accurately predict long-term survival and other outcomes in these patients in the cost-effectiveness analyses.	The company ran analyses using a range of alloSCT rates in ACD Response Appendix Section 2.3.
4.16 Treatment costs	Include the costs of allogeneic stem cell transplant because the survival benefit is captured in the survival data for both arms of the model.	The company ran alloSCT scenarios with two estimates for alloSCT costs.
4.16 Treatment costs	Exclude the costs of mini-BEAM (carmustine, etoposide, cytarabine and melphalan) and DexaBEAM	The company excluded the costs of mini-BEAM and DexaBEAM but used slightly different costs to the

ACD section	Summary of preferred assumptions	ERG confirmation of analysis
	(dexamethasone, carmustine, etoposide, cytarabine and melphalan).	ERG, citing inability to replicate ERG costs. An additional cost analysis was conducted using SoC costs derived from a UK physician survey.
4.17 Utility values	Use the pre-progression utility values used by the ERG in its base case.	The company provided more precise utilities than were available to us when we calculated weighted utilities. The utility scores provided by the company are in compliance with NICE's request.
4.18 Utility values	Use post-progression utility values that are the same across all treatments.	The company complied with NICE's request.
4.19 Results of CEA	Use probabilistic ICERs	Probabilistic ICERs included (appendix table 16), but these were only for the company's revised base case, which did not use alloSCT rates from the UK.
4.20 Results of CEA	Provide an analysis using a range of subsequent allogeneic stem cell transplant rates that more closely match UK practice.	The revised base case analysis uses the proportion of patients receiving alloSCT as from the ERG analyses (company response appendix table 11). UK specific rates (based on the outputs of the clinician survey) were explored in scenario analyses (company response appendix 2.3). A range of rates of alloSCT uptake were presented as deterministic sensitivity analyses.

Error checking the company's submitted analyses

Due to the large number of analyses submitted and the short time period available to the ERG to evaluate the newly submitted model, the ERG has checked only the key models for error. The company did not conduct individual analyses incorporating committee-preferred assumptions one at a time to show their effect on their basecase analysis. Instead, preferred assumptions were consolidated into one analysis, with changes made to the model that were not requested by NICE. The company's revised base case did not incorporate all of the committee's preferred assumptions in that it did not use UK rates of alloSCT. However, the company did conduct analyses that included this preferred assumption in Section 2.3.1 of the Company Response to the ACD Appendix. The company conducted analyses that used two alternative costs, one (Scenario 1) derived from NHS Reference Costs (£33,072) and one (Scenario 2) derived from Radford and colleagues (£110,374). The costs in Scenario 2 derived from Radford and colleagues were considered more realistic by the ERG and more

consistent with current guidelines in development as these are the costs used in the brentuximab vedotin STA. Therefore the ERG has only assessed analyses that use Radford and colleagues cost data for alloSCT (Scenario 2). In addition to using two sets of costs for alloSCT, multiple sets of survival data were used for SoC: survival data from Cheah were used with and without investigational agents, and survival data derived from UK clinician estimates for SoC were used. As the stated preference of the committee was to include investigational agents in SoC, analyses explicitly omitting investigational agents have not be evaluated. The committee did request data derived from UK sources on survival, and the expert opinion of UK clinicians could be a source of this, so the ERG has considered this analysis. The company performed an additional change to the model that was not requested: censoring nivolumab patients who went on to have alloSCT.

The company submitted 13 models, we checked the following three considered most relevant to the NICE committee's preferred assumptions:

- Revised base case, alloSCT Scenario 2 (using alloSCT cost = £110,374) (Section 1.1.2 of ACD Response Appendix, Table 14)
- Clinician survey analysis, alloSCT Scenario 2 (using alloSCT cost = £110,374), SoC survival from Cheah (Section 2.3.2 of ACD Response Appendix, Table 31)
- Clinician survey analysis, alloSCT Scenario 2 (using alloSCT cost = £110,374), SoC survival from clinician survey (Section 2.3.2 of ACD Response Appendix, Table 30)

Table 2 shows the results of these three analyses.

