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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Micah Rose (Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Petra Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; Maria Chorozoglou (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Joanna Picot (Senior

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AE	Adverse events
AIC	Academic in Confidence
alloSCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
ASHAP	Doxorubicin, methylprednisolone, cytarabine and cisplatin
BMS	Bristol-Myers Squibb
BOR	Best overall response
BSC	Best supportive care
BCSH	British Committee for Standards in Haematology
BTX	Brentuximab vedotin
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
cHL	classical Hodgkin lymphoma
CI	Confidence interval
CIC	Commercial in confidence
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DexaBEAM	Dexamethasone, carmustine, etoposide, cytarabine and melphalan
DHAOx	Dexamethasone, cytarabine and oxaliplatin
DHAP	Dexamethasone, cytarabine and cisplatin
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EPAR	European Public Assessment Report
EQ-5D	EuroQoL five dimension questionnaire
ERG	Evidence Review Group
ESHAP	Etoposide, methylprednisolone, cytarabine and cisplatin
FDA	Food and Drug Administration
GDP	Gemcitabine, vinorelbine and liposomal doxorubicin
GEM-P	Gemcitabine, cisplatin and methylprednisolone
GVD	Gemcitabine, vinorelbine and liposomal doxorubicin
HL	Hodgkin lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
ICE	Ifosfamide, carboplatin and etoposide
ICER	Incremental cost-effectiveness ratio
IGEV	Ifosfamide, gemcitabine and vinorelbine
IPD	Individual patient data
IRRC	Independent regulatory review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IGEV	Ifosfamide, gemcitabine and vinorelbine
IWG	International Working Group
MAIC	Matching-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare products Regulatory Agency
MINE	Mitoxantrone, ifosfamide, vinorelbine and etoposide
MIMS	Monthly Index of Medical Specialities
Mini-BEAM	Carmustine, etoposide, cytarabine and melphalan
mOS	Median overall survival
mPFS	Median progression-free survival
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PET	Positron emission tomography
PFS	Progression free survival
PIM	Promising Innovative Medicine
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QoL	Quality of life
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
ScHARRHUD	School of Health and Related Research Health Utilities Database
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of Care
STA	Single technology appraisal
TA	Technology appraisal
VAS	Visual analogue scale
VBA	Visual Basic for Applications

SUMMARY

Scope of the company submission

The company's submission (CS) on the whole reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE), although evidence is presented for only one of the patient groups included in the NICE scope. The submission focuses on assessing the clinical effectiveness and cost effectiveness of nivolumab for the treatment of adults with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant (ASCT) and brentuximab vedotin. The second population specified in the final scope issued by NICE, "People with relapsed or refractory classical Hodgkin lymphoma following at least 2 prior therapies when autologous stem cell transplant is not a treatment option", is not considered by the CS (presumably because the second population is not encompassed by the proposed indication for nivolumab). Nivolumab therapy is compared to 'Standard of Care' (SoC), which the company defines as being comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine, based on a real-world retrospective study because only single-arm studies of nivolumab are available. The comparator broadly matches one of the comparators described in the NICE scope: "Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine." However, the Evidence Review Group (ERG) notes that there is some uncertainty, due to differences in treatment practices, about how well the real-world retrospective study data based on patients from the USA presented in the submission to represent SoC reflects the experience of patients treated in the UK. In the economic model, patients may receive best supportive care (BSC) as subsequent therapy following nivolumab treatment or the comparator SoC. BSC consists primarily of palliative care, including palliative chemotherapy.

Summary of submitted clinical effectiveness evidence

The company's systematic review of clinical effectiveness identified two relevant non-comparative single-arm studies of nivolumab. In these, nivolumab was administered by intravenous infusion at a dosage of 3mg/kg every two weeks.

- The CheckMate 205 parallel cohort study (phase II) included classical Hodgkin lymphoma patients ≥ 18 years old who failed ASCT. The study has three cohorts: A, B and C. Only patients in cohorts B (n=80) and C (n=100) meet the inclusion criteria for the CS systematic review. The difference between cohorts B and C is that patients in cohort B had brentuximab vedotin treatment after failure of ASCT, whereas patients in Cohort C could have brentuximab vedotin either before or after ASCT. Patients in cohort

A (n=63) were brentuximab vedotin-naïve and therefore they are outside the NICE scope.

- The CA209-039 open-label study (phase I) included 23 patients with classical Hodgkin lymphoma, but only 15 of these patients had received prior ASCT and brentuximab vedotin. Therefore it is the subgroup of 15 patients from this study who meet the population defined in the NICE scope.

The primary outcome in both studies was the objective response rate (ORR) as assessed by the independent regulatory review committee (IRRC) in CheckMate 205, but as assessed by investigators in CA209-039 (both IRRC and investigator assessments of ORR were reported by both studies). Additional outcomes included those listed in the NICE scope [overall survival (OS); progression-free survival (PFS); response rates; adverse effects; health-related quality of life (HRQoL)] as well as outcomes not specified in the NICE scope (e.g. duration of complete response, time to complete response). Both of these single-arm non-comparative studies appear to be of reasonable quality (though by design they are inherently weak) and the ERG believes that it is likely that the company has identified all relevant studies on nivolumab and potential comparators.

CheckMate 205 and CA209-039 are still ongoing and continuing to generate evidence on longer-term outcomes, including OS and PFS. Published and unpublished results are reported in the CS for each study. For CheckMate 205, results have been published for Cohort B [follow-up ≥6 months; insufficient follow-up for interim analysis of cohort C (median follow-up of 2.83 months)] and unpublished results are presented at a later follow-up point for cohort B (median follow-up 15.7 months) and cohort C (median follow-up 8.9 months). For study CA209-039, results from an analysis at median follow-up of 40 weeks have been published and unpublished results are also presented (median follow-up 23.3 months). A large proportion of the clinical effectiveness evidence is academic in confidence (AIC).

Due to the lack of head-to-head data from randomised controlled trials of nivolumab, an indirect comparison approach was required to compare nivolumab to comparators defined in the NICE scope and decision problem. The overall effect of nivolumab was obtained by pooling data from all patients in the CheckMate 205 and CA209-039 studies who had previously received both ASCT and brentuximab vedotin. The nivolumab pooled cohort included data from 193 patients

[CheckMate 205 Cohort B n=80 (median follow-up 15.7 months); CheckMate 205 Cohort C n=98 (median follow-up 9.0 months); CA209-039 n=15 (median follow-up 23.5 months)].

Comparator data were drawn from [redacted] potential comparator studies that were identified by one of the company's systematic reviews. However, of these, [redacted] studies were reported only as conference abstracts and [redacted] The remainder were [redacted]. One retrospective USA database study published in 2016 by Cheah and colleagues was identified in the CS as providing evidence on the outcomes of interest in a population where the majority of patients had received prior ASCT and had failed brentuximab vedotin. This study was used as the primary source of comparator evidence. In this study the [redacted] patients with disease progression either did not receive any further treatment [redacted] or were reported as having received one of the following types of therapy: investigational agent; gemcitabine; bendamustine; other alkylator; brentuximab vedotin retreatment; platinum based; ASCT; and 'other'. The CS speculates that the some of the 'investigational agent' group were likely to have received nivolumab and for this reason the 'investigational agent' group was excluded from some analyses as shown below. The comparator studies contribute to indirect comparisons that were made for four scenarios:

1a) [redacted]

1b) [redacted]

2a) [redacted]

2b) [redacted]

The company conducted both unadjusted indirect comparisons and matching-adjusted indirect comparisons (MAICs) for each of the four scenarios for the outcomes of ORR, CR rate, PR rate, OS, and PFS.

The primary outcome, ORR, was [redacted] for the study defined primary endpoints at the longest follow-up points in both nivolumab studies. The median duration of objective response is reported for cohort B [redacted] at median follow-up of 15.7 months) and cohort C [redacted] at median follow-up of 8.9 months), but as the CheckMate 205 study is still ongoing this is likely to change as more data accrue. [redacted]

[redacted] In the indirect comparisons the ORR for the nivolumab pooled cohort (n=193) was [redacted] compared to [redacted] for the Cheah 2016 study [redacted]). Across all the indirect comparisons conducted (either unadjusted or MAIC and for the four scenarios) the range of values for the comparator ORR range from the [redacted] obtained for the Cheah 2016 study [redacted] to [redacted]. Response outcomes from the unadjusted indirect comparison were used in the economic model base case to stratify pre-progression utility based on response and outcomes from both the unadjusted indirect comparison and the MAIC are used in scenario analyses. IRRS-derived response data are used in a sensitivity analysis.

OS data are not yet complete and median OS has not been reached in either CheckMate 205 cohorts B and C or the CA209-039 study at the longest follow-up periods reported in the CS. In CheckMate 205 Cohort B, there had been [redacted] deaths among the 80 patients at median follow-up of 15.7 months, in Cohort C [redacted] deaths among 103 patients at a median follow-up of 8.9 months and in CA209-039 [redacted] deaths among 15 patients at a median follow-up of 23.3 months. The six-month OS for Cohorts B and C are 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively and in CA209-039 the one year OS rate is [redacted] In the indirect comparisons a median OS period was predicted for the nivolumab pooled cohort of [redacted] (based on extrapolation of the patient level data). In comparison the median OS obtained by unadjusted indirect comparison with the overall Cheah data set was [redacted] (range of values for comparator OS across the different indirect comparisons is [redacted] to [redacted] Overall survival is included in the economic model.

Similarly to OS, PFS data are not yet complete. Median PFS ranges from just over 11 months (CheckMate 205 cohort C, median follow-up 8.9 months) to 14.78 months (CheckMate 205 cohort B IRRC assessment, median follow-up 15.7 months). For the investigator assessments of CheckMate 205 Cohort B and CA209-039 median PFS had not been reached at these time points. In all the indirect comparisons investigator assessments were used, hence in the unadjusted indirect comparison a median PFS was predicted for the nivolumab pooled cohort of [redacted] In comparison the median PFS with the overall Cheah data set was [redacted] (range of values for comparator PFS across the different indirect comparisons, both unadjusted and MAIC, is [redacted] to [redacted] Progression-free survival is included in the economic model.

In both nivolumab studies, patients were able to continue treatment beyond progression if they met pre-specified criteria. The number of patients reported in the CS who have received such treatment is low (CheckMate 205 cohort B at median follow-up of 8.92 months: [redacted] patients; CA209-039 at median follow-up of 23.3 months: [redacted] patients). In all, [redacted] of the [redacted] patients treated beyond progression maintained tumour reduction in the target lesion.

Of the post-ASCT, post-brentuximab vedotin patients who received nivolumab, [redacted] went on to receive allogeneic stem cell transplant (alloSCT). The CS states that there have been no deaths due to disease progression and preliminary evidence available from all patients (i.e. including those in the included studies who are not relevant to this appraisal) who have received post-nivolumab alloSCT suggests that [redacted]. Transplant-related mortality is not reported for the separate cohorts but overall (including those who are not of relevance to this appraisal), among 40 patients undergoing alloSCT, there were six deaths due to transplant-related mortality.

Limited data for health-related quality of life (HRQoL) are presented in the CS from CheckMate 205 cohort B after a minimum follow-up of six months (median follow-up 8.92 months). HRQoL data are not reported for cohort C. In the absence of a comparator arm, these data are difficult to interpret. For the EORTC-QLQ-C30 a minimal important difference (a score difference of 10) is reported in role function at week 9 and in social function and insomnia at week 33. The average EQ-5D visual analogue score (VAS) [redacted] over time and the CS states that it [redacted] the average baseline score by [redacted] minimal important difference from [redacted]

Adverse event data are presented in the CS for the total CheckMate 205 study population [n=240 in cohorts A (not relevant to the decision problem), B and C] and separately for Cohort B, in both cases at the 8.9 month follow-up. For study CA209-039 data are presented for the total population (n=23, so includes eight patients not relevant to the decision problem) from the published 40-week follow up point and the unpublished 23.3 month follow-up. All patients in both studies received at least one dose of nivolumab.

Drug related AEs of any severity grade were reported for 70% of the overall CheckMate 205 population (88% of Cohort B) and 82.6% of CA209-039. Diarrhoea, nausea, fatigue, pyrexia,

rash and pruritus were the most common adverse events in both studies affecting 10% or more of the participants. The majority of these events were of grade 1 or 2. Infusion related reaction stood out as differing between the two studies affecting 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039. In CheckMate 205 there were three Grade 5 AEs (multi-organ failure and two patients with atypical pneumonia and dyspnoea) but no Grade 5 AEs were reported for CA208-039. Laboratory parameter abnormalities were also reported which were mostly Grade 1-2. The most common grade 3-4 haemotological abnormality was decreased lymphocytes in [redacted] (CheckMate 205 18.8% in Cohort B and 13.4% in the overall population[redacted]. The proportion of patients who discontinued nivolumab treatment due to a drug-related adverse event was 3.8% in CheckMate 205 (overall population and Cohort B) and 8.7% in CA209-039. A serious drug-related adverse event was experienced by 9.6% of the CheckMate 205 study (6.3% of Cohort B) and 13.0% of CA209-039.

Identification of AEs of special clinical interest was conducted to characterise any AEs that are potentially associated with the use of nivolumab. Skin abnormalities were the most frequently reported of these adverse events, irrespective of causality, in CheckMate 205 Cohort B (41%). The other categories where more than 10% of the participants experienced an event were: Gastrointestinal abnormalities (26%), hypersensitivity or infusion-related reaction (21%) and endocrine (18%). Most adverse events of special interest were of grades 1 or 2 and no grade 5 events were reported. In CA209-039[redacted]

Summary of submitted cost effectiveness evidence

The CS includes:

i) A review of published economic evaluations of the management of Hodgkin lymphoma in adult patients,

ii) An economic evaluation undertaken for the NICE STA process. The cost effectiveness of nivolumab is compared with that of SoC, comprised of chemotherapy, brentuximab vedotin treatment and bendamustine.

A systematic search of the literature was conducted by the company to identify economic evaluations of the management of Hodgkin lymphoma in adult patients. The review identified 14

studies, but none of them report on nivolumab as an intervention for patients with Hodgkin lymphoma or report on interventions in patients with relapsed or refractory Hodgkin lymphoma following ASCT and treatment with brentuximab vedotin.

The economic evaluation used a semi-Markov survival model (developed in Microsoft Excel) to assess the cost effectiveness of nivolumab compared with SoC in adult patients with relapsed or refractory Hodgkin lymphoma following ASCT and brentuximab vedotin. The model adopted a time horizon of 50 years to capture lifetime costs and health outcomes, with a cycle length of one month and half-cycle correction. The model consisted of three health states: pre-progression, progression and death. Analyses were presented from the NHS and Personal Social Services perspective.

The model uses pooled efficacy data (PFS, OS, treatment response, adverse events) from the CheckMate 205 and CA209-039 studies for the nivolumab arm and from Cheah and colleagues for the SoC arm. The company fitted parametric survival curves to these data for progression free survival and overall survival and selected the most appropriate curves on the basis of the goodness of fit and clinical plausibility. The lognormal function was selected for progression-free survival and the Weibull function for overall survival for the nivolumab arm. The exponential function was selected for pre-progression-free survival and overall survival for the SoC arm. Utility estimates were taken from EQ-5D data obtained from the company's CheckMate 205 study for the nivolumab arm, and from a study by Swinburn and colleagues that used time-trade off methods for the SoC arm.

Nivolumab is administered intravenous and the recommended dose, based on patient weight, is 3.0 mg/kg given once every two weeks. Nivolumab has been provided with a confidential patient access scheme (PAS) price discount in the company analyses.

The results of the economic model were presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-years (QALYs). In the base analysis, the model estimated that there would be an additional 2.8 discounted QALYs for nivolumab compared to SoC. The results of the cost effectiveness analyses with the PAS discount price for nivolumab showed an incremental cost effectiveness ratio (ICER) of £19,882 per QALY compared to SoC (Table 1).

Table 1 Company base case analysis results

Parameters	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
SoC	£21,090	-	0.932	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,882

The ICER with a list price for nivolumab was [redacted] per QALY. In probabilistic sensitivity analyses, the probability that nivolumab is cost-effective versus SoC was 94.8% at a willingness-to-pay threshold of £30,000 per QALY.

The company conducted a large number of scenario analyses. The ERG was unable to replicate some analyses, which led to requests for clarification on how analyses were run and updated analysis parameters from the company. In general, all analyses produced results under £50,000 per QALY and two analyses, that assessed alternative post-progression utility scores, produced results above £30,000 per QALY.

Commentary on the robustness of submitted evidence

Strengths

The company's systematic review of clinical effectiveness was generally of good methodological quality. The ERG does not consider that any key studies of nivolumab or of potential comparators are missing. Two single-arm studies provide evidence for the effectiveness of nivolumab for adults with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin. Twelve studies provide evidence on outcomes following treatments that are considered potential comparators for nivolumab.

The company conducted systematic reviews to identify cost-effectiveness, HRQoL and cost studies and values from this review were utilised in the model. The model structure is generally representative of the clinical pathway for patients with Hodgkin lymphoma.

Weaknesses and Areas of uncertainty

The evidence base for potential comparators is limited in terms of quality (the studies were predominantly phase 1 or 2 single-arm studies), and completeness of reporting (seven only reported as conference abstracts, limited follow-up up periods, outcomes of PFS and OS often not reported). The degree to which the populations in the 12 comparator studies match those in the nivolumab studies and reflect the UK population is also uncertain. As the modelled

comparison between nivolumab and SoC is based on this evidence, rather than a randomised controlled trial, there is considerable uncertainty around modelled efficacy.

There is considerable uncertainty regarding the extent to which the clinical benefits of nivolumab exceed those of potential comparator treatments. This uncertainty is due to the immaturity of the evidence base for nivolumab and comparators and because indirect comparisons are needed due to the absence of direct evidence. The CS base case used a population for SoC that excluded patients that received investigational agents, rather than using the overall population from the Cheah study. Including investigational agents reflects clinical practice and improves the efficacy of SoC.

Additionally, there is uncertainty around the composition of treatments used for patients receiving SoC and therefore the treatment costs for this group are uncertain. The costs for alloSCT have not been included in the base case analysis even though patients received alloSCT in the nivolumab and SoC arms.

Summary of additional work undertaken by the ERG

In order to address the issues identified above we undertook a series of scenario analyses that adapted a company scenario wherein patients could have alloSCT and used the company's higher estimate for alloSCT costs.