Table 2 Results of key analyses presented by the company in ACD Response Appendix

	Nivolumab		**SoC**		
Scenario	**Costs**	**QALY**	**Cost**	**QALY**	**ICER**
ACD Revised Company Base Case	[redacted]	[redacted]	£23,668	1.212	£15,181
ACD Survey SoC efficacy & alloSCT rates	[redacted]	[redacted]	£37,639	1.900	£16,607
ACD Survey alloSCT rates, Cheah SoC efficacy	[redacted]	[redacted]	£31,732	1.591	£16,773

We identified an influential inconsistency from NICE's preferred analyses that was not disclosed by the company. We believe this was made in error. For both treatment arms, the utility scores after patients discontinued treatment (i.e. transitioned to BSC) were left as in

the company's original base case, instead of being revised to the committee's preferred assumption that that pre-progression utilities be derived from the Checkmate studies and post-progression utilities be identical for all treatments. Table 3 below shows the parameters as they are in the model, and as they should have been according to NICE preferred assumptions.

Table 3 BSC utility inconsistencies between ACD response and NICE preferred assumptions

	Company ACD Response		NICE preferred	
Treatment Specific Health State Utility	**Mean**	**SE**	**Mean**	**SE**
BSC for SoC				
Complete Remission	0.760	0.073	[redacted]	[redacted]
Partial Remission	0.760	0.073	[redacted]	[redacted]
Stable Disease	0.760	0.073	[redacted]	[redacted]
Progressed Disease	0.380	0.028	[redacted]	[redacted]
BSC for Nivolumab				
Complete Remission	[redacted]	[redacted]	[redacted]	[redacted]
Partial Remission	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressed Disease	[redacted]	[redacted]	[redacted]	[redacted]

Company ACD Response results with corrections for errors and non-preferred assumptions

In general, the company analyses were broadly consistent with NICE requests for additional analyses. However, in all analyses the company performed an unrequested adjustment that may bias the analyses in favour of nivolumab. The company censored individual patients in the nivolumab trials if they went on to receive alloSCT. The effect of this was to increase both progression free survival (PFS) and overall survival (OS) for nivolumab. It is unclear whether a similar effect would happen with SoC, as it is not possible to censor SoC patients that went on to receive alloSCT without individual patient data, which is unavailable. It is the opinion of the ERG that censoring OS for nivolumab but not for SoC is methodologically flawed and is less appropriate than leaving intact the potential double counting of benefits (occurring in both arms) from individuals who go on to have alloSCT among those who do not have alloSCT.

The magnitude of differences between survival curves used in the ACD response (See ACD Response Appendix Table 31) and those used in the ERG base case is demonstrated by Figure 1.

Figure 1 Overall survival for the company's revised base case Scenario 2 with UK specific alloSCT uptake and overall Cheah population compared to ERG base case

Figure 1 shows the overall survival curves for SoC and nivolumab for the company's revised base case (Scenario 2) with UK specific alloSCT uptake and the overall Cheah population (ACD Response Appendix Table 31) compared to the ERG base case (reported in the ERG report). The figure shows that the survival of patients with nivolumab are much improved by the company's assumptions with about [redacted] of patients remaining alive after 40 years. The ERG considers the overall survival estimated by the company's base case to be potentially unrealistic for this patient group.

We show how individual changes affect the company model results in Table 4. Correcting for the two modifications not requested by NICE (ie nivolumab censoring and correcting BSC utility values) substantially affects the ICERs of all relevant analyses.

Table 4 Demonstration of effects of individual changes to key assumptions of company model

	Nivolumab		SoC		
Scenario	**Costs**	**QALY**	**Cost**	**QALY**	**ICER**
ERG Base Case	[redacted]	[redacted]	£23,043	2.102	£36,525
ACD Revised Company Base Case (Table 14 ACD Response Appendix)					
ACD Revised Company Base Case	[redacted]	[redacted]	£23,668	1.212	£15,181
--Remove nivolumab censoring	[redacted]	[redacted]	£23,668	1.212	£20,828
--Remove censoring and correct BSC utility values	[redacted]	[redacted]	£23,668	1.870	£26,664
ACD Survey SoC efficacy, alloSCT rates (Table 30 ACD Response Appendix)					
ACD Survey SoC efficacy, alloSCT rates	[redacted]	[redacted]	£37,639	1.900	£16,607
--Remove nivolumab censoring	[redacted]	[redacted]	£37,639	1.900	£20,541
--Remove censoring and correct BSC utility values	[redacted]	[redacted]	£37,639	2.239	£22,900
ACD Survey alloSCT rates, Cheah SoC efficacy (Table 31 ACD Response Appendix)					
ACD Survey alloSCT rates, Cheah SoC efficacy	[redacted]	[redacted]	£31,732	1.591	£16,773
--Remove nivolumab censoring	[redacted]	[redacted]	£31,732	1.591	£20,415
--Remove censoring and correct BSC utility values	[redacted]	[redacted]	£31,732	2.206	£24,623

ERG modifications to the ACD Response

Where possible, we have sought to replicate the key analyses produced by the company and to compare them to the ERG base case.