Our base case contained the following elements (see Table 2 for results):

- A structure that allowed patients to receive alloSCT treatment, and included both costs and benefits for alloSCT
- alloSCT rates derived from the trials (CheckMate 205 and Cheah and colleagues)
- Pre-progression survival derived from Cheah and colleagues for patients receiving SoC
- Alternative pre-progression utilities based on CheckMate 205 (EQ-5D) and weighted by treatment response for each intervention independently
- Post-progression utilities based on CheckMate 205 (EQ-5D) for all interventions, including alloSCT
- Survival curves modelled using the initial treatment curves for each intervention independently
- SoC treatment costs that assume that patients do not receive treatment with mini-BEAM or DexaBeam

Table 2 ERG base case analysis results

Parameters	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
SoC	£23,043	-	2.102	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	£36,525

The resultant ICER of the ERG base case was £36,525 per QALY gained. The ERG conducted sensitivity analyses on the ERG base case varying treatment costs for SoC, assumptions about the survival curve parameterisations, and the assumptions about treatment response and associated utilities. The ICERs for these additional analyses varied between £25,647 per QALY and £42,226 per QALY.

1 Introduction to the ERG Report

This report is a summary and critique of the company's submission (CS) to NICE from Bristol-Myers Squibb (BMS) on the clinical effectiveness and cost effectiveness of nivolumab (OPDIVO®) for treating relapsed or refractory classical Hodgkin lymphoma. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by NICE and the ERG on 29 November 2016. A response from the company via NICE was received by the ERG on 15 December 2016 and this can be seen in the NICE committee papers for this appraisal.

The ERG found that there were inconsistencies in the marking of data as academic in confidence (AIC) or commercial in confidence (CIC). The same data could be found unmarked in some places, but marked as AIC or CIC in other places in the submission. The ERG has taken a conservative approach and marked up, as AIC or CIC, any unmarked data whenever we were aware it was marked as AIC or CIC elsewhere in the submitted evidence.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG considers that the CS provides a clear and accurate overview of classical Hodgkin lymphoma in section 3 (CS p. 28-32).

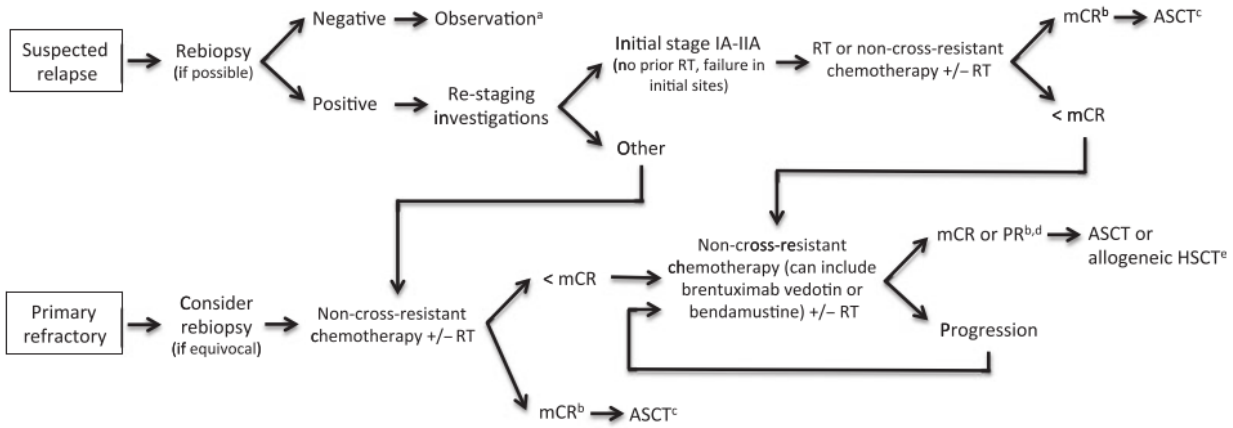
Classical Hodgkin lymphoma is a subtype of Hodgkin lymphoma which is a haematological malignancy that accounts for approximately one in five lymphomas diagnosed. The classical Hodgkin lymphoma type of Hodgkin lymphoma accounts for about 95% of Hodgkin lymphoma with the remaining 5% of Hodgkin lymphoma being nodular lymphocyte-predominant Hodgkin lymphoma. Hodgkin lymphoma has been reported to have a bi-modal age distribution with peaks of cases among people aged 20-24 years and people aged 75-79 years. During 2013 there were 1,954 new cases of Hodgkin lymphoma in the UK and just under half of these (49%) were diagnosed in people aged 45 years or over. The one year survival rate for patients diagnosed in

England and Wales during 2010-2011 is predicted to be 91.4%, with ten-year survival estimated at 80.4%.

2.2 Critique of company's overview of current service provision

The CS provides a clear and accurate overview of current treatment options for people with classical Hodgkin lymphoma (CS section 3.2 p. 28) and cites the British Committee for Standards in Haematology (BCSH) treatment guidelines,[1] stating that these form the best available evidence to inform current clinical practice for the treatment of Hodgkin lymphoma in the UK. The CS notes that NICE are currently appraising the use of brentuximab vedotin for the treatment of two groups of patients with CD30-positive Hodgkin lymphoma: those who have relapsed or refractory disease following ASCT or who are at high risk of residual disease following ASCT; those who have had at least two previous therapies when ASCT or multi-agent chemotherapy is not a treatment option. This guidance is expected to be published in February 2017. The ERG notes that NICE intend to appraise Pembrolizumab for classical Hodgkin lymphoma (expected guidance publication February 2018), but a scope for this STA is not available at the time of writing (December 2016).

The company describes current first-line treatment options for Hodgkin lymphoma and highlights that 15-30% of patients do not achieve long-term remission following first-line therapy, either due to primary refractory disease or relapse. Based on the information provided about the number of new cases of Hodgkin lymphoma in the UK in 2013, this would mean approximately 278-558 of the classical Hodgkin lymphoma patients diagnosed in the UK in 2013 would require salvage therapy at some point in the future. The goal of salvage therapy (chemotherapy and/or radiotherapy) is to achieve a sufficient response such that ASCT can be carried out. The recommended treatment pathway for those who do not achieve long-term remission and who are eligible for ASCT is presented in the CS (Figure 8, p. 29) based on BCSH treatment guidelines[1] and this is reproduced below (Figure 1). However, ASCT is not a treatment option for patients who are unable to achieve a sufficient response or for those who age or co-morbidities prevent ASCT being a treatment option. The clinical experts we consulted suggested that, of those who do not achieve long-term remission following first-line therapy, about 30% would not be eligible for ASCT (due to age or co-morbidities). For the remaining 70%, there would probably be a 70-80% change of achieving a good enough remission for transplant.



[a] clinical factors may warrant intervention
[b] partial response by CT criteria is sufficient for consideration of ASCT although a PET-guided approach is recommended
[c] in selected cases observation may be appropriate, e.g. in those relapsing >5 years from primary therapy; observe if ASCT contra-indicated
[d] those with minimal response or stable disease may be considered appropriate candidates for allogeneic SCT; further attempts at cytoreduction are recommended if ASCT is being contemplated
[e] allogeneic HSCT may be favoured for those requiring >2 lines of salvage therapy to achieve a response, or in those with < mCR

Fig 1. Flow diagram of recommended treatment pathway for patients deemed eligible for potential high dose consolidation therapy. RT, radiotherapy; CT, computerized tomography; PET, positron-emission tomography; mCR, metabolic complete response; PR, partial response; ASCT, autologous stem cell transplantation; HSCT, haematopoietic stem cell transplantation.

Figure 1 BCSH and British Society of Blood and Marrow Transplantation treatment guidelines diagram of the recommended treatment pathway for patients deemed eligible for potential high dose consolidation therapy[1]

ASCT is a potentially curative treatment and it will be effective for about 50% of the people who are eligible to receive it. However, the CS states that outcomes for patients who relapse following ASCT have historically been very poor. The aim of treatment in these patients is to attain a sufficient response to allow consideration of allogeneic stem cell transplant (alloSCT), but again not all patients will be eligible for this route and the most appropriate option for some will be a palliative approach. The BCSH guidelines do not indicate a standard therapy at this point but do indicate that brentuximab vedotin should be considered as a possible treatment option. As noted above, NICE are currently assessing the use of brentuximab vedotin with guidance due to be published in February 2017.

For patients who have failed ASCT and who subsequently receive brentuximab but who do not achieve a response or who achieve only a partial response, there are no currently recommended treatment options and the prognosis remains poor for these patients. It is this patient group who would be eligible to receive nivolumab.

The ERG believes the company has presented an accurate description of current service provision and the treatment options available to patients with Hodgkin lymphoma at different points in the treatment pathway.

2.3 Critique of company's definition of decision problem

The decision problem is summarised in CS Table 1 (p. 13).

Population

The population is defined in the company's decision problem as people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin. This is one of two populations specified in the final scope issued by NICE and the ERG believes that this population is appropriate for the potential use of nivolumab in the NHS. The second population specified in the final scope issued by NICE "People with relapsed or refractory classical Hodgkin lymphoma following at least 2 prior therapies when autologous stem cell transplant is not a treatment option" are not considered by the CS. The CS does not provide a reason for this but the ERG believes that this is because the proposed wording of the license indication for nivolumab is "OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin (BTX)" as described in CS Table 2 (CS p. 15). Thus the second population specified in the final scope issued by NICE is not encompassed by the proposed indication for nivolumab. These patients would predominantly be those over 70 years who are not eligible for transplants and a small proportion of patients under 70 years of age. The clinical experts were not certain how many patients this might be, but estimated perhaps around 300 patients each year.

Intervention

The intervention described in the company's decision problem is nivolumab (brand name: Opdivo®), and this is in line with the final scope issued by NICE. Nivolumab first received marketing authorisation on 19th June 2015 as a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. Since then the licensed indication has been extended to four other indications (CS p. 24) and a positive opinion for nivolumab as monotherapy for the treatment of adult patients with relapsed or

refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin was made available by the Committee for Medicinal Products for Human Use (CHMP) on 13 October 2016. Nivolumab is a monoclonal antibody that acts as a programmed death-1 (PD-1) immune checkpoint inhibitor and, according to the company, "stimulates the patient's own immune system to directly destroy cancer cells" (CS p. 15).

As outlined in the CS Table 3 (p. 25), nivolumab is provided as an intravenous infusion at a dosage of 3mg/kg over a period of 60 minutes every two weeks. Treatment should be continued as long as a clinical benefit is observed or until treatment is no longer tolerated by the patient. An anticipated duration of treatment is not reported in the CS. Dose escalations or dose reductions are not recommended, but dosing delay or discontinuation may be required based on individual safety and tolerability issues. No retreatment with nivolumab is anticipated.

Comparators

The NICE scope describes comparators according to the populations set out in the decision problem. As the CS has only considered the population of people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin, it consequently only considers the comparators relevant for this population. The CS describes the base case comparator as:

- Standard of Care (SoC) - comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine, based on a real world retrospective study by Cheah and colleagues.[2]

This comparator broadly matches one of the comparators described in the NICE scope: “Established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine.” However the ERG notes that there is some uncertainty about how well the Cheah study,[2] which drew on data from patients treated in the USA and which provides the base case comparator data, reflects the experience of patients treated in the UK. There is a lack of detail in the Cheah and colleagues publication about the precise composition of the treatment regimens received by patients who had received ASCT and brentuximab vedotin. Many patients for whom outcome evaluations were available (28/67; 42%) were enrolled onto trial protocols and received what is described as ‘Investigational agent’, but there is no further detail about which therapies may have been classified under this heading. To find

out whether PD-1 inhibitors (such as nivolumab) were included among the 'Investigational agent' treatments, the ERG contacted the authors of the Cheah and colleagues study and were informed that only a couple of patients in the study received PD-1 inhibitors. The next most common regimens received by patients in the Cheah and colleagues study were gemcitabine-based (12/67; 18%) or bendamustine-based (11/67; 16%).

Clinical advice to the ERG suggests that gemcitabine regimens such as GDP (gemcitabine, dexamethasone, cisplatin) are commonly used in this patient population in the UK but platinum-containing regimens such as ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) and DHAP (dexamethasone, cytarabine, cisplatin) are also in common use. In the Cheah study 12/67 (18%) of patients with outcome evaluations received gemcitabine and just 4/67 (6%) of patients received platinum-based regimens.

However, despite the uncertainty about how closely the experience of patients from the USA may match that of patients in the UK, the ERG is not aware of a more appropriate source of data for the comparator population.

In addition to the base case analysis with SoC comparator the model includes scenario analyses comprising:

- SoC including investigational agents
- Chemotherapy only
- Best supportive care (BSC) (Due to the uncertainty around the composition of BSC for the patient group relevant to this STA the composition of BSC is assumed to be chemotherapy, palliative care and participation in clinical trials (CS Section 5.2.2.3 p. 102 and Section 5.5.2.3 p. 131).

Evidence for the clinical efficacy of BSC is not presented within the clinical effectiveness section of the CS (CS section 4, p. 33) and the CS states that evidence to describe the efficacy of BSC in the post-ASCT post brentuximab vedotin classical Hodgkin lymphoma population has not been identified (CS Section 5.3.1, p. 103). The scenario analyses describing BSC were therefore based on the efficacy of SoC.

Outcomes

The company has listed all the outcomes specified in the final scope in their decision problem:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rates [in the CS decision problem this is covered by objective response rate (ORR) and complete response/remission rate (CR) with a note stating that rate of partial response (PR) and stable disease (SD) are also considered of interest]
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

These outcomes are appropriate and clinically meaningful to patients. The ERG considers that the company has included all important outcomes in the decision problem.

Economic analysis

The economic analysis specified in the decision problem matches the final scope and is appropriate for the NHS. The company have conducted a cost-utility analysis with a lifetime horizon which is appropriate for considering differences in costs and outcomes between treatments for patients with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin. Costs are considered from the NHS and Personal Social Services perspective.

On CS page 127 the company state that a Patient Access Scheme (PAS) has been proposed. Approval by the Department of health is stated to have been given in [redacted] for a discount of [redacted] from the nivolumab list price. The economic evaluation presented in the CS applies the PAS in the base case analysis. The comparator is not subject to a PAS.

Other relevant factors

The CS states that no subgroups are specified in the NICE scope and indicates that the CS will provide subgroups for analysis wherever data allows (including age-specific groupings). The CS presents subgroup analysis (two of which are clearly indicated to be post-hoc) in section 4.8 (CS p. 67-68).

The ERG notes that the NICE scope requests that, if the evidence allows, a scenario analysis including alloSCT as a subsequent treatment after nivolumab or its comparators should be considered. The CS does include modelling of scenarios including alloSCT (CS section 5.8.3.2, p. 152).

No equity or equality issues were specified in the final scope or identified by the company. The ERG is not aware of any issues related to equity or equality in the use of nivolumab in patients with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin.

The company highlights that few patients in the 75-79 years age category undergo ASCT so therefore there is very little evidence for patients in this age category who are post-ASCT and post-brentuximab vedotin. Treatment options are stated to be fewer in this age group (which is one of the peaks of Hodgkin lymphoma incidence), so there is a high level of unmet need.

The other peak of Hodgkin lymphoma incidence is in people aged 20-24 years, who would benefit from a therapy that could act as a bridge to alloSCT.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports five systematic literature searches.

- Clinical Effectiveness Search 1 (Appendix 2) (searched from database inception to October 2016)
- Clinical Effectiveness Search 2 (Appendix 4) (searched from database inception to March 2016)
- Cost Effectiveness (Appendix 5) (searched from database inception to March 2016)
- Measurement and valuation of health effects (Appendix 5) (searched from database inception to April 2016)
- Resource identification, measurement and valuation review (Appendix 5) (searched from database inception to April 2016)

The ERG considers the searches overall to be fit for purpose, despite an apparent error in one of the clinical effectiveness strategies. They are reasonably well designed, well documented and transparent (e.g. the numbers of references returned by each line of the search is reported).

The first clinical effectiveness search covered Hodgkin lymphoma linked to post-ASCT and post-brentuximab vedotin interventions. The CS reported this yielded a "paucity" of evidence and undertook a second clinical effectiveness search aimed to identify all treatment options in Hodgkin lymphoma post-ASCT to provide a basis for indirect comparison. Consequently, brentuximab vedotin not overtly linked to ASCT, as in the first search. Core databases were searched for both clinical effectiveness reviews: Embase, Pubmed and the Cochrane Library. Conference proceedings were recorded as searched. Company in-house databases were not recorded as searched. The only ongoing trials databases documented as examined was clinicaltrials.gov.

The searches were constructed with a balance of descriptors and free text terms, including the use of search filters e.g. to limit the results to English Language publications. There is an error in combining sets in the first search documented in Appendix 2 at line 26 " #24 or #25 or #25", this would leave line #23 (which represents the search terms for brentuximab) redundant. It is noted

that these lines are correctly linked in the Pubmed and Cochrane search strategies. The ERG checked Embase with the sets correctly linked and deemed the error in the documented search to be a mere transcription error. Additionally, in mitigation, the second search was designed to retrieve any treatment which would therefore have obviated the error had it occurred. The choice of descriptors and free text and use of truncation were satisfactory. Search filters to identify specific types of trial such as RCTs were not applied to either search. This was in line with the wide trial inclusion criteria of RCTs, non-randomised controlled trials, longitudinal cohort studies and registries. PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) charts were provided for both reviews separately and the text matched the numbers in the diagram. The first search has an end date of October 2016 and the second March 2016 which is inconsistent. The ERG searched Medline, Medline in Process and Embase for nivolumab, since it did not appear in either strategy linked to Hodgkin disease. This did not retrieve additional relevant results that were not already documented in the CS.

The three economic searches to identify cost effectiveness, valuation of health and resource use, contained a balance of free text and descriptor terms with correct truncation and linked sets. Core databases searched included Pubmed, Embase, Cochrane and Econlit. It is noted that NHSEED was not searched separately on the CRD website. It appears from a quick check that it was searched via the Cochrane Library (of which it is one of the constituent databases). It may have been useful to search using only the Hodgkin lymphoma terms specifically on NHSEED since this part of the database just covers economic papers. The same conferences were searched as for the clinical effectiveness searches. The ERG additionally searched ScHARRHUD (the School of Health and Related Research Health Utilities Database) to identify any HRQoL utility papers relating to Hodgkin lymphoma, however nothing further of relevance was identified that was not already referenced in the CS.

In summary, it is considered that the searches conducted by the company to support the systematic reviews in the submission are generally comprehensive and are reported transparently.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The CS clearly states what are described as the “main inclusion criteria” and these are “adult patients with relapsed or refractory cHL following prior ASCT and BTX” (CS p. 33) receiving any

intervention aimed at managing classical Hodgkin lymphoma. Studies could assess any outcome of interest including OS, PFS, CR rate, PR rate, ORR or rate of SD. Unlike the NICE final scope, the inclusion criteria do not explicitly list HRQoL or adverse events (AE) as required outcomes. An overview of the inclusion/exclusion criteria is available in the appendices (CS Appendix 2). The included population is in line with the decision problem and the proposed licensed indication of nivolumab, but as stated earlier only relates to one of the populations listed in the final NICE scope. The company did not specify treatment setting as an inclusion criterion nor place any limits on inclusion relating to the quality of the RCTs, which is appropriate.

The CS includes a flow diagram (CS Figure 9, p. 34) illustrating the number of records included and excluded at each stage of the main systematic literature review (SLR), based on adult patients with relapsed or refractory classical Hodgkin lymphoma and prior ASCT and brentuximab vedotin treatment. The flowchart records 53 additional records identified through other sources, but the nature of the sources is unclear. The company response to clarification request A9 about the nature of the sources, identifies these as conference proceedings. Reasons for the exclusion of full-text publications are detailed in the flow diagram and associated papers are referenced appropriately (CS Appendix 7).

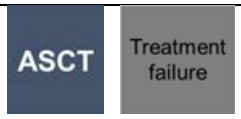
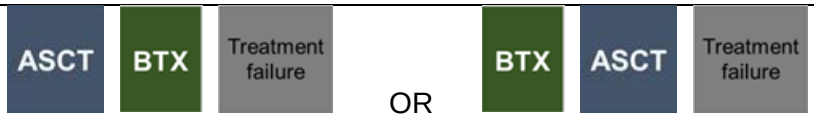
Overall, the ERG considers that the eligibility criteria used in the main systematic review were appropriate and matched the decision problem according to the proposed licensed indication of nivolumab. The SLR is also utilised to inform an indirect treatment comparison (CS Appendix 3). In addition, the company conducted a SLR for the treatment of relapsed or refractory Hodgkin lymphoma with prior ASCT only, i.e. without brentuximab vedotin (CS Appendix 4). This population is not relevant to the decision problem (nor does it meet the proposed licensed indication for nivolumab) and it is therefore not discussed any further by the ERG.

3.1.3 Identified studies

No relevant RCTs evaluating nivolumab for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin were identified. The SLR identified [redacted]. Two of these studies were described as relevant evidence for the effectiveness of nivolumab for the treatment of relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin therapy. Both studies are non-comparative, single-arm studies. All of the [redacted] are included in an indirect treatment comparison presented in the CS (Section3.1.7).

The first study presented in the CS using nivolumab as an intervention is a phase II parallel-cohort study named CheckMate 205,[3,4] which included classical Hodgkin lymphoma patients ≥ 18 years old who failed ASCT, either because of refractory disease or because of disease relapse after ASCT. The study has three cohorts (see Table 3), with patients in cohort B (n=80) and C (n=100) said to be most relevant to the submission (CS section 4.2 p. 36). The ERG agrees that both of these cohorts are of interest, as the NICE final scope does not specify a particular order of treatment with regard to ASCT or brentuximab vedotin. Patients in cohort A (n=63) were brentuximab vedotin-naïve. The study [redacted][3] and is still ongoing. Published and unpublished interim results are available with a data cut-off as of August 2015[3,4] for cohort B (follow-up ≥6 months; insufficient follow-up for interim analysis of cohort C with a median follow-up of 2.83 months) and unpublished results available for cohort B and C with a data cut-off as of April 2016 (median follow-up of 15.7 months and 8.9 months respectively). The CS notes that it is anticipated that additional follow-up results from all cohorts will become available during the NICE appraisal process (CS p. 40).

Table 3 Previous treatment history of cohorts in CheckMate 205

Cohort	Previous treatment history of patient cohorts
A n=63	 • Cohort A patients were brentuximab vedotin-naïve (being naïve to brentuximab vedotin treatment was part of the eligibility criteria for cohort A).
B n=80	 • Cohort B patients had received prior brentuximab vedotin treatment as a salvage therapy after failure of ASCT. Patients with a treatment history of brentuximab vedotin before first ASCT were not eligible for entry into cohort B.
C n=100	 • Cohort C patients could have received prior ASCT and brentuximab vedotin in any treatment order (it was also possible for these patients to have received BTX both before and after ASCT).

ASCT, autologous stem cell transplant; BTX, Brentuximab vedotin.
Table is based on CS Figure 10 p. 39.

The second included study (CA209-039[5,6]) was an open-label, phase I study of nivolumab for the treatment of haematological malignancies, including classical Hodgkin lymphoma. Of the included 23 patients, all had classical Hodgkin lymphoma, but only 15 patients had received previous treatment with both ASCT and brentuximab vedotin and were therefore relevant to the submission (see Table 4). This study was based in the USA and included no UK patients. Published results are available with a cut-off as of 16 June 2014[5] (median follow-up 40 weeks) and unpublished results from the most recent database cut-off (11 August 2015; median follow-up 23.3 months).[6]

Table 4 Summary of study details of the CS included non-RCTs

Parameters	CheckMate 205[3,7,8] Cohort B n=80; Cohort C n=100*	CA209-039[4,6,9] Subgroup n=15
Eligibility criteria (CS p. 40 & p. 57)	• Adults, age ≥18 years • ECOG status 0 or 1 • Prior chemotherapy followed by ASCT as a part of salvage therapy for cHL • Confirmed cHL after failure of ASCT or after ASCT and BTX *Cohort B:* • Failed BTX treatment after failure of ASCT *Cohort C*: • Failed ASCT and prior treatment with BTX at any time point (including as an initial therapy or salvage therapy before ASCT, and/or BTX treatment after ASCT	• Adults, age ≥18 years • ECOG status 0 or 1 • Histological confirmation of relapsed or refractory hematologic malignancy • HL patients ≥1 lesion >1.50 cm + additional lesion for biopsy • >100 days post-ASCT • ≥1 prior chemotherapy, off therapy ≥3 weeks • Prior palliative radiation, completed ≥2 weeks prior study • Prior BTX treatment or BTX-naïve (not required to have failed treatment)
Nivolumab treatment (CS p. 41 & p. 57)	Nivolumab at 3 mg/kg patient's body weight (by IV infusion over 60 minutes) on day one of each two-week cycle (no less than 12 days between doses and no more than three days after the scheduled dosing date). Dose reductions and escalations were not permitted. Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria. Treatment was permanently discontinued according to pre-specified criteria, due to AE,	Nivolumab 3 mg/kg (by IV infusion).The first dose was followed by a three-week evaluation period, with subsequent doses administered every 2 weeks. Dose reductions and escalations were not permitted. Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria.

	preparation for alloSCT or ASCT, or disease progression.	
Design (CS p. 39 & p. 57)	Non-comparative, parallel-cohort, single-arm phase II study	Non-comparative, escalating dose, open-label, single-arm, phase I study
Treatment beyond investigator-assessed disease progression (CS p. 41 & p. 58/59)	Defined by relapsed disease (after CR) or progressive disease. Based on pre-specified criteria, including: • Investigator-assessed clinical benefit and do not have rapid disease progression • Stable performance status • Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression • Tolerance of study drug.	Pre-specified criteria: • Investigator-assessed clinical benefit • Disease progression is not rapid • Stable performance status • Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression • Tolerance of study drug. • Patients have provided written informed consent prior to receiving additional treatment
Length of follow-up (CS p. 45/52 & p. 56)	• Cohort B as of the 20 August 2015 data cut-off date - minimum of six months • Cohort B and C as of the April 2016 data cut-off date - a median follow-up of 15.7 months in cohort B and 8.9 months in cohort C (preliminary analysis of patient-level data)	• Up to 2 years, with the potential for retreatment in eligible patients. Patients with a CR may have continued to receive study therapy until response confirmation or for an additional 16 weeks (whichever is longer) and then enter the follow-up period. • Published data based on a database lock on 16 June 2014 (median follow-up: 40 weeks)[5] • Unpublished data from the most recent database lock (11 August 2015; median follow-up: 23.3 months)[6]

AE, adverse events; alloSCR, allogenic stem cell transplant; ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; cHL, classical hodgkin lymphoma; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response.
* Cohort C included 2 patients that had not previously received Brentuximab vedotin (CS p. 53)

Evidence from the two included studies is provided consecutively in the CS. The ERG has presented the evidence from the two studies side-by-side for a clearer overview where possible.

The CS presents demographics/baseline characteristics and patient disposition for cohort B at data cut-off 20 August 2015 (not reported by the ERG) and at a second later data cut-off April 2016 (see Table 5). For the later data cut-off, the majority of the information is marked AIC. The CS presents the same information for the total population of CA209-039, which includes eight patients who do not meet the licenced indication for nivolumab; all of the patient disposition data is marked AIC. Following a clarification request the company provided patient demographics and baseline characteristics for the subgroup of 15 patients who do meet the licenced indication for nivolumab (Clarification response A5). The ERG reports on the subgroup of 15 patients from CA209-039 who are relevant to the decision problem.

The median age in the two cohorts of the CheckMate 205 study and the post-ASCT post-brentuximab vedotin subgroup of the CA209-039 study varies between [redacted] years and [redacted] years, with mean age only reported in CheckMate 205. The maximum age of patients in CheckMate 205 was higher ([redacted] to 72 years) compared to CA209-039 ([redacted] years). The majority of patients in the two cohorts of CheckMate 205 were aged between 30 and 65 years (cohort C [redacted] in cohort B), and [redacted] of patients are aged 65 or over. A break-down by age groups was not reported in CA209-039. The majority of patients included were white ([redacted] to [redacted]) and predominantly male ([redacted]). The Eastern Cooperative Oncology Group (ECOG) status was fairly similar across the cohorts and subgroup, and nearly equally divided between grade 0 (Fully active, able to carry on all pre-disease performance without restriction) and grade 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work) in the cohorts. Details for the number of prior systemic regimen received by patients was grouped differently in the two studies, but cohort B of CheckMate 205 had the highest proportion of patients ([redacted]) that had received ≥5 prior systemic regimens [redacted] Patients who had received with prior radiotherapy ranged between 70% to 87%.

Cohort B of CheckMate 205 appears to have had a slightly higher proportion of patients with a higher disease stage at study entry and more prior systemic treatments compared to cohort C, which may be related to patients in cohort B being slightly older. However, the ERG notes that there is very little evidence in the CS for the 75 to 79 year age group, as acknowledged in the CS.

Table 5 Baseline characteristics of patients in CheckMate 205 and CA209-039

Parameters n (%)	**CheckMate 205 (April 2016 data cut-off)**		**CA209-039**
	Cohort B (n=80)	**Cohort C** (n=100)	**Post-ASCT, post-BTX subgroup (n=15)**
Age (years), mean (standard deviation)	38.7 (13.00)	[redacted]	NR
Median (Min, Max)	37.0 (18-72)	[redacted]	[redacted]
< 30	27 (33.8%)	[redacted]	NR
≥30 and <65	50 (62.5%)	[redacted]	NR
3 (3.8%)	3 (3.8%)	[redacted]	NR
Gender, male	51 (63.8)	[redacted]	[redacted]
Race			
White	71 (88.8)	[redacted]	[redacted]
Black or African American	4 (5.0)	[redacted]	[redacted]
Asian	1 (1.3)	[redacted]	[redacted]
American Indian Or Alaska Native	0	[redacted]	[redacted]
Native Hawaiian Or Other Pacific Islander	0	[redacted]	[redacted]
Other	4 (5.0)	[redacted]	[redacted]
Ethnicity			
Hispanic Or Latino	1 (1.3)	[redacted]	NR
Not Hispanic Or Latino	63 (78.8)	[redacted]	NR
Not Reported	16 (20.0)	[redacted]	NR
Performance Status - ECOG			

Parameters n (%)	CheckMate 205 (April 2016 data cut-off)		CA209-039
	Cohort B (n=80)	**Cohort C** (n=100)	**Post-ASCT, post-BTX subgroup (n=15)**
0	42 (52.5)	[redacted]	[redacted]
1	38 (47.5)	[redacted]	[redacted]
Disease Stage At Study Entry			
Stage I	1 (1.3)	[redacted]	NR
Stage II	11 (13.8)	[redacted]	NR
Stage III	14 (17.5)	[redacted]	NR
Stage IV	54 (67.5)	[redacted]	NR
Not Reported	0	[redacted]	NR
Bulky Disease At Baseline	17 (21.3)	[redacted]	NR
Extra Lymphatic Involvement At Baseline	36 (45.0)	[redacted]	NR
Bone Marrow Involvement At Baseline	8 (10.0)	[redacted]	NR
Median Time: Initial Diagnosis To First Dose Of Study Therapy, Years (Min – Max)	6.15 (1.3–25.1)	[redacted]	NR
Median Time: Most Recent Transplant To First Dose Of Study Therapy, Years (Min–Max)	3.37 (0.2–19.0)	[redacted]	NR
Number Of Prior Systemic Regimen Received			
≤2	0	[redacted]	[redacted]
3	19 (23.8)	[redacted]	
4	22 (27.5)	[redacted]	[redacted]
≥ 5	39 (48.8)	[redacted]	
≥ 6	NR	[redacted]	[redacted]
Median (Min, Max)	4 (3, 15)	[redacted]	NR
Number Of Prior ASCT			
1	74 (92.5)	[redacted]	NR

Parameters n (%)	CheckMate 205 (April 2016 data cut-off)		CA209-039
	Cohort B (n=80)	**Cohort C** (n=100)	**Post-ASCT, post-BTX subgroup (n=15)**
≥ 2	6 (7.5)	[redacted]	NR
Prior ASCT	80 (100)	100 (100)	[redacted]
Best Response To Most Recent ASCT			
CR Or PR	29 (36.3)	[redacted]	NR
Stable disease	6 (7.5)	[redacted]	NR
Relapse/PD	37 (46.3)	[redacted]	NR
Unable To Determine/Not Reported	8 (10.0)	[redacted]	NR
Best Response To Regimen Post Most Recent ASCT			
CR Or PR	37 (46.3)	[redacted]	NR
Stable disease	10 (12.5)	[redacted]	NR
Relapse/PD	25 (31.3)	[redacted]	NR
Unable To Determine/Not Reported	8 (10.0)	[redacted]	NR
Prior Radiotherapy	59 (73.8)	[redacted]	[redacted]
Prior BTX Therapy	80 (100.0)	[redacted]	[redacted]
Extranodal involvement	NR	NR	[redacted]
Histologic findings			
Nodular sclerosis	NR	NR	[redacted]
Mixed cellularity	NR	NR	[redacted]

ASCT: autologous stem cell transplant; BTX: brentuximab vedotin; ECOG: Eastern Cooperative Oncology Group CI: confidence interval; CR: complete remission; IRRC: independent radiological review committee; NA: not available; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PR: partial remission.
Table based on CS Table 12, p.54 and Table 15, p. 61.

We agree that the three populations presented from the two studies (cohort B and C from CheckMate 205, and the subgroup from CA209-039) meet the inclusion criteria of the review. There are some differences between the studies (and between the two cohorts of CheckMate 205) in patient's baseline characteristics as noted above. However, the ERG is not aware that any of these would have a major impact on the response of the participants to treatment with nivolumab.

Both of the studies were sponsored by the company and copies of all the cited references were received electronically.

3.1.4 Description and critique of the approach to validity assessment

The CS provides two quality assessments for the included non-RCTs, one based on the RCT criteria in the NICE report template[10] and another based on criteria for non-RCTs. The assessments appear to have been based on published data (Younes and colleagues[4] and Ansell and colleagues[5]), which in the case of the CheckMate 205 study only encompasses cohort B, as no cohort C data have been fully published. The ERG assessed both of the studies using the Downs and Black instrument[11] as utilised in the CS, which is one of two methods recommended by Cochrane for the assessment of methodological quality or risk of bias in non-RCTs,[12] based on a systematic review by Deeks and colleagues[13] published in 2003.[12]

The ERG generally agrees with the CS assessment of the studies (Table 6). As the studies are as yet not fully published, there are some minor points of note. Both the studies are ongoing and therefore outcome data will change; the data in the assessed Younes publication (CheckMate 205) was for cohort B only with a cut-off date of August 2015, whereas the CS also provided data for cohort B and C with a later data cut-off (April 2016); and the adverse events data available in the Ansell publication (CA209-039) is for the whole cohort (n=23) and not the subgroup of interest (n=15), although the number of participants in the study is small. The interim clinical study report (CSR)[6] for CA209-039 does report adverse event data for the smaller subgroup, but with a much earlier data cut-off ([redacted]) than the data in the CS. The ERG judged that the external validity of the studies was difficult to determine because details were not reported about the source populations that study participants were recruited from, and it is not known whether there were differences between those who agreed to participate in the studies and those who did not. Most of the criteria for internal validity and confounding are not applicable to one-armed studies (see Table 6).The ERG agrees with the CS in that results of the quality assessment suggest that the two non-comparative, single-arm studies appear to be of reasonable quality (but by design they have serious limitations), although data is largely not peer-reviewed.