The ERG considers that the Gompertz curve is not an appropriate curve for modelling either PFS or OS. Both the PFS and OS curves derived using the Gompertz function have points at which it is no longer possible for the survival event to occur (progression for PFS, death for OS). At approximately three years after alloSCT, there is approximately zero chance of progression (graft rejection, disease relapse) if the Gompertz curve is used for post-alloSCT PFS (See Figure 2). Approximately four years after alloSCT, patients in the model do not die

due to the disease (they may still die due to all-cause mortality) if the Gompertz curve is used to estimate OS (See Figure 3). We considered neither of these consequences of choosing the Gompertz curve realistic. Therefore, we suggest alternative curves should be used for post-alloSCT survival.

Figure 2 UK-specific post-alloSCT survival: progression-free survival (ACD Response Appendix, Figure 4)

Figure 3 Uk-specific post-alloSCT survival: disease-specific overall survival (ACD Response Appendix, Figure 3)

When the ERG attempted implementing alternative survival curves to the Gompertz in the company's submitted models, it caused logical and parameter errors to occur. Given the short time horizon available for the ERG to check the models submitted by the company, it was not feasible to identify the source of the errors and correct them. Instead, we have worked backwards from the ERG base case, which was derived from a company submitted model and did not contain the error.

The ERG checked the magnitude of effects on the ERG base case by instituting changes requested by the committee, and changes that the company undertook on their own initiative. Each change was first applied individually to the ERG base case, and then combined to demonstrate that the company analysis could be replicated by working from the ERG base case. The largest effects belonged to censoring of nivolumab patients that go on to have alloSCT and using incorrect utilities for BSC, two elements of the company's analyses that were not requested by NICE. Using NICEs preferred MAIC method of deriving SoC efficacy with only Cheah and nivolumab studies included also had a substantial impact on the ERG base case ICER. Table 5 shows the results of working from the ERG base case

in a stepwise manner. Analysis A is the ERG base case. Analysis B is the company's revised base case submitted in the ACD Response Appendix (Table 14); and Analysis C is the analysis that we believe most closely resembles the preferred committee assumptions in the ACD (ACD Response Appendix, Table 31) as it uses UK-specific rates of alloSCT uptake and SoC efficacy derived from Cheah and colleagues and MAIC. The effects of each of the individual components of the company's revised analysis are shown in analyses 1-6.

Table 5 The effect of NICE preferred assumptions and the company's unrequested model changes on the ERG base case

		Nivolumab		SoC		
#	**Analysis**	**Costs**	**QALY**	**Cost**	**QALY**	**ICER**
A	ERG10 (ERG base case)	[redacted]	[redacted]	£23,043	2.102	£36,525
B	ACD Response Revised Basecase (Scenario 2, inv. Included)	[redacted]	[redacted]	£23,668	1.212	£15,181
C	ACD Response, UK alloSCT rates, Cheah SoC efficacy (Scenario 2, inv. Included) (See ACD Response Table 31)	[redacted]	[redacted]	£31,732	1.591	£16,770
1	alloSCT censoring (nivolumab)	[redacted]	[redacted]	£23,043	2.102	£20,895
2	Incorrect BSC Utilities	[redacted]	[redacted]	£23,043	1.240	£24,166
3	Gompertz curves for post-alloSCT survival	[redacted]	[redacted]	£23,569	2.234	£31,587
4	MAIC using Cheah only for SoC effectiveness	[redacted]	[redacted]	£22,750	1.712	£29,821
5	Company SoC costs	[redacted]	[redacted]	£23,332	2.102	£36,355
6	UK alloSCT rates	[redacted]	[redacted]	£28,224	2.110	£39,754
1+2	All unrequested parameters	[redacted]	[redacted]	£23,043	1.208	£17,177
1+2 +3	All non-recommended parameters (Gompertz curve post alloSCT survival)	[redacted]	[redacted]	£23,569	1.307	£16,414
1 - 5	Should replicate B	[redacted]	[redacted]	£23,674	1.195	£15,102
1 - 6	Should replicate C	[redacted]	[redacted]	£31,042	1.543	£16,699

As shown in Table 5, by working from the ERG base case, we were able to achieve close matches to the ACD Response Appendix Revised Base Case results submitted by the manufacturer (see ACD Response Appendix, Table 14), and the ACD Response Appendix

scenario analysis where UK alloSCT rates were used (as requested by the committee), and Cheah and colleagues efficacy was used for SoC (see ACD Response Appendix, Table 31). These are the combined analyses, i.e. analyses 1-5 and analyses 1-6.