Table 6 Company and ERG assessment of trial quality

Description of criteria		Younes (2016) [4] (CheckMate 205, Cohort B)	Ansell (2015) [5] (CA209-039)
Is the hypothesis/aim/objective of the study clearly described?	CS	Yes	Yes
	ERG	Yes	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	CS	Yes	Yes
	ERG	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	CS	Yes	Yes
	ERG	Yes	Yes
Are the interventions of interest clearly described?	CS	Yes	Yes
	ERG	Yes	Yes
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
Are the main findings of the study clearly described?	CS	Yes	Yes
	ERG	Yes	Yes
ERG comment: While both studies are clearly described both studies are ongoing. Published data are based on the pre-specified minimum follow-up period of 6 months for CheckMate 205 cohort B and for a median follow-up of 40 weeks for CA209-039.			
Does the study provide estimates of the random variability in the data for the main outcomes?	CS	Yes	Yes
	ERG	Yes	Yes
ERG comment: Complete 95% CIs are not always available due to the immaturity of the data.			
Have all important adverse events that may be a consequence of the intervention been reported?	CS	Yes	Yes
	ERG	Yes	Yes
ERG comment: Ansell – data available only for the whole population (n=23) not the n=15 post-ASCT post-brentuximab vedotin patients. Data for the subgroup are not reported in the CS but are available in the interim CSR (cut-off date August 2015).[6]			
	CS	Yes	Yes

Description of criteria		Younes (2016) [4] (CheckMate 205, Cohort B)	Ansell (2015) [5] (CA209-039)
Have the characteristics of patients lost to follow-up been described?	ERG	Yes	Yes
Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
External validity			
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	CS	Yes	Yes
	ERG	Unable to determine	Unable to determine
ERG comment: Details of the size and demographics of the source population are not stated, so unable to determine whether participants are representative of the entire population from which they were recruited.			
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	CS	Yes	Yes
	ERG	Unable to determine	Unable to determine
ERG comment: The proportion of the eligible population who agreed to participate was not stated. It is not known whether there were differences between those who agreed to participate and those who did not.			
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	CS	Yes	Yes
	ERG	Yes	Yes
Internal validity – bias			
Was an attempt made to blind study subjects to the intervention they have received?	CS	No	No
	ERG	No	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	CS	No	No
	ERG	No	No

Description of criteria		Younes (2016) [4] (CheckMate 205, Cohort B)	Ansell (2015) [5] (CA209-039)
If any of the results of the study were based on “data dredging”, was this made clear?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
Were the statistical tests used to assess the main outcomes appropriate?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
Was compliance with the intervention/s reliable?	CS	Yes	Yes
	ERG	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	CS	Yes	Yes
	ERG	Yes	Yes
Internal validity - confounding (selection bias)			
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
Were study subjects randomised to intervention groups?	CS	No	No
	ERG	No	No
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
	CS	Not applicable	Not applicable

Description of criteria		Younes (2016) [4] (CheckMate 205, Cohort B)	Ansell (2015) [5] (CA209-039)
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	ERG	Not applicable	Not applicable
Were losses of patients to follow-up taken into account?	CS	Not applicable	Yes[a]
	ERG	Not applicable	Not applicable
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	CS	Not applicable	Not applicable
	ERG	Not applicable	Not applicable
ERG comment: The Younes publication (Cohort B) states the planned sample size of 60 patients provided roughly 93% power to reject the null hypothesis.			

[a] In the assessment of methodological quality of studies presented in CS appendix 2, the judgement differs and is 'not applicable'.
Table based on CS Table 6 p. 38.

3.1.5 Description and critique of company's outcome selection

The outcomes in the CS match those listed in the final NICE scope (CS Table 1, p. 13). The CS lists rate of partial response and stable disease as outcome measures of interest in association with response rates, although objective response rate and complete response rate cover the specified outcome of response rates in the final NICE scope. Other outcomes reported in the CS but not specified in the NICE final scope were:

CheckMate 205:

- Duration of complete response (CR)
- Six-month progression-free survival (PFS) rate
- Six-month overall survival (OS) rate
- Tumour burden change in patients receiving nivolumab beyond progression
- Graft-versus-host disease after post-study transplant

For CA209-039:

- Time to objective response (TTR)
- Time to CR
- Time to PR

Outcome assessments were carried out by investigators, an independent regulatory review committee (IRRC) or both. The primary efficacy endpoint of CheckMate 205 was IRRC-assessed ORR, whereas the primary endpoint of CA209-039 was investigator assessed ORR.

Outcome Definitions

ORR

- IRRC-assessed ORR for CheckMate 205 (primary endpoint) and CA209-039 (secondary endpoint) was defined as the proportion of patients with a best overall response (BOR) of CR or PR, when response was assessed according to the 2007 International Working Group (IWG) criteria.[16]
- Investigator-assessed ORR was a secondary endpoint in CheckMate 205 but ORR was defined in the same way as IRRC-assessed ORR. For CA209-039 investigator assessed ORR was the primary endpoint and also defined as the proportion of the total number of patients whose BOR was either CR or PR however in this case the International Workshop to Standardized Response Criteria for Lymphomas[17] were used for evaluation of response.
- BOR definitions differed
  - CheckMate 205 defined BOR as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent therapy, whichever occurred first. For patients without documented progression or subsequent anticancer therapy, all available response designations contributed to the BOR determination. For patients who continued treatment beyond progression, the BOR was determined based on response designations recorded up to the time of initial progression (CS p.42).
  - CA209-039 defined BOR as the best response between the date of the first dose and the last efficacy assessment before subsequent therapy (CS p. 59).

Duration of response

- CheckMate 205: the time from first response (CR or PR) to the date of the first documented tumour progression (IRRC assessment)
- CA209-039: time between the date of the first response and the date of first progression or the date of death.

PFS

- CheckMate 205: the time from the first dosing date to the date of the first documented tumour/disease progression or death due to any cause, whichever occurred first (IRRC-assessment)
- CA209-039 the time from the date of the first dose of study medication to the date of first disease progression or the date of death.

OS

- CheckMate 205: the time from first dosing date to the date of death.

TTR

- CheckMate 205: not defined
- CA209-039: The time from the date of the first dose to the date of the first response.

Duration of a response

- CA209-039: The time between the date of the first response and the date of first progression or the date of death.

Health-related quality of life (HRQoL) was only measured in CheckMate 205 and only reported for Cohort B (August 2015 data cut-off). Two measures were used, the EORTC-QLQ-C30 questionnaire version 3 to assess cancer-related quality of life (QoL) and the generic health status measure EQ-5D. Both are validated measures. The CS provides a full description of the EORTC-QLQ-C30 items/scales and data interpretation, as well as details for the EQ-5D. Some of the information is marked AIC, although most of the details are freely available.

The EORTC-QLQ-C30 has:

- 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) - higher scores = better HRQoL

- a global health status/quality of life scale: higher scores = better HRQoL
- 3 symptom scales (fatigue, nausea, and pain) - lower scores = better status
- 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties)

Positive change scores indicate improvement in HRQoL compared to baseline. By contrast, lower scores for symptom scales indicate better status; negative change scores indicate improvement in symptoms compared to baseline. The scale scores range from 0 to 100 and a score difference of 10 is used as an estimate of the minimal important difference (MID) for all subscales of the EORTC-QLQ C30 including the symptom scales (analysis was performed on patients who had an assessment at baseline and ≥1 post baseline assessment).

EQ-5D

The EQ-5D visual analogue scale elicits patients' ratings of their health status on a 0 to 100 scale with 0 being the worst imaginable health state and 100 being the best imaginable health state. Utility valuation for application within the economic section is described in Appendix 7 (CS p. 51).

Adverse events

The format of presenting AEs for the two studies in the CS differs, and makes comparisons difficult. For CheckMate 205, a summary of drug-related AEs impacting on ≥10% of the population is presented. However, AEs are only reported for cohort B (n=80, data cut-off August 2015) or the total population (n=240) which includes the cohort A patients who were brentuximab vedotin naive and therefore not relevant to the decision problem. Data are reported for AEs and laboratory parameters, categorised as any grade or grade three to four AEs. Grade five AEs are discussed in text format. For CA209-039, a more detailed account of AEs is provided. A summary of drug-related AEs at the 40-week and the 23.3-month follow-up is provided, albeit for all the twenty-three participants of the study and not the subgroup of 15 post-ASCT post-brentuximab vedotin patients of interest to this submission. AE terms were coded and grouped according to system organ class using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0, and toxicity grade using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Identification of AEs of special clinical interested was conducted to characterise any AEs that are potentially associated with the use of nivolumab. The criteria for identifying these adverse events were:

[redacted]

The adverse events that were identified as being of special interest [redacted]. These were reported under the following group headings [redacted] For CA209-039 these outcomes were tabulated separately in the CS for all patients within 100 days of the last dose of nivolumab at 23.3-months follow-up.

Not all of the outcomes reported in the clinical effectiveness section contributed data to the economic model. Response rates were mostly restricted to use in scenario analyses.

3.1.6 Description and critique of the company's approach to trial statistics

The CS reports the results for all the measured outcomes listed in CS Section 4.7.1.4 (CheckMate, 205, p. 42) and CS Section 4.7.1.4 (CA209-039, p. 57-58). All the data presented are based on interim data and cut-off dates (and relevant population/s in case of CheckMate 205) are clearly stated. The CS notes that further data cuts from these studies are going to be presented as they become available.

The CS reports the statistical methods used to analyse data and the power calculations (CS p. 43-58) that were used to determine sample size. For CheckMate 205, the sample size for cohort B (n=60) was determined in order to produce a confidence interval (CI) which would exclude an ORR of 20% (because an ORR of 20% is not considered clinically relevant) and to provide sufficient safety information (CS p.43). As 80 patients were recruited to cohort B this was adequately powered. The sample size for cohort C however, was empirically determined with the aim of capturing less common safety events. For CA209-039, approximately 23 patients were expected to be enrolled and the possible lower limits for the 90% one-sided CI for ORR, false negative rates and false positive rates were calculated. As the nivolumab studies were single-arm studies there were no within-study comparisons to make with comparator data.

Results are reported narratively and consecutively for the two included studies and summarised using descriptive statistics (e.g. percentages, medians, ranges). Indirect comparisons were conducted to compare the efficacy of nivolumab with comparator data (further details of this reported in Section 3.1.7 below).

With regards to HRQoL, we note that the CS presents limited data for EORTC-QLQ-C30, restricted to weeks with clinically meaningful improvements from baseline for role functioning, social functioning and insomnia. The CS states that [redacted]

There are also limited results reported for the EQ-5D in the clinical effectiveness section, but the CS states that utility valuation for application within the economic model is described in CS Appendix 7.

3.1.7 Description and critique of the company's approach to the evidence synthesis

As stated earlier no randomised trials of nivolumab were identified by the systematic review (CS p. 36), only single-arm studies are available so consequently pairwise meta-analysis is not possible.

A narrative review of the evidence from the key nivolumab studies, CheckMate 205 (cohorts B and C) and study CA209-039 is presented in the CS Section 4 (p. 33 – 69). Where possible the ERG has checked key data presented in the CS against those in the publications[4,5] and found only one minor discrepancy.

To enable comparison of nivolumab against the comparators defined in the NICE scope and decision problem, for which there is no direct evidence, the company conducted an unadjusted indirect comparison and a matching-adjusted indirect comparison (MAIC) (CS p. 70 – 76 and CS Appendix 3).

Evidence on nivolumab was obtained from patient-level data for:

- Cohort B of the CheckMate 205 study (n = 80); median follow-up (OS): 15.7 months.
- Cohort C of the CheckMate 205 study (n = 98; two patients who had not received brentuximab vedotin excluded); median follow-up (OS): 9.0 months.
- Post-ASCT/brentuximab vedotin patients from CA209-039 (n = 15); median follow-up (OS):

23.5 months.

The patient-level data from the patients in each of these groups was combined to create a nivolumab pooled cohort (n=193) (CS Appendix 3 p. 20). The median follow-up period for the nivolumab pooled cohort was not reported.

A systematic review was undertaken to identify studies that could provide comparative effectiveness data on adult patients with relapsed or refractory classical Hodgkin lymphoma, following prior ASCT and brentuximab vedotin, who had subsequently received any intervention aimed at managing classical Hodgkin lymphoma. The identified studies had to report on any outcome of interest including OS, PFS, CR rate, PR rate, ORR or rate of SD (CS p.71).

A total of [redacted] studies (represented by [redacted] citations) met the inclusion criteria for the systematic review, these [redacted] studies included the [redacted] accounting for [redacted] citations). Therefore there were [redacted] studies that met the inclusion criteria and provided information on potential comparator interventions. [redacted] of the [redacted] studies of potential comparators in the post-ASCT post-brentuximab vedotin population were reported only as conference abstracts (the majority from 2014 to 2016 but one dates back to 2012) which present limited data. [redacted] study was [redacted], the remainder were [redacted]. The [redacted] studies published as full papers are:

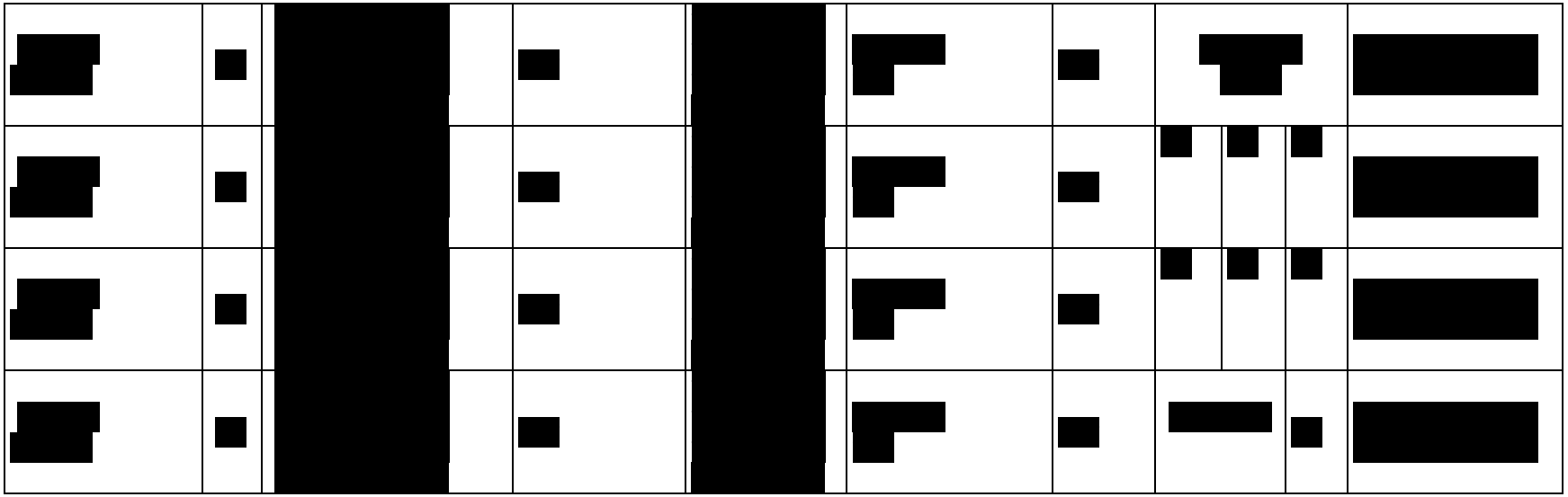
[redacted]

[redacted]

An overview of the [redacted] comparator studies is provided in Table 7.

Table 7 Overview of the potential comparator studies identified by systematic review

First Author (year)	PT	Study design (name)	Cohort size (N)	Patients	Median age (range)	% Male	ECOG, %			Intervention
							0	1	≥2	



The ERG notes that the company did not provide an overview of the similarities and differences between the participants in the comparator studies and those in the nivolumab studies. As can be seen from Table 7 the median age of participants in the comparator studies (where reported) ranges from [redacted] to [redacted] years, which likely represents a [redacted] population than the nivolumab pooled cohort which had a median age of [redacted] years. The proportion of males in the comparator studies ranges from [redacted] to [redacted] (where reported) resulting in an overall proportion of [redacted] male (comparator studies combined) in comparison to [redacted] in the pooled nivolumab cohort which is [redacted]. Data on ECOG performance status was [redacted] of the comparator studies. In the remainder, [redacted] had an ECOG performance status [redacted] which is [redacted] pooled nivolumab cohort, where [redacted] had an ECOG status of [redacted] and [redacted] of [redacted].

All the participants in the nivolumab studies had received a prior ASCT and prior brentuximab. [redacted] the systematic review inclusion criteria to identify comparator studies specified that patients must previously have received ASCT and brentuximab [redacted]

[redacted] of the studies reporting on potential comparators reported survival outcomes for the subgroup of patients who had received prior ASCT and brentuximab. One study, by Cheah and colleagues,[2] was identified in the CS as providing evidence on the outcomes of interest in a population where the majority had received prior ASCT and had failed brentuximab vedotin and was used as the primary source of comparator evidence. Due to the importance of the Cheah and colleagues[2] study within the CS the ERG have summarised its key aspects below.

Cheah and colleagues[2] conducted a retrospective review of their institutional database (at the MD Anderson Cancer Center, Texas) to identify patients who had been treated with brentuximab vedotin

between June 2007 and January 2015. To be included in the study patients had to meet the following criteria:

- A histologically confirmed diagnosis of classical Hodgkin lymphoma
- Treatment with brentuximab vedotin for relapsed Hodgkin lymphoma
- Disease progression at any time after treatment with brentuximab vedotin

The aim of the study was to determine PFS and OS following disease relapse after brentuximab vedotin therapy. Secondary outcomes were to analyse the efficacy of subsequent therapeutic strategies and to explore candidate prognostic factors for PFS and OS.

There is a discrepancy between the abstract and main text of the paper which report either 100 or 97 patients respectively meeting the inclusion criteria for the study. The abstract states that 71/100 patients had prior ASCT [whereas the main text of the paper reports 66/97 (68%) ASCT and 4 (4%) allo-SCT conducted at the time of second remission]. Data were available on subsequent therapy for 83 patients with disease progression following brentuximab vedotin therapy and these data are reproduced below in Table 8. The proportion of patients who had prior ASCT among the 83 patients with disease progression is not reported.

Table 8 Therapies received by patients in the Cheah and colleagues study[2] who had disease progression following brentuximab vedotin therapy (based on CS Table 37, p. 103)

Treatment	n	Evaluated	CR (%)	PR (%)	ORR (%)	mPFS (months)	mOS (months)
Investigational agent	28	28	4 (14)	3 (11)	7 (25)	2.4	47.7
Gemcitabine	15	12	4 (27)	4 (27)	8 (53)	2.1	NR[b]
Bendamustine	12	11	2 (17)	4 (33)	6 (50)	3.7	34.0
Other alkylator	6	4	1 (17)	1 (17)	2 (33)	5.0	9.5
BTX retreatment	6	4	0 (0)	2 (33)	2 (33)	3.5	10.4
Platinum based	4	4	0 (0)	1 (25)	1 (25)	0.9	25.2
ASCT	3	3	1 (33)	0 (0)	1 (33)	[a]	11.9

Other	5	1	0 (0)	0 (0)	0 (0)	[a]	24.9
Overall	**79**	**67 (85%)**	**12 (15)**	**15 (16)**	**27 (34)**	**3.5**	**25.2**
No treatment received	4 due to poor performance status and/or patient decision						
TOTAL	**83**						

ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PR, partial response.

The CS used the data on outcomes from subsequent therapy (Table 8) in two ways in their analyses: using the overall Cheah population (i.e. including efficacy from all the treatments listed above) or using the Cheah population but excluding efficacy data for the n=28 patients who received investigational agents. Because the Cheah study reported an OS Kaplan-Meier curve only for the overall Cheah population, the company had to derive an OS Kaplan-Meier curve for Cheah excluding investigational agents (this is further described in section 4.3.5). It is worth noting that the Cheah study authors did not describe the interventions that constituted their 'Investigational Agent' grouping, however they do indicate that the study period included brief overlap with the availability of PD-1 inhibitors on investigational protocols at their centre. The CS speculates that the 'Investigational Agent' group was therefore likely to have included nivolumab (CS p. 102 and 110). The ERG contacted the authors of the Cheah study and was informed that only a couple of patients in the study received PD-1 inhibitors (although numerical data to support this statement were not provided). The Cheah study authors note that patient selection bias for patients willing and able to travel long distances to an academic centre may limit the generalisability of their findings and that outcomes among other patient groups (e.g. those in community settings), may be less favourable.

As already indicated above, all the participants in the nivolumab studies had received an ASCT in comparison to 68% of participants in the Cheah and colleagues study. In CheckMate 205 cohort C, 33 patients received brentuximab vedotin before ASCT and 8 patients received brentuximab vedotin both before and after ASCT, whereas in the Cheah and colleagues study brentuximab vedotin was only received after relapse of classical Hodgkin lymphoma (Patients' treated with brentuximab vedotin as part of frontline classical Hodgkin lymphoma therapy were excluded).

Indirect comparison was conducted for the outcomes of OS, PFS, CR rate, PR rate and ORR [redacted] The rationale for the selection of outcomes for which indirect comparison was

conducted is not described in the CS or Appendix 3. The comparability of outcome measures across studies was also not reported on and the ERG notes that there were differences in how PFS was defined between the nivolumab studies and Cheah and colleagues.[2] In the two nivolumab studies, PFS was defined as the time from the first dosing date to the date of the first documented tumour progression or death. In contrast, the PFS definition in Cheah and colleagues[2] was the time in months measured from date of confirmed disease relapse following brentuximab vedotin to disease progression or death. NICE and the ERG therefore asked for clarification from the company regarding the time between earlier treatment failure and the first does of nivolumab (clarification questions A2). The company response indicates that the median times from brentuximab vedotin failure to nivolumab treatment in CheckMate 205 cohorts B and C were [redacted] and [redacted] respectively. If the company's definition of PFS had been the same as that reported in Cheah and colleagues (i.e. from date of disease relapse instead of from dates of first nivolumab dosing) then [redacted]. A NICE DSU Technical support document on methods for population-adjusted indirect comparisons was published during the course of this evidence review[30] but it was not available to the company as their submission was prepared.

[redacted]

The data extracted from the [redacted] studies providing comparative effectiveness data for use in indirect comparisons, were used in four scenarios (CS p. 72; Appendix 3 p.21).

1a) [redacted]

[redacted]

The unadjusted indirect comparison (Appendix 3 p. 21)

An unadjusted indirect comparison compares the outcomes from the individual arms of two different studies as if they had been arms in the same RCT. It is generally considered an inappropriate method when an adjusted indirect comparison is possible because a common control group is available. However, in this case the nivolumab studies are single-arm trials and no common comparator is available. The NICE DSU Technical Support Document[30] highlights that an unadjusted indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. Outcomes from unadjusted indirect comparisons were used in the base case of the economic model.

For response rates the unadjusted indirect comparison for scenarios 1a and 1b, where evidence came from [redacted] For scenarios 2a and 2b where [redacted] The NICE DSU Technical Support Document[30] indicates that indirect comparisons should be made on a log transformed scale but it is not clear from the CS whether a log scale was used for the indirect comparison of response outcomes where the comparison is reported as an adjusted relative risk.

[redacted]

[redacted]

The MAIC

MAICs use individual patient data (IPD) from a study of one treatment (in this case pooled data from the single-arm nivolumab studies) to match aggregate (summary) baseline statistics reported from trials of another treatment (in this case from the potential comparator studies). MAIC is a form of propensity score weighting in which individuals in the IPD population are weighted to balance the covariate distribution with that of the aggregate population, so that treatment outcomes can then be compared across balanced study populations. In the CS there are only single-arm studies for both the intervention and comparator, and in this case the indirect comparison is said to be "unanchored" (in contrast, if there is a common comparator arm in each trial in a network the indirect comparison is said to be "anchored"). In theory an unanchored MAIC (i.e. an MAIC where only single-arm study data are available) could improve on an unadjusted indirect comparison by taking into account the different distributions of prognostic factors and effect modifiers in the two studies that are being compared. However, to have confidence that this is the case the MAIC method needs to be used appropriately. [redacted]

[redacted]MAIC outcomes were not used in the base case of the economic model but were used in scenario analyses.

[redacted]

[redacted] The NICE DSU Technical Support Document[30] indicates that MAIC, in common with other types of indirect comparisons, should be made on a log transformed scale, [redacted]

As noted above indirect comparisons, were made for four scenarios:

- [redacted]

[redacted]

[redacted]

Summary of the company's approach to the evidence synthesis

The ERG agrees that, in the absence of data from randomised or controlled trials of nivolumab, an indirect comparison approach is required to compare outcomes of interest following nivolumab treatment to those obtained from the comparators defined in the NICE scope and decision problem.

The ERG also agrees that there is not currently a better published data source for the comparator population than the Cheah and colleagues study.

During the course of the evidence review by the ERG a NICE DSU Technical support document on methods for population-adjusted indirect comparisons was published,[30] but this was not available to the company when the submission was prepared.

The CS has conducted both unadjusted indirect comparisons and MAICs for four scenarios. A MAIC could improve on an unadjusted indirect comparison by taking into account the different distributions of prognostic factors and effect modifiers in the two studies that are being compared.

However, the ERG does not believe that the MAICs reported in the CS are likely to be robust because:

[redacted]

3.2 Summary statement of company's approach

The ERG's quality assessment of the review in the CS is summarised in Table 9. Processes for inclusion or exclusion of studies and for data extraction for the systematic reviews were not described in the CS so NICE and the ERG requested clarification from the company about this (clarification A8). The company responded indicating that both screening and data extraction were conducted by one reviewer and checked by a second reviewer. Where there were discrepancies a third reviewer was involved to provide resolution. The systematic reviews would have been methodologically more rigorous if the first and second reviewer had conducted their screening and data extractions independently (instead of the second reviewer checking what the first reviewer had done) but the ERG accepts that the process that was used was adequate. Included studies were subject to critical appraisal. Overall, the ERG considers the study selection, data extraction and critical appraisal processes to have been adequate and they followed standard accepted review methodology

The ERG concludes that the submitted evidence reflects the decision problem defined in the CS, although the ERG notes that the CS decision problem omits one of the population groups listed in the NICE scope. The ERG considers the overall risk of systematic error in the systematic review to be low.

Table 9 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Inclusion and exclusion criteria are clearly stated.
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes. There was a substantial effort to search for all relevant studies. The restriction of the evidence to English Language only is unlikely to have resulted in any missed studies.
3. Is the validity of included studies adequately assessed?	Yes. Quality assessment (using the Downs and Black instrument) of the two included nivolumab studies is presented in the CS. The ERG assessment agreed with the company assessment. Quality assessment for the comparator studies is presented in CS Appendix 2 (the ERG did not independently check these assessments). As eight of 12 comparator studies were reported as conference abstracts the details necessary for comprehensive quality assessment are likely to be lacking.
4. Is sufficient detail of the individual studies presented?	Yes. Methodology, patient characteristics and outcomes of the included studies are presented in sufficient detail. NICE and the ERG asked the company for details of the subgroup of 15 patients in study CA209-039 (clarification question A5) who had received previous treatment with ASCT and brentuximab vedotin and who were therefore relevant to the decision problem because much of the reporting for this study was for the whole population (n=23). The company provided this information.
5. Are the primary studies summarised appropriately?	Yes. The primary studies are summarised appropriately both for the studies of nivolumab and for the comparator studies with details provided in tables and figures in the main body of the CS or appendices.

3.3 Summary of submitted evidence

In this section the ERG focuses on the main outcomes of the included single-arm studies CheckMate 205 and CA209-039 and the indirect comparisons made with potential comparator studies. There are two data cut-off points for each of the included nivolumab studies as shown in Table 10. The results from the first data cut off dates are published for CheckMate 205, cohort B[4] and CA209-039[5] but other results are not yet published and consequently are still AIC. The CS presents the results of the CheckMate 205 study first, and then the results of the CA209-039 study. For the CA209-039 study the results are reported for the whole population (n=23) instead of for the population that matches that described in the scope for this appraisal (n=15). Where available, the ERG report presents results for the later time points of the studies (i.e. longest follow-up periods), which are based on the interim CSRs.[3,6] Where evidence feeds into the economic model this is indicated and cross-references are provided to the economic section of the ERG report.

Table 10 Data analysis points and duration of follow-up for the included studies

Parameter	CheckMate 205			CA209-039	
	Cohort B		Cohort C		
Database lock	Clinical: 05/10/2015 IRRC: 20/10/2015			16/06/2014 (CS p. 57)	11/08/2015 (CS p. 57)
Data cut-off date	20/08/2015 (CS p. 40)	April 2016 (CS p. 40)	April 2016 (CS p. 40)		
Median follow-up	8.92 months (minimum of 6 months follow-up) (CS p. 46)	15.7 months (CS p. 40)	8.9 months (CS p. 40)	40 weeks (CS p. 57)	23.3 months (CS p. 57)

3.3.1 Summary of response outcomes from CheckMate 205 and CA209-039

The objective response rate assessed by the IRRC was the primary efficacy endpoint of the CheckMate 205 study whereas the primary efficacy endpoint of CA209-039 was the investigator assessed objective response rate.

The objective response rate was [redacted] at the later time points in both studies and [redacted] for the study defined primary endpoints (Table 11). There were slight differences [redacted] between the IRRC and investigator assessed objective response rates for cohorts B and C of the

CheckMate 205 study, whereas [redacted] in the CA209-039 study where investigators and IRRC used different versions of response criteria to assess response outcomes. Differences between investigator and IRRC assessments were greater in the CheckMate 205 study when considering complete and partial remission outcomes individually.

[redacted]

Median time to response in CA209-039 [redacted] For CheckMate 205 median time to response was only reported for Cohort B at the earlier follow-up period (median 3.92 months, minimum of 6 months) where the median time to objective response was just over 2 months (2.10 months by IRRC assessment and 2.17 month by investigator assessment). The time to complete remission was approximately 4.5 months (4.44 months by IRRC assessment and 4.75 months for investigator assessment). All responses were achieved within six months of treatment initiation and 58.5% of the 53 responders had achieved a response by the time of their first scan (9 weeks).

Table 11 Response outcomes from CheckMate 205 and CA209-039

Parameter	CheckMate 205				CA209-039	
	Cohort B (n=80) Median follow-up 15.3 months		Cohort C, (n=100) Median follow-up 8.9 months		Post BTX/ASCT (n=15) Median follow-up 23.3 months	
Primary endpoint (in bold type)	**IRRC**	**Investigator**	**IRRC**	**Investigator**	**IRRC**	**Investigator**
Objective response rate, n (%)	**54 (67.5)**	[redacted]	**73 (73.0)**	[redacted]	9 (60)	**13 (87)**
(95% CI)	**(57.2, 77.8)**	[redacted]	**(64.3, 81.7)**	[redacted]		[redacted]
Additional endpoints						
Duration of response: events	[redacted]	[redacted]	[redacted]	[redacted]		

Median duration of response, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time to response, months					[redacted]	[redacted]
CR, n (%)[a]	6 (7.5)	[redacted]	17 (17.0)	[redacted]	0	2 (13)
PR, n (%)[a]	48 (60.0)	[redacted]	56 (56.0)	[redacted]	9 (60)	11(73)
SD, n (%)[a]	17 (21.3)	[redacted]	17 (17.0)	[redacted]	5 (33)	2 (13)
Relapsed or PD, n (%)[a]	7 (8.8)	[redacted]	[redacted]	[redacted]		
UTD/NA, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of CR: events	[redacted]	[redacted]	[redacted]	[redacted]		
Median duration of CR, months	[redacted]	[redacted]	[redacted]	[redacted]		
Median time to CR, months					[redacted]	[redacted]
Duration of PR: events	[redacted]	[redacted]	[redacted]	[redacted]		
Median duration of PR, months	[redacted]	[redacted]	[redacted]	[redacted]		
Median time to PR, months					[redacted]	[redacted]

BTX, brentuximab vedotin; CI, confidence interval; CR, complete remission; IRRC, independent radiological review committee; NA, not available; ORR, objective response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial remission; SD, stable disease; UTD, unable to determine.
[a] Outcomes not annotated as n (%) in CS table 15 (p. 55), but % reported in text.

Indirect comparisons for response outcomes of objective response rate, complete remission and partial remission were made with potential comparator data identified by the systematic literature review. Response outcomes from the unadjusted indirect comparison were used in the economic model base case to stratify pre-progression utility based on response (CR, PR or SD) and outcomes from both the unadjusted indirect comparison and the MAIC are used in scenario analyses, including the scenario analyses on alloSCT (see below for cross references to the cost-effectiveness section of this report). IRRS-derived response rate data are used in a sensitivity analysis (ERG Table 64).

[redacted]

[redacted]

[redacted] Results obtained from the MAIC were very similar to those obtained from the unadjusted indirect comparison.

Table 12 Indirect comparison outcomes for objective response rate

Scenario	Objective response rate			
	Unadjusted indirect comparison		MAIC	
	[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]

MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

In addition to conducting indirect comparisons for the outcome of objective response rate, the CS also presented indirect comparison evidence for complete remission and partial remission (the two categories of response that contribute to the objective response rate). The results of these indirect comparisons can be seen in Table 13 and Table 14. Data from Table 13 and Table 14 can also be

found in the cost-effectiveness section in ERG Table 32 and Table 40. These data are also used in model scenarios #27 to #36 reported in ERG Table 59.

Table 13 Indirect comparison outcomes for complete remission

Scenario	Complete Remission			
	Unadjusted indirect comparison		MAIC	
	[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]

MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

Table 14 Indirect comparison outcomes for partial remission

Scenario	Partial remission			
	Unadjusted indirect comparison		MAIC	
	[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]

MAIC, matching-adjusted indirect comparison; SLR, Systematic literature review.

[redacted]

3.3.2 Summary of overall survival results from CheckMate 205 and CA209-039

The CS presents the overall survival results for both data cut-off points of each study (CheckMate 205 cohort B CS p.47-48 and p. 50; cohorts B and C CS p. 55-56; CA209-039

CS p. 62-63 and p. 65). In the CS the results for each study and each data cut-off are presented in separate tables. The ERG presents an overview of the two studies at the latest time point (longest follow-up) for each study.

In CheckMate 205 Cohort B there had been [redacted] deaths among the 80 patients enrolled over a median follow-up of 15.7 months and in Cohort C [redacted] deaths among 100 patients over a median follow-up of 8.9 months. Median survival had not been reached in either cohort at these follow-up points. The six-month overall survival for Cohorts B and C is 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively. Median overall survival was'not available' (which the ERG takes to mean not reached) for the 15 participants in CA209-039 study who are relevant to the scope of this appraisal. At a median follow-up of 23.3 months there had been [redacted] deaths and [redacted]. The One year overall survival rate is [redacted]

Table 15 Overall survival results for CheckMate 205 and CA209-039 at the longest reported follow-up

	CheckMate 205		CA209-039
Additional endpoints	**Cohort B (n=80) Median follow-up 15.7 months**	**Cohort C, (n=100) Median follow-up 8.9 months**	**Post BTX/ASCT (n=15) Median follow-up 23.3 months**
Overall survival events	[redacted]	[redacted]	[redacted]
Median overall survival (95% CI), months	[redacted]	[redacted]	[redacted]
Six-month overall survival rate (95% CI), %	96.1 (92.0, 100)	94.0 (89.1, 98.9)	NR
One-year overall survival rate (95% CI), %	NR	NR	[redacted]

ASCT, Autologous stem cell transplant; BTX, brentuximab vedotin; NA, Not available; NR, Not reported
[a] Percentage value calculated by reviewer

The CS presents Kaplan-Meier plots for overall survival for CheckMate 205 Cohort B at the earlier follow-up period of 8.92 months (minimum of 6 months follow-up, Figure 2) and for CA209-039 at 23.3 months follow-up (Figure 3).

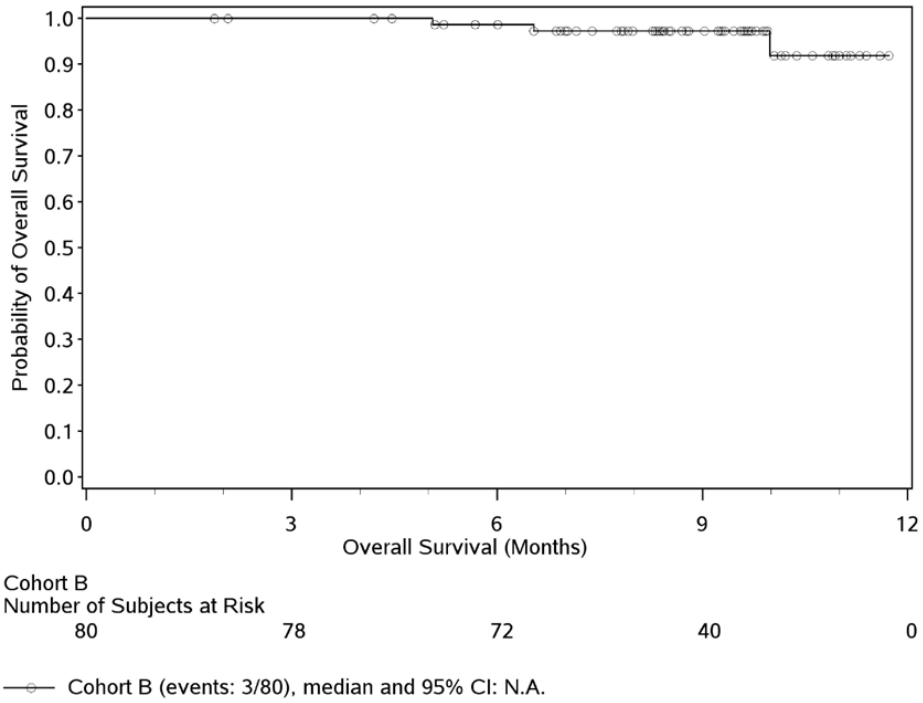


Figure 2 Overall survival CheckMate 205 Cohort B (CS Figure 13, p. 50)

Figure 3 Overall survival CA209-039 subgroup of 15 patients with prior failure of ASCT and brentuximab vedotin (CS Figure 16 top panel, p. 65)

To provide an indication of comparative effectiveness, indirect comparisons were made with potential comparator data identified by the SLR (Table 16). Overall survival is included in the economic model (ERG report section 4.3.5 page 104, Table 30 and Table 31).