As noted elsewhere, the company had some assumptions that were not requested, errors, and used Gompertz curves to predict post-alloSCT survival that we thought may be unrealistic. We have corrected the following assumptions and errors in the ACD Response Appendix analyses conducted by the company for the analysis which most closely resembles that requested by NICE—this is found in Table 31 in the ACD Response Appendix:

- No censoring of nivolumab patients who went on to have alloSCT
- Utilities as requested by NICE for BSC, and alloSCT
- Gompertz post-alloSCT survival curves replaced with Weibull curves

In addition to modifying assumptions and errors to more closely resemble NICE preferences stated in the ACD, we have run sensitivity analyses around post-alloSCT survival, and run an analysis with no alloSCT. There is substantial uncertainty in the survival of these patients in this population after having alloSCT.

Table 6 ERG analyses in line with NICE preferred assumptions in ACD

Analysis #		Nivolumab		SoC		
	Analysis	**Costs**	**QALY**	**Cost**	**QALY**	**ICER**
0	ERG10 (ERG base case)	[redacted]	[redacted]	£23,043	2.102	£36,525
1	NICE preferred,[1] Gompertz post-alloSCT survival	[redacted]	[redacted]	£30,609	2.161	£24,557
2	NICE preferred,[1] Weibull post-alloSCT survival	[redacted]	[redacted]	£30,213	1.981	£31,031
3	NICE preferred,[1] Lognormal post-alloSCT survival	[redacted]	[redacted]	£30,280	1.997	£30,366
4	NICE preferred,[1] post-alloSCT survival as company alloSCT analyses in CS (derived from Cheah patients with alloSCT)	[redacted]	[redacted]	£32,538	2.598	£17,513
5	NICE preferred,[1] post-alloSCT survival as Cheah whole population (both arms) (Exponential, λ = [redacted])	[redacted]	[redacted]	£29,321	1.745	£47,408
6	NICE preferred,[1] post-alloSCT survival as Nivolumab whole population (both arms)	[redacted]	[redacted]	£29,941	1.904	£34,866

Analysis #		Nivolumab		SoC		
	Analysis	**Costs**	**QALY**	**Cost**	**QALY**	**ICER**
7	NICE preferred,[1] no alloSCT for this population	[redacted]	[redacted]	£19,425	1.693	£28,234
[1]NICE Preferred Analysis assumptions: UK post-alloSCT survival (Lafferty), SoC efficacy (survival and disease response status) derived from MAIC of Cheah and nivolumab studies, utilities and costs as ERG base-case, alloSCT rates from UK (clinician survey)						

Table 6 shows a range of possibilities for the cost-effectiveness of nivolumab, but it is unclear which of these is the most plausible ICER. As the key driver of cost effectiveness is survival, including post-alloSCT, we have shown the the post-alloSCT survival curves used in Analysis 1 – 7 in Figure 4.

Figure 4 Post-alloSCT OS curves

Figure 4 Post-alloSCT OS curves show that the Cheah survival data from alloSCT patients in that study is optimistic, and not likely to be suitable to predict UK outcomes. The Gompertz curve is inappropriate because it flattens out too quickly with no potential deaths due to disease after a certain point in the curve. There is a zero probability of death occurring due to the disease which appears unrealistic. Using the survival data from all patients, in either the nivolumab or the Cheah data does not appear to be consistent with t UK clinical practice in the UK, as represented by clinical expert testimony during the 1st

appraisal committee meeting and by the Lafferty data submitted with the ACD Response Appendix. Therefore, we consider the most appropriate data for post-alloSCT is either the Weibull or Lognormal post-alloSCT OS estimates from Lafferty. There is little difference between these curves, but in the interest of making conservative estimates, the ERG believes that the most plausible ICER for nivolumab compared to SoC is £31,031 per QALY.

Given the small numbers of patients in all analyses of alloSCT survival, caution is warranted. There is also still substantial uncertainty on the effectiveness of nivolumab that makes projection of outcomes without alloSCT problematic. More data are necessary to make any confident predictions of survival in this population group.