[redacted]

Table 16 Indirect comparisons for overall survival

Scenario	Overall Survival		
	Unadjusted indirect comparison [redacted]	MAIC [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]

MAIC, matching-adjusted indirect comparison; NR, Not reported; SLR, Systematic literature review.

[redacted]

3.3.3 Summary of Progression-free survival results from CheckMate 205 and CA209-039

The CS presents the progression-free survival results for both data cut-off points of each study (CheckMate 205 cohort B CS p.47-49; cohorts B and C CS p. 55-56; CA209-039 CS p. 62-64).

The CS reports progression-free survival for cohorts B and C of CheckMate 205 and for the 15 patients in study CA209-039 who meet the population defined in the scope for this appraisal (Table 17). Progression-free survival was assessed both by the IRRC and by the investigator and results are provided for both assessments. For each study the IRRC identified a slightly greater number of PFS events than investigators did. Clinical advice to the ERG was that this slight difference in IRRC and investigator assessments was not surprising.

Median PFS ranged from just over 11 months (CheckMate 205 cohort C, median follow-up 8.9 months) to 14.78 months (CheckMate 205 cohort B IRRC assessment, median follow-up 15.7 months. [redacted] CA209-039 study [at the 40 week follow-up period PFS at 24 weeks was 85% (95% CI 52 to 96)].

Table 17 Progression-free survival results for CheckMate 205 and CA209-039 at the longest reported follow-up

Additional endpoints	CheckMate 205				CA209-039	
	Cohort B (n=80) Median follow-up 15.7 months		Cohort C (n=100) Median follow-up 8.9 months		Post BTX/ASCT (n=15) Median follow-up 23.3 months	
	IRRC	Investigator	IRRC	Investigator	IRRC	Investigator
PFS, events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	14.78 (11.33, NA)	[redacted]	11.17 (8.51, NA)	11.40 (11.17, NA)	12.65 (5.91. NA)	NA (8.87, NA)

Six-month PFS rate, % (95% CI)	79.7 (71.2, 89.4)	[redacted]	74.4 (65.5, 84.4)	79.2 (71.0, 88.4)	[redacted]	[redacted]
One-year PFS rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASCT, Autologous stem-cell transplant; BTX, brentuximab vedotin; IRRC, Independent radiological review committee; NA, not available; NC, Not calculated; NR, Not reported; PFS, Progression-free survival.

The CS presents Kaplan-Meier plots for progression-free survival assessed by either the investigators (reproduced from the CS as Figure 4 in this report) or the IRRC (Figure 5) for CheckMate 205 Cohort B at the earlier follow-up period of 8.92 months (minimum of 6 months follow-up) and for CA209-039 assessed by the investigators at 23.3 months follow-up (Figure 6).

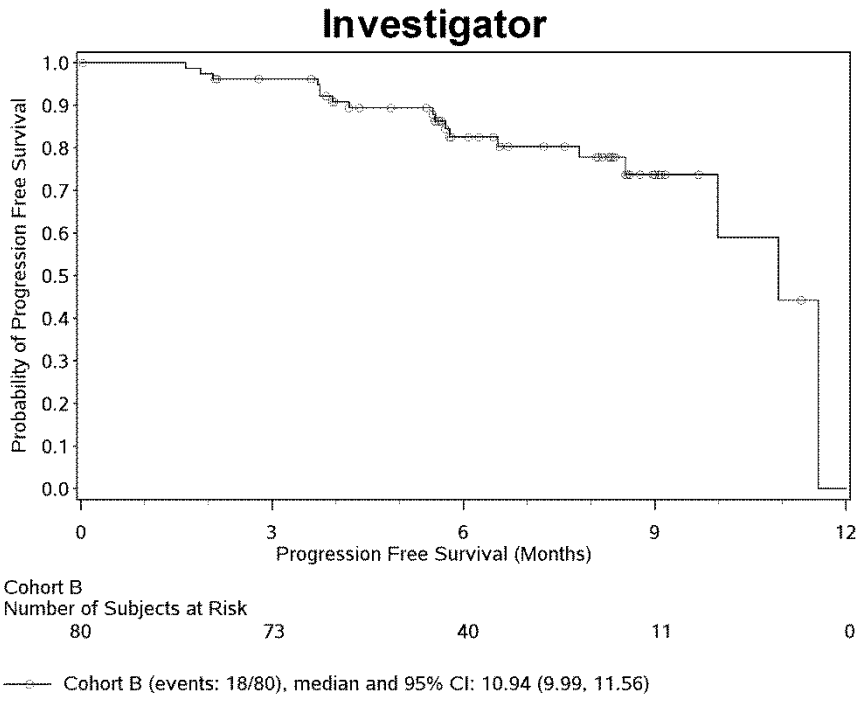


Figure 4 Investigator-assessed progression-free survival CheckMate 205 Cohort B (CS Figure 12, p. 49)

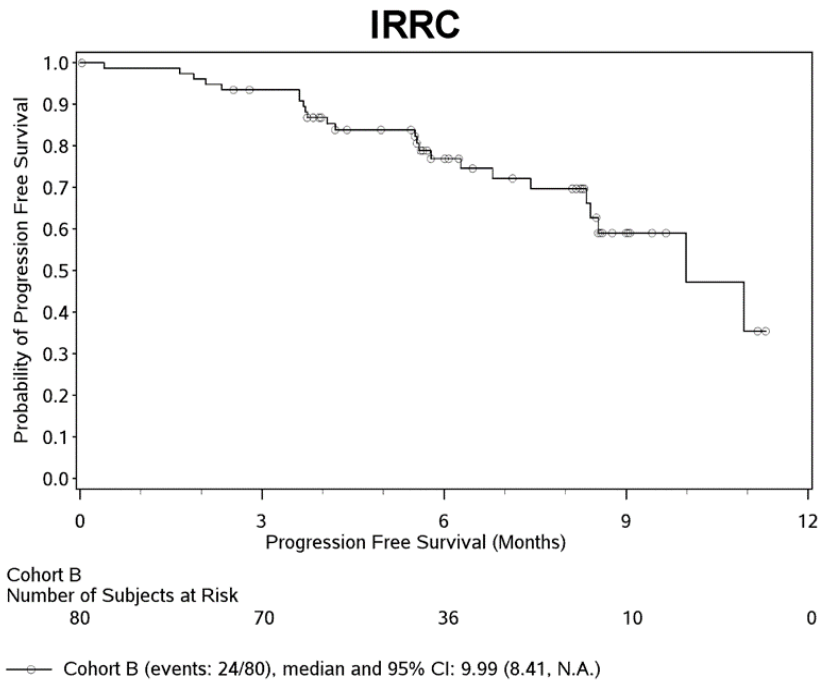


Figure 5 IRRC-assessed progression-free survival CheckMate 205 Cohort B (CS Figure 11, p. 49)

Figure 6 Investigator-assessed progression-free survival CA209-039 for the subgroup of patients post-ASCT and post-brentuximab vedotin (CS Figure 15 top panel, p. 64)

Similarly to overall survival already described (section 3.3.1) indirect comparisons for progression-free survival were made with potential comparator data identified by the systematic literature review (Table 18). Progression-free survival is included in the economic model (ERG report section 4.3.5 page 104, Table 30 and Table 31).

[redacted]

[redacted]

Table 18 Indirect comparison outcomes for progression-free survival

Scenario	Progression-free survival (Investigator assessed)		
	Unadjusted indirect comparison [redacted]	MAIC [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]

MAIC, matching-adjusted indirect comparison; NR, Not reported; SLR, Systematic literature review.

[redacted]

3.3.4 Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression

In both CheckMate 205 and CA209-039, patients who met the criteria for progression were eligible to continue receiving nivolumab providing they met pre-specified criteria (CS p. 42 and CS p.58). The number of patients who continued to receive treatment beyond progression were only reported for CheckMate 205 cohort B at median follow-up of 8.92 months [redacted]patients) and for CA209-039 at median follow-up of 23.3 months [redacted] patients) (Table 19). These data do not contribute to the modelling of cost-effectiveness.

Table 19 Patients from CheckMate 205 and CA209-039 treated beyond progression

Parameter	CheckMate 205 Cohort B (n=80) Median follow-up 8.92 months (minimum 6 months)	CA209-039 Post BTX/ASCT (n=15) Median follow-up 23.3 months
Investigator best overall response before progression	[redacted]	[redacted]
Patients on treatment beyond progression, n	[redacted]	[redacted]
Number of doses received after progression, range	[redacted]	[redacted]
Duration of treatment beyond progression, months	[redacted]	[redacted]

[a] Data from CSR, [redacted]
ASCT, Autologous stem cell transplant; BTX, Brentuximab vedotin; NR, Not reported.

The investigator-assessed tumour burden change in patients who were treated beyond progression was shown in graphical format in the CS and the plots are reproduced below. In CheckMate 205 Cohort B, [redacted] patients treated beyond progression maintained tumour reduction in the target lesion in comparison to baseline (Figure 7) and in CA209-039 [redacted]treated beyond progression maintained tumour reduction with respect to baseline (Figure 8).

Figure 7 Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression in CheckMate 205 Cohort B (CS Figure 14, p. 51)

Figure 8 Investigator-assessed tumour burden change in patients receiving nivolumab beyond progression in CA209-039 (CS Figure 17 left panel, p. 66)

3.3.5 Outcomes following alloSCT: CheckMate 205 and CA209-039

The CS summarises outcomes following alloSCT within CS section 4.13.4.1 p. 93 (Interpretation of clinical effectiveness and safety evidence). The CS states that there is 'significant potential for nivolumab to act as bridge to curative transplant in some patients' due to the high levels of responses achieved as either partial or complete remission. AlloSCT is modelled in a scenario analysis based on response data from the nivolumab trials (ERG report section 4.3.5).

Among the patient groups relevant to this appraisal (i.e. post-ASCT and post-brentuximab vedotin), the number of patients who had received post-nivolumab alloSCT as of June 2016 was [redacted] from CheckMate 205 Cohort B and [redacted] from Cohort C, and [redacted] for the post-ASCT post-brentuximab vedotin subgroup of CA209-039 (clarification response to question B4 from the company indicates that [redacted] patients in this subgroup had received alloSCT). Thus at least [redacted] patients of relevance to this appraisal have received post-nivolumab alloSCT. The CS states that there have been no deaths due to disease progression. Disease status after alloSCT is not available in the CS

from study CA209-039 and was not reported separately for Cohorts B and C (CS p. 93). The CS states that the preliminary evidence available from all patients who have received post-nivolumab alloSCT suggests that [redacted]. Similarly transplant-related mortality is not reported for the separate cohorts but overall (including those in Cohort A, who are not of relevance to this appraisal); among 40 patients undergoing alloSCT there were six deaths due to transplant-related mortality.

3.3.6 Summary of health related quality of life

The CS presents limited data for HRQoL (CS p. 52) from CheckMate 205 Cohort B (minimum follow-up six months; median follow-up 8.92 months), and most of the data are AIC. Although HRQoL data from CheckMate 205 are used in the economic model the model uses the UK EQ-5D 3l with the UK tariff and not the EQ-5D VAS which is reported here.

The analysis of EORTC-QLQ-C30 was performed on cohort B patients, who had an assessment at baseline (93.8%) and at least one post-baseline assessment (completion rates remained >80% for each visit for patients that were still participating in the study recorded from baseline to the week 33 visit). The CS states that [redacted] The CS states that EORTC-QLQ-C30 scores [redacted] but with mean changes described as 'trending towards [redacted] across functional and symptom scales'. The CS reports a minimal important difference (a score difference of 10) in role function at week 9 (mean change=10.7, SD 29.0) and in social function (mean change = 10.6, SD 23.5) and insomnia (mean change = -12.2, SD 25.6) at week 33.

The average EQ-5D VAS score for CheckMate 205 Cohort B [redacted] over time and the CS states that it [redacted] the average baseline score [redacted] minimal important difference [redacted].

It should be noted that results for both HRQoL measures are difficult to interpret without a data from a comparator arm.

3.3.7 Sub-group analyses results: CheckMate 205 Cohort B

A variety of subgroup analyses were conducted in CheckMate 205 Cohort B in CS Section 4.8 (CS p. 67 - 69) and summarised in Table 20 below. The follow-up period for these analyses is not reported. These results do not feed into the economic model.

Table 20 Summary of sub-group analyses conducted on CheckMate 205 Cohort B data

Subgroup analyses	Outcome	Finding
Post-hoc analyses of 10 variables	IRRC-assessed objective response rate	Objective response rate remained constant across subgroups.
Post-hoc analysis of efficacy by prior response to brentuximab vedotin therapy	IRRC-assessed best overall response to nivolumab	Objective responses following nivolumab are durable regardless of the response to most recent prior brentuximab vedotin.
Efficacy by baseline PD-L1 expression status	IRRC-assessed best overall response to nivolumab	Objective responses for three subgroups are reported: PD-L1 expression at baseline ≥1% (n=57 patients); PD-L1 expression <1% at baseline (n=6 patients); PD-L1 was not quantifiable (n=17).
Efficacy by 9p24.1 alteration	IRRC-assessed objective response rate	Objective response rate was similar across three categories of chromosome 9p24.1 alteration (amplicfication; copy gain; polysomy).

3.3.8 Summary of adverse events

The CS presents data on AEs in CS section 4.12 (p. 81). In this section of the CS data are presented for cohort B (n=80) and the total CheckMate 205 study population (n=240 in cohorts A, B and C). The 63 patients in cohort A had not received brentuximab vedotin prior to nivolumab therapy and so are not relevant to the decision problem. Data from Cohort C are not presented separately. The CheckMate 205 data comes from the 8.9 month follow-up although the company have stated that they will present updated safety data reflecting the April 2016 cut-off when it is available (CS p. 82). For study CA209-039 data are presented for the total population (n=23) from the published 40-week follow up point[5] (which is not reproduced in this ERG report) and the unpublished 23.3 month follow-up. The CA209-039 data therefore include the eight patients who

had not received both prior ASCT and prior brentuximab vedotin, and who are not relevant to the decision problem.

When considering AE data it is worth bearing in mind the extent of exposure to nivolumab that patients had in the CheckMate 205 and CA209-039 studies. The CS states that the median duration of study therapy was not reached in any cohort of the CheckMate 205 study [redacted] All patients in both studies received at least one dose of nivolumab. The extent of nivolumab exposure is summarised in Table 21, but note that this will change with increasing length of follow-up.

Table 21 Extent of nivolumab exposure (based on CS Table 29 p. 82 and CS Table 31 p. 85)

Parameter	CheckMate 205 (8.9 months follow-up)[3]		CA209-039 (23.3 months follow-up)[6]
	Cohort B (n=80)	Total population (n=240)	Total population (n=23)
Number of doses received			
Mean (standard deviation)	16.1 (5.82)	10.9 (6.57)	[redacted]
Median (Range)	17.0 (3 to 25)	10.0 (1, 25)	[redacted]
Cumulative dose (mg/kg)			
Mean (standard deviation)	47.91 (17.295)	32.26 (19.487)	[redacted]
Median (Range)	50.88 (9.0 to 75.8)	29.68 (2.9, 75.8)	[redacted]
Relative dose intensity (n)			
≥110%	0	1 (0.4%)	[redacted]
90-110%	61 (76.3%)	198 (82.5%)	[redacted]
70-90%	16 (20.0%)	34 (14.2%)	[redacted]
50-70%	3 (3.8%)	7 (2.9%)	[redacted]
<50%	0	0	[redacted]
Time between date of first dose date and last known date alive or death (months)			
Mean (standard deviation)	8.62 (2.02)	5.44 (3.251)	[redacted]
Median (Range)	8.92 (1.9 to 11.7)	5.09 (0.3, 11.7)	[redacted]

Overall adverse events

For CheckMate 205, the CS presents a summary of any grade and grade 3-4 drug-related AEs occurring in ≥10% of the population for cohort B (n=80) and the total population (n=240), using data from the August 2015 data cut-off (8.9 months follow-up) (CS Table 30, p. 82). Grade 5 AEs are not included in the CS table, but are reported in the text: one drug related Grade 5 AE of multi-organ failure in Cohort B, two patients in the overall study population with Grade 5 AEs of atypical pneumonia and dyspnoea. For CA209-039, a more detailed summary (CS Table 32, p. 85-87) reporting any grade, grade 3 and grade 4 - 5 AEs relating to published (40 weeks) and unpublished data (23.3-month follow-up) is presented for the total population. The ERG notes that neither table indicates what format the data are being presented in, but the ERG assumes it is number and percentage of participants affected. The ERG presents an overview of the two CS overall adverse events tables (ERG Table 22) reporting only data for the longer follow-up period of study CA209-039. In addition, for ease of comparison, only percentage data are reported for those AEs that affected ≥10% of either of the study populations. The incidence of treatment-related grade 3-4 AEs feeds through to the cost-effectiveness section (ERG report Table 36).

Drug related AEs of any grade and of grades 3 or above were reported in similar proportions in the two studies (for AEs of any grade 88% of CheckMate 205 Cohort B and 70% of the overall population versus 82.6% of CA209-039). In both studies the individual adverse events affecting 10% or more of participants were diarrhoea, nausea, fatigue, pyrexia, rash and pruritus. The majority of these events were of grade 1 or 2. One adverse event stands out as differing between the two studies and that is infusion related reaction, which affected 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039 (Table 22).

Laboratory parameter abnormalities in CheckMate 205 (identified from tests during nivolumab treatment or within 30 days of the last treatment dose) were mostly Grade 1-2 in both Cohort B and the overall study population. The grade 3-4 haematological abnormalities that were reported in ≥5% of each study cohort were decreased lymphocytes (18.8% in Cohort B and 13.4% in the overall population) and neutropenia (6.3% in Cohort B and 3.3% in the overall population). The ERG notes that although there appear to be minor discrepancies between CS text in section 4.12.1.6 p. 83 and CS Table 30 p. 82 (the latter data being reproduced in ERG Table 22) this may be due to differences in the outcomes being reported (i.e. ‘decreased lymphocytes’ reported in the text may not be the same outcome as ‘Lymphocytes’ reported in the table). In study CA209-039 laboratory

abnormalities (reported during nivolumab treatment or within 100 days of the last treatment dose) were also mostly of [redacted]. At the 23.3-month follow-up, [redacted] was the most common [redacted] haematological abnormality. Grade 3-4 hepatic abnormalities reported were [redacted]

Table 22 Summary of drug-related adverse events affecting ≥10% of CheckMate 205 participants or ≥5% of CA209-039 participants

Parameters	CheckMate 205 8.9 month follow-up[3]				CA209-039 23.3 month follow-up[6]		
	Cohort B (n=80)		Overall (n=240)		Overall n=23		
Grade of event	**Any**	**3-4**	**Any**	**3-4**	**Any**	**3**	**4-5**
Any drug-related AE, %	88	25.0	70	15.4	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders,[a] %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Diarrhoea, %	10.0	0	10.8	0.4	[redacted]	[redacted]	[redacted]
Nausea, %	12.5	0	10.8	0	[redacted]	[redacted]	[redacted]
General disorders & administration site conditions, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Fatigue, %	25.0	0	16.3	0.4	[redacted]	[redacted]	[redacted]
Pyrexia, %	13.8	0	8.8	0	[redacted]	[redacted]	[redacted]
Skin & subcutaneous tissue disorders, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Rash, %	16.3	1.3	9.6	0.8	[redacted]	[redacted]	[redacted]
Pruritus, %	10.0	0	8.3	0	[redacted]	[redacted]	[redacted]
Musculoskeletal & connective tissue disorders, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Respiratory, thoracic & mediastinal disorders, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Injury, poisoning & procedural complications, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Infusion related reaction, %	20.0	0	12.9	0.4	[redacted]	[redacted]	[redacted]
Metabolism & nutrition disorders, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]

Endocrine disorders, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Blood & lymphatic system disorders, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Laboratory abnormalities							
Haemoglobin (anaemia), %	77.5	1.3	76.3	2.5	[redacted]	[redacted]	[redacted]
Platelets (thrombocytopaenia), %	45.0	3.8	39.6	2.5	[redacted]	[redacted]	[redacted]
Leukocytes, %	40.0	2.5	34.6	2.9	[redacted]	[redacted]	[redacted]
Lymphocytes, %	72.5	18.8	60.4	13.4	NR	NR	NR
Lymphocyte decreased, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Absolute neutrophil count (neutropaenia), %	38.8	6.3	27.1	3.8	[redacted]	[redacted]	[redacted]
ALT, %	31.3	2.5	28.8	1.7	[redacted]	[redacted]	[redacted]
ALP, %	45.0	6.3	40.0	4.2	[redacted]	[redacted]	[redacted]
AST, %	40.0	3.8	26.3	2.1	[redacted]	[redacted]	[redacted]
Lipase increased, %	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]

AE, adverse event; ALT, alanine aminotransferase, ALP, alkaline phosphatase; AST, aspartate aminotransferase, NR, Not reported.

[a] Grey shaded lines indicate summary data for a group of adverse events. If any of the adverse events contributing to the group were experienced by 10% or more of either study population then these are shown in the unshaded rows below.

[b] [redacted], this summary value is reported here because infusion related reaction appears under this heading and this was reported by >10% of participants in CheckMate 205.

Discontinuation due to adverse events

Some drug-related AEs did cause patients to discontinue nivolumab treatment, however the proportion of patients affected was low (Table 23).

Table 23 Discontinuation due to adverse events

Parameters	CheckMate 205 8.9 month follow-up		CA209-039 23.3 month follow-up
	Cohort B (n=80)	Overall (n=240)	Overall n=23
Discontinuation due to drug-related AE of any grade	3 (3.8%)[a]	9 (3.8%)[b]	[redacted]

The AEs that caused discontinuation were:
[a] Grade 3-4 autoimmune hepatitis (n=1); Grade 3-4 increases in ALT and AST (n=1); Grade 5 multi-organ failure (n=1)
[b] Grade 3-4: n=5 (2.1%); Grade 5: n=2 (0.8%)
[c] [redacted]

Deaths

During the follow-up periods reported, only 2.9% of the overall CheckMate 205 study died in comparison to [redacted] of the CA209-039 overall study population (Table 24).

Table 24 Deaths

Parameters	CheckMate 205 8.9 month follow-up		CA209-039 23.3 month follow-up
	Cohort B (n=80)	Overall (n=240)	Overall n=23
Deaths	3	7 (2.9%)[a]	[redacted]
- due to disease progression	1	4	
- due to undetermined cause (patient lost to follow-up)	1		
- Grade 5 AE of multi-organ failure	1[c]		

[a] The reason for one death is not given (the 4 deaths due to disease progression presumably included one death for this reason in Cohort B, 2 other patients in Cohort B died due to other reasons leaving 1 patient in the overall study whose reason for death is not given).
[b] [redacted]
[c] The CS notes that this event was changed by the investigator to Epstein-Barr virus positive peripheral T-cell lymphoma, and was considered unrelated to the study drug.

Drug-related serious adverse events

In CheckMate 205 (at 8.9 months follow-up) 6.3% of Cohort B experienced a drug-related serious adverse event in comparison to 9.6% of the overall study population. The most common drug-

related serious adverse event was infusion related reaction (Cohort B 2.5%; overall 2.1%). In CA209-039 (at 23.3 month follow-up) 13.0% of the overall study population had a drug-related serious adverse event. These were a Grade 2 lymph node pain (n=1), Grade 3 pancreatitis (n=1) and Grade 3 myelodysplastic syndrome (n=1). [redacted]

Adverse events of special interest

In CheckMate 205 Cohort B most adverse events of special interest were of grades 1 or 2, and most were considered to be drug related [redacted] No grade 5 events were reported for any category of select AEs in CheckMate 205 cohort [redacted]. The most frequently reported of these adverse events, irrespective of causality was skin abnormalities (41%) [redacted] (Table 25). Gastrointestinal abnormalities (26%), hypersensitivity or infusion-related reaction (21%) and endocrine (18%) events were the other categories in CheckMate 205 Cohort B, where more than 10% of the participants experienced an event. [redacted] In CheckMate 205, cohort B pneumonitis was reported in two patients (one grade 2 and one grade 3) and both cases were considered to be drug related (which resolved with corticosteroid treatment). It is therefore not clear why only one event was reported for the pulmonary of select AEs in this study. Full details of adverse events of special interest are reported in the CS, pages 84 and 88-89.

Table 25 Adverse events of special interest

Parameters	CheckMate 205 8.9 month follow-up Cohort B (n=80)	CA209-039 23.3 month follow-up overall n=23		
	Any grade	Any grade	Grade 3-4	Grade 5
Endocrine				
All-causality	14 (18%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]
Gastrointestinal				
All causality	21 (26%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]
Hepatic				
All-causality	8 (10%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]
Pulmonary				
All causality	1 (1%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]
Renal				
All-causality	4 (5%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]
Skin				
All-causality	33 (41%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]
Hypersensitivity/infusion reaction				
All-causality	17 (21%)	[redacted]	[redacted]	[redacted]
Drug-related		[redacted]	[redacted]	[redacted]

3.4 Summary

The systematic review of clinical effectiveness evidence in the CS identified two single-arm studies for nivolumab as a treatment for people with relapsed or refractory classical Hodgkin lymphoma following ASCT and brentuximab vedotin (CheckMate 205, Cohorts B and C; CA209-039). The decision problem in the CS did not include the second of the populations specified in the NICE

scope which was people with relapsed or refractory classical Hodgkin lymphoma following at least two prior therapies when ASCT is not a treatment option. The company provided supporting evidence from a population who had received ASCT only, but the ERG has not assessed this because the population does not meet the NICE scope (or the company's own decision problem).

The two single-arm nivolumab studies were judged to be of reasonable methodological quality but clearly the single-arm study design has inherent methodological limitations, the most obvious being that there is no comparator group against which to judge the efficacy of the study drug. Follow-up of participants from both studies is continuing and patients are still being recruited to the CA209-039 study.[36] The chief clinical efficacy outcomes reported in the CS are OS, PFS and response rates which are reported for both of the nivolumab single-arm studies.

As there is no direct evidence comparing the efficacy of nivolumab against the comparator (SoC comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine) the company conducted indirect comparisons. The data from the nivolumab studies were pooled to create a nivolumab pooled cohort in these comparisons. A systematic review identified [redacted] studies of potential comparator treatments but [redacted] of these studies were reported only as conference abstracts and therefore limited data were reported. In [redacted] of the studies [redacted] One study (a retrospective database review), by Cheah and colleagues,[2] was identified as providing evidence on the outcomes of interest in a population where the majority had received prior ASCT and had failed brentuximab vedotin so this study was used as the primary source of comparator evidence. One subgroup of the patients (n=28) identified in the Cheah and colleagues study had received what were described as 'investigational agents'. The interventions that constituted investigational agents were not described but the CS speculates that it was likely to have included nivolumab and on this basis, conducted an indirect comparison using the full Cheah and colleagues data set and in a second scenario omitted the subgroup of patients who had received investigational agents. The ERG have been informed that only a couple of patients in the Cheah study received PD-1 inhibitors. The [redacted] studies providing comparative effectiveness data for use in indirect comparisons, were used in four scenarios

[redacted]

[redacted]

The objective response rate as the primary efficacy endpoint of both the CheckMate 205 study (when assessed by the IRRC) and the CA209-039 study (investigator assessed objective response rate). The objective response rate was [redacted] for the study defined primary endpoints. Median time to response was [redacted] and was just over 2 months (2.10 months by IRRC assessment and 2.17 month by investigator assessment) in Cohort B at median 9.92 months follow-up. The time to complete remission in Cohort B at this same time point was approximately 4.5 months. Indirect comparisons [redacted] Results obtained from the MAIC were very similar to those obtained from the unadjusted indirect comparison. Indirect comparisons were also conducted for complete remission and partial remission, the two categories of response that contribute to the objective response rate outcome.

Median overall survival had not been reached in CheckMate 205 Cohort B (median follow-up 15.7 months) or in Cohort C (median follow-up 8.9 months). The six-month overall survival for Cohorts B and C was 96.1% (95% CI 92.0 to 100) and 94.0% (95% CI 89.1 to 98.9) respectively. Median overall survival had also not been reached for the 15 post-ASCT post-brentuximab vedotin patients in study CA209-039 at median follow-up of 23.3 months. The one-year OS rate is [redacted] A predicted value for median overall survival of [redacted] was calculated for the nivolumab pooled cohort which was used in indirect comparisons. The median OS from unadjusted indirect comparison [redacted] in the four scenarios (1a, 1b, 2a, 2b) with comparator data. The overall survival estimates obtained by MAIC were [redacted] than those obtained by the unadjusted indirect comparison for each scenario.

PFS was assessed both by the IRRC and by the investigators and results are provided for both assessments. In CheckMate 205 [redacted] (Cohort C, median follow-up 8.9 months) to 14.78 months (Cohort B IRRC assessment, median follow-up 15.7 months. Median PFS was not reached using data from the investigator assessments of CheckMate 205 Cohort B and was also not reached in study CA209-039. Indirect comparisons of PFS utilised the investigator assessments of PFS and therefore a predicted value for median PFS had to be calculated for the nivolumab pooled cohort. The predicted value was [redacted] and in comparison the median PFS obtained by unadjusted indirect comparison with [redacted] The overall median progression-free survival estimates obtained by MAIC were [redacted] than those obtained by the unadjusted indirect comparison for each scenario.

Response rates, OS and PFS outcomes provide data which is used to inform clinical effectiveness parameters in the economic model.

Results were also presented on tumour burden change in patients receiving nivolumab beyond progression, outcomes following alloSCT, and a very limited amount of data on HRQoL but the data presented were not used in the economic model. A variety of subgroup analyses were conducted and reported for CheckMate 205 Cohort B.

Adverse events are reproduced in the ERG report for cohort B (n=80) and the total CheckMate 205 study population (n=240 in cohorts A, B and C) after 8.9 months follow-up. The 63 patients in cohort A are not relevant to the decision problem. AEs for CA209-039 are presented for the total population (n=23, at the 23.3 month follow up point). The CA209-039 data therefore also include the eight patients who are not relevant to the decision problem. All patients in both studies received at least one dose of nivolumab but, as patients are still being followed up the extent of nivolumab exposure is increasing and not fully captured by the data presented in the CS.

Drug related AEs of any grade were reported for 70% of the overall CheckMate 205 population (88% of Cohort B) and 82.6% of CA209-039. Diarrhoea, nausea, fatigue, pyrexia, rash and pruritus were the most common adverse events in both studies. The majority of these events were of grade

1 or 2. Infusion related reaction stood out as differing between the two studies affecting 20% of participants in CheckMate 205 Cohort B and 12.9% of the overall population in comparison to [redacted] of participants in CA209-039. In CheckMate 205 there were three Grade 5 AEs (multi-organ failure and two patients with atypical pneumonia and dyspnoea) but no Grade 5 AEs were reported for CA208-039. Laboratory parameter abnormalities were also reported which were mostly Grade 1-2. The most common grade 3-4 haemotological abnormality was [redacted] The proportion of patients who discontinued nivolumab treatment due to a drug-related adverse event was [redacted]. A serious drug-related adverse event was experienced by 9.6% of the CheckMate 205 study population (6.3% of Cohort B) and 13.0% of those in study CA209-039.

Identification of AEs of special clinical interested was conducted to characterise any AEs that are potentially associated with the use of nivolumab. Skin abnormalities were the most frequently reported of these adverse events, irrespective of causality, in CheckMate 205 Cohort B [redacted]

There is uncertainty about the effectiveness of nintedanib in comparison to alternative treatment options because the two key studies of nivolumab are single-arm studies. In its interpretation of the clinical evidence, the company highlights that ORR in both studies has been good. [redacted] patients have achieved complete response in CheckMate 205 and [redacted] in CA209-039, when response was assessed by investigators. At the follow-up times reported in the CS the median progression-free survival was at least 11 months in CheckMate 205 Cohorts B and C and had not been reached in CA209-039 [redacted]

To compare the efficacy of nivolumab with potential comparators an indirect comparison approach was used. The company undertook a systematic review to identify evidence on potential comparators and found 12 studies that provided data in a population, at least some of whom had received prior ASCT and prior brentuximab vedotin. The ERG believes it is likely that the company's systematic review identified all the relevant evidence, but this is limited in terms of quality (the studies were predominantly phase 1 or 2 single-arm studies), and completeness of reporting (seven only reported as conference abstracts, limited follow-up up periods, outcomes of PFS and OS often not reported). [redacted]

[redacted] Therefore the ERG believes that at present, there is considerable uncertainty regarding the extent to which the benefits of nivolumab exceed those of potential comparator treatments. This uncertainty should reduce as data for the nivolumab studies and the potential comparator studies at increased lengths of follow-up becomes available. One of the comparator studies, by Cheah and colleagues, was identified as providing evidence on the outcomes of interest in a population where the majority had received prior ASCT and had failed brentuximab vedotin and was used as the primary source of comparator evidence. This study reported data from a retrospective review of an institutional database in the USA. Following disease progression after brentuximab vedotin, patients had received a variety of treatments but there is some uncertainty about how well these reflect the treatments that patients might receive in the UK and how well the Cheah patients match those in the nivolumab studies.

The two key issues that the ERG has identified can therefore be summarised as:

- considerable uncertainty regarding the extent to which the benefits of nivolumab exceed those of potential comparator treatments. This uncertainty is due to the immaturity of the evidence base for nivolumab and comparators and the need to undertake indirect comparisons.
- Uncertainty about how well the comparator populations, particularly those in the Cheah study, match those in the nivolumab studies and UK patients.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of the management of Hodgkin lymphoma in adult patients.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of nivolumab is compared with standard of care for adults with refractory Hodgkin lymphoma following ASCT and brentuximab vedotin.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of adult patients with Hodgkin lymphoma. See section 3.1.1 of this report for the ERG critique of the search strategy. The inclusion and exclusion criteria for the systematic review are listed in appendix 5 of the CS. The inclusion criteria state that economic evaluations of the management of Hodgkin lymphoma in adult patients would be included.

Twenty two studies were identified from screening 1424 titles and abstracts. Fourteen of the studies were included for full review and the remaining eight studies were excluded, mainly because the population (4) or study type (4) did not meet the inclusion criteria.

The checklist suggested by NICE[37] has been applied to the included references. The CS does not discuss the quality assessment of the studies or comment on which studies are of most relevance to this appraisal. The studies identified are shown in Table 26 (CS Table 5, appendix 5). Of the 14 studies identified, none of them are for nivolumab for patients with Hodgkin lymphoma or for interventions in patients with relapsed or refractory Hodgkin lymphoma following ASCT and treatment with brentuximab vedotin.

Table 26 Study characteristics of economic modelling studies in CS review

Study	Intervention and management strategy	Patient population
Barosi (1999)	CVD (cyclophosphamide, carmustine and etoposide)	Patients who first underwent a ASCT between August 1994 and May 1997.
Cerci (2010)	Fluorine-18–fluorodeoxyglucose positron emission tomography (FDG-PET)	Patients with Hodgkin lymphoma with unconfirmed complete remission (CRu) or partial remission (PR) after first-line treatment
Chen (2009)	Lipid screening	Survivors of Hodgkin lymphoma
Engstrom (2014)	Brentuximab vedotin compared to standard chemotherapy and allogeneic stem cell transplant	Swedish patients with relapsed or refractory Hodgkin lymphoma
Gallamini (2011)	Interim PET response adapted therapy	Patients with ABVD-treated, advanced-stage Hodgkin lymphoma
Guadagnolo (2006)	Computerized Tomography (CT) scan in the Routine Follow-Up of Patients After Primary Treatment for Hodgkin lymphoma.	Patients who have had a complete response (CR) to primary treatment for Hodgkin lymphoma.
Hatam (2015)	IEV (ifosfamide, epirubicin and etoposide) Drug Regimen Versus ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) Drug Regimen	Patients with Relapsed and Refractory Hodgkin and Non-Hodgkin lymphoma in Iran
Meza-Torres (2014)	Brentuximab Vedotin	Patients with Refractory/Relapsed Hodgkin lymphoma
NG (2001)	Staging and treatment options in early-stage Hodgkin lymphoma	Patients with early-stage, favourable prognosis Hodgkin lymphoma
Norun (1996)	Stages I and II HL treated with ChlVPP (chlorambucil, vinblastine, procarbazine and prednisone), ABOD (doxombicin (or epirubicin), bleomycin, vincristine and dacarbazine) or ABVP [doxorubicin (or epirubicin), bleomycin, vinblastine and prednisone] Stages III and IV treated with ABOD, ChlVPP or alternating ABOD/ChlVPP regimens	Patients with Hodgkin lymphoma
Ramsey (2015) and Roth (2014)	Brentuximab Vedotin Vs. Best Supportive Care Following Autologous Stem Cell Transplant	Adult Hodgkin lymphoma patients at high risk of relapse following ASCT
Wattson (2013) and Wattson (2014)	Low-Dose Chest Computed Tomography for Lung Cancer Screening	Hodgkin lymphoma Survivors

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The NICE reference case requirements have been considered for critical appraisal of the submitted economic evaluation, in Table 27.

Table 27 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	Described in CS Table 1, p. 13
Comparator: As listed in the scope developed by NICE	Yes	
Perspective on costs: NHS and PSS	Yes	CS Table 36, p. 101
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	40 years. CS Table 36, p. 101
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	Health effects measured in QALYs; EQ-5D used for nivolumab arm and TTO for SoC arm.
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	For nivolumab arm; utility estimated from general public for SoC arm.
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% p.a. for costs and health effects	Yes	CS Table 36, p. 101

4.3.2 Model structure

The company presented a Markov model consisting of three primary health states. The model has a time horizon of 40 years (lifetime), monthly cycle length, applies appropriate discounting (3.5% per annum for costs and benefits), and half-cycle correction is run as a sensitivity analysis. The company did not include half-cycle correction in the base case analysis. We found the cycle length sufficiently short to represent transitions and that the company's approach to half-cycle correction was appropriate given the marginal effect of transition timing when cycles are short.

The model is built in Microsoft Excel, however, the model is executed almost entirely in the Visual Basic (VBA) programming language. The spreadsheets cannot be used to generate any calculations or model results independently of the VBA code — macros are required to produce all types of results: base-case, deterministic sensitivity analyses, scenario analyses, and probabilistic sensitivity analyses. Inputs into the model must take very specific forms or risk crashing the VBA code that is responsible for producing results. These limitations of the model rendered the model opaque and difficult to validate. All scenario analyses required manual modification of input parameters and not all analyses could be replicated, due either to insufficient explanation of methods or due to potential parameter discrepancies. NICE and the ERG requested clarification for the modelling methods and parameters used in scenario analyses. The company provided an adequate response to the clarification request.

A model schematic is presented in the CS (see CS Figure 23 p. 98), but more complex transitions are not included in the model schematic. The base case model is similar to the standard three state cancer model seen in many STAs. Patients enter the model in the pre-progression state, receiving initial therapy (i.e. nivolumab or SoC in the base case analysis). Within the pre-progression state, there are sub-states for alternative levels of response: complete response, partial response, and stable disease (CR, PR, and SD in Figure 9). Patients in the pre-progression state may remain on treatment in the pre-progression state, discontinue treatment in the pre-progression state, progress, or die. Following discontinuation, patients may enter the state represented as subsequent therapy within the pre-progression state; in the base case analysis, this is best supportive care (BSC), but in scenario analyses this may be subsequent chemotherapy. BSC consists primarily of palliative care, including palliative chemotherapy. Once patients have progressed they receive BSC. In the progressed state patients may either remain in that state or die.

The model allows several treatment switches to occur, with additional options either having their own overall survival curves or continuing the survival curve of the baseline therapy. In the base case, overall survival is derived from baseline therapy for all future treatments. However, more complicated transitions are modelled when incorporating allogenic stem cell transplant (alloSCT) into the model and when changing whether patients may continue receiving SoC after discontinuation. The structural means to execute these analyses were not clearly described in the CS, therefore additional clarification was requested from the company on the methods and parameters used in scenario analyses. In response to clarification question B2, the company presented an updated Markov flow diagram with further explanation on how therapies subsequent to the initial line of therapy are modelled. Figure 9 shows this diagram.

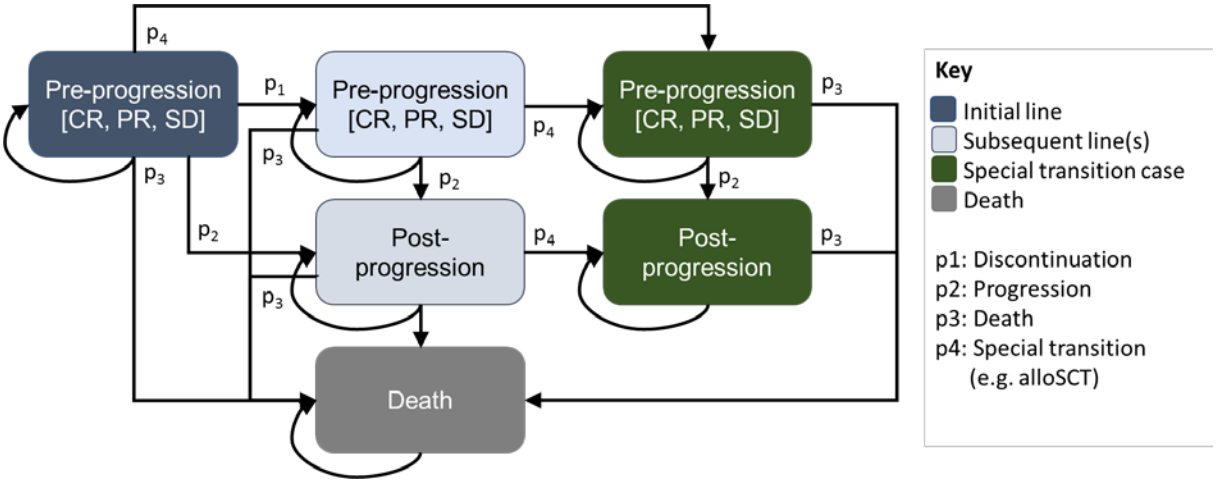


Figure 9 Amended Markov flow diagram in response to clarification question B2 (Company Clarification Response Figure 3)

The model uses survival modelling to predict PFS and OS. Alternative survival curve parameterisations are explored and presented as scenario analyses. The ERG discusses the survival modelling in section 4.3.5.

The ERG considers the model structure to be an adequate representation of the biological processes of relapsed or refractory classical Hodgkin lymphoma and adequately represents the treatment pathway. The company presented the model structure with sufficient justification for their methodological and structural choices (CS Section 5.2). In general, the modelling approach appears appropriate.

4.3.3 Population

In accordance with the final scope issued by NICE, the population of interest is people with relapsed or refractory classical Hodgkin lymphoma following ASCT (post-ASCT) and brentuximab vedotin (post-brentuximab vedotin). This is in accordance with the marketing authorisation for nivolumab. However, as described in Section 2.3, this is only one of the two populations specified in the final scope issued by NICE.

The company uses data from the CheckMate 205 and CA209-039 studies for the clinical parameters for nivolumab in the economic model. According to the CS, pooled data for 193 patients from Cohorts B (n=80) and Cohort C (n=98) of the CheckMate 205 study and a sub-group (n=15) from the CA209-039 study, matching the population of interest were used. As discussed in the clinical effectiveness section 3.1 above, these studies were single-arm, non-randomised, non-comparative, parallel cohort studies. Nivolumab efficacy data were derived from these studies while SoC efficacy data was derived from the Cheah and colleagues study[2]. In Cheah and colleagues, between 68% (66/97 reported in full paper) and 71% (71/100 reported in abstract) of the sample population were both post-ASCT and post-brentuximab vedotin patients (see Section 3.1.3).

Table 28 Comparison of patient characteristics

Parameter		CheckMate 205[a]		CA209-039 (n=23)[a]	Cheah et al. (n=89)[b]
		Cohort B (n=80)	Cohort C (n=100)		
Age(years), median		[redacted]	[redacted]	[redacted]	32
Disease Stage	Stage I	1	[redacted]	not reported	2
	Stage II	11	[redacted]		25
	Stage III	14	[redacted]		18
	Stage IV	54	[redacted]		39

[a] Nivolumab treatment
[b] Standard of care (SoC) treatment

Table 28, shows the patients' characteristics in terms of age and disease stage from the three studies used in this assessment (intervention and comparator studies). The median age of the population in these studies is similar ranging from 32 to 37 years. The Cheah study also states that details regarding the outcome of the last therapy before brentuximab vedotin were available in 84 patients, of whom only 31 (36%) were refractory. Therefore, the sample population in the Cheah

study is not a complete match with the population of interest in this appraisal. However, the ERG agrees with the company that due to the paucity of evidence available for nivolumab and its comparators in the relevant population, the two nivolumab single-arm trials (CheckMate 205 and CA209-039) and the single-arm comparator trial, Cheah and colleagues, are the most appropriate studies to inform comparisons.

4.3.4 Interventions and comparators

The CS compares nivolumab to SoC, in line with the NICE scope for this appraisal. SoC is defined as established clinical management without nivolumab, including chemotherapy such as gemcitabine and bendamustine. The base case analysis assumes that SoC comprises the therapies described within the Cheah study,[2] as shown in Table 29. These are: investigational agents, gemcitabine, bendamustine, brentuximab vedotin retreatment, platinum based therapies, ASCT and other alkylator therapies. The composition of SoC in terms of the actual chemotherapies used is unclear, and the regimens used are described in more detail in section 4.3.7 and shown in Table 42. The company conducts a scenario analysis that compares nivolumab to BSC, which is comprised of palliative care and chemotherapy (CS page 156).

The modelled doses and administration schedule of nivolumab are in line with the marketing authorisation. The Cheah study was conducted in the USA. The CS makes the assumption that the patient characteristics and the clinical management observed in this Cheah study are generalisable to UK clinical practice. The company states that it was considered unlikely that there are significant differences to patients seen in UK clinical practice. The ERG, advised by clinical experts, agrees that the Cheah study currently is the best available evidence for this assessment.

4.3.5 Treatment effectiveness and extrapolation

As described above (section 4.3.2) the economic model incorporates three health states which represent pre-progression, post-progression and death. The model predicts the proportion of patients who experience a progression or death event in monthly cycles.

In the company's base case analysis, patients enter the model following failure of prior therapies (post-ASCT and post–brentuximab vedotin) and receive either nivolumab or SoC. Patients may discontinue treatment from their initial therapy and these patents then receive BSC (comprised of

palliative care/chemotherapy). For the base case analysis, BSC is the final line of therapy and it is assumed that patients do not discontinue BSC.

Survival outcomes were modelled using survival equations fitted to data from the two studies for nivolumab and for the SoC arm, were derived from the Cheah study.[2] Survival curves were applied to estimate PFS and OS in each treatment arm. AE rates were used to derive the costs associated with each treatment arm and the disutilities experienced by the patients. This section outlines the PFS, OS, response rates, time to treatment discontinuation and AEs rates for both nivolumab and SoC.

4.3.5.1 Survival outcomes (clinical events)

Parametric extrapolation of survival data from the studies was used to inform the long-term economic model. Parametric survival functions were fitted to the patient-level pooled nivolumab data (total n=193) and fitted to a number of different distributions, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised gamma survival distribution. The Akaike and Bayesian Information Criteria were implemented evaluating the goodness-of-fit, with smaller values demonstrating a more appropriate fit. The clinical plausibility of extrapolation was assessed by clinical experts. Clinicians visually assessed the survival curves and the corresponding hazards over time and determined the most plausible distribution.

Clinical data informing OS and PFS for patients treated with nivolumab were derived from Cohort B and Cohort C of the CheckMate 205 (n=178) and the post-ASCT / post-brentuximab vedotin patients from the CA209-038 (n=15) study. These studies provide follow-up data for 15.7, 8.9 and 23.3 months respectively. There is little available data for the SoC comparator. The company used data from Cheah and colleagues to inform SoC therapy in the model.[2] A proportion of 71% of patients within the Cheah study had previously received both ASCT and brentuximab vedotin. The company states that in the base case, efficacy inputs for SoC are derived from the population of patients who did not receive investigational agents (n=51). Despite this, tables and data within the CS refer to the full sample (n=79). The treatments administered within the Cheah and colleagues study[2] and the outcomes from these therapies are presented in Table 29 for the whole population (n=79). The company also conducted scenario analyses assessing the impact of applying efficacy from the overall population, and using the shortest and longest survival estimates. Whilst data is available on comparators, the company considered Cheah and colleagues the best available evidence believing that it is the most representative study of the SoC treatment (a mix of

chemotherapy) whereas other studies used in the ITC are single-arm studies consisting entirely of investigational agents. Whilst we agree that the ITC comparators are as representative of SoC as Cheah and colleagues, we stress that Cheah and colleagues data is best used including investigational agents, and that there are still significant limitations of the data given the single-arm nature of the study (see Section 3.1.3 for further critique).

Table 29 Therapies administered and outcomes - Cheah study (2016), (CS Table 37, p. 103)

Treatment	*n*	Eval	CR (%)	PR (%)	ORR (%)	mPFS (m)	mOS (m)
Investigational agent	28	28	4 (14)	3 (11)	7 (25)	2.4	47.7
Gemcitabine	15	12	4 (27)	4 (27)	8 (53)	2.1	NR
Bendamustine	12	11	2 (17)	4 (33)	6 (50)	3.7	34.0
Other alkylator	6	4	1 (17)	1 (17)	2 (33)	5.0	9.5
BTX retreatment	6	4	0 (0)	2 (33)	2 (33)	3.5	10.4
Platinum based	4	4	0 (0)	1 (25)	1 (25)	0.9	25.2
ASCT	3	3	1 (33)	0 (0)	1 (33)	-	11.9
Other	5	1	0 (0)	0 (0)	0 (0)	-	24.9
Total	**79**	**67 (85)**	**12 (15)**	**15 (19)**	**27 (34)**	**3.5**	**25.2**

ASCT, autologous stem cell transplant; BTX, brentuximab vedotin; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PR, partial response.

Nivolumab survival outcomes

Progression free survival

Progression events derived from the PFS data are based on the investigator-assessed outcomes. Figure 10 presents the parametric survival functions fitted to the patient-level data. The lognormal was considered the most appropriate fit, on the basis that the Akaike and Bayesian Information Criteria, had the smallest values (Figure 10). Clinicians also determined that the lognormal distribution for PFS was the most plausible describing long-term outcomes in clinical practice. This was based on the assumption that there would be an initial increase in hazard, followed by a gradual decline over time. Alternative distributions were assessed in scenario analyses. Figure 10, shows the Kaplan-Meier data for the nivolumab pooled cohort (n=193), survival functions and extrapolations. Communication with our clinical experts confirmed their agreement to the approach chosen by the company. On balance, the ERG considered that the choices made by the company in the base case were the most appropriate extrapolation choices. The choice of lognormal for PFS appears reasonable. The parameters describing investigator-assessed PFS for nivolumab and SoC applied in the model are shown in Table 30. The CS presents scenario analyses for alternative survival models for nivolumab (Table 50).

Figure 10 Extrapolation of PFS curves (years 0-5): nivolumab, (CS, Figure 25)

Table 30 Parameters describing PFS and OS for nivolumab (CS, Table 39)

	Nivolumab
PFS	Lognormal; μ: 2.825 σ: 1.109
OS	Weibull Scale (A): 76.74 Shape (B): 1.326
OS overall survival PFS: progression-free survival.	

Overall survival

For the nivolumab arm the company stated that the exponential parametric function provides the best fit, based on Akaike and Bayesian Information Criteria values (Figure 11). However, as this

distribution would predict survival beyond 60 years for a proportion of patients, the company decided that a more conservative approach was appropriate. Clinicians considered that the PFS and OS hazards would have similar long-term extrapolation, however given the paucity of data to inform OS, the Weibull distribution was considered to provide a more appropriate fit for OS. The survival functions fitted are presented in Table 30. Kaplan-Meier data, the long-term extrapolations and the median survival estimates are shown in Figure 11.

The ERG considered that the choice of Weibull for OS to be an appropriate choice. We noted that there was a large range in the OS outcome, from 41.7 months for the Gompertz distribution to 394 months for the lognomal distribution (Figure 11), due to the short follow-up of the study. The CS provided scenario analyses varying the distributions used for survival (CS Table 67) but changing the distribution used for OS did not appear to have a large effect on the model results (Table 50).

Figure 11 Extrapolation of OS curves (years 0-5): nivolumab, (CS, Figure 26)

SoC survival outcomes

Progression free survival

The Cheah and colleagues study[2] provides Kaplan-Meier data describing PFS for the overall population. The median PFS for the specific therapies ranged from 0.9 to 5.0 months, with investigational agents reporting a median PFS of 2.4 months. Figure 12, shows the PFS for the overall population from the Cheah study and the Cheah population excluding investigational agents compared to the PFS from the two studies for nivolumab.

The CS used the population from Cheah excluding the group of 28 patients who received investigational agents. The justification given by the company is that the group of patients who received investigational agents is likely to contain patients receiving nivolumab. The ERG contacted the authors of Cheah and colleagues, and were informed that there was only a small number of patients who received PD-1 inhibitors, such as nivolumab, in the 'investigational agents' group [personal communication]. The ERG considers that the company should have used the overall population from Cheah, i.e. including those patients receiving investigational agents.

Figure 12 Long-term extrapolation of PFS: SoC (CS, Figure 29)

Given the limited evidence for this population, the company used an exponential curve fitted to these data, based on the rationale that an exponential distribution should be considered the default parametric function for long term extrapolation. The CS stated that this was in line with the method proposed by Bagust and Beale.[38] This methodological recommendation from Bagust and Beale is not without debate. An alternative method is the one recommended by the NICE Decision Support Unit guide by Latimer.[39] The company follows the systematic testing of alternative survival curves recommended by Latimer for all nivolumab curves but did not do so for SoC curves. We did not feel that the choice of survival model was sufficiently justified for SoC in the CS, which led NICE and the ERG to request clarification on the model fit of alternative survival curves (Clarification question B5). The company provided survival curves and fit statistics comparable to CS Figure 25 and CS Figure 26 for all patients from Cheah and colleagues (including those patients receiving investigational agents). The parameters used in the model for the SoC PFS survival curve are shown in Table 31. We consider that the exponential is an appropriate choice of survival model for PFS of SoC

Table 31 Parameters describing OS and PFS for SoC (CS, Table 41; App. 6, Table 13)

Parameter	SoC
PFS	Exponential λ: 0.160
OS	Exponential λ: 0.036

OS, overall survival; PFS, progression-free survival.

Overall survival

Figure 13 shows the OS for SoC based on the population excluding investigational agents and for the overall population from the Cheah study compared to the OS from the two studies for nivolumab. Kaplan-Meier data from the Cheah study provided a median estimate of OS of 25.2 months. Median OS for specific therapies ranged from 9.5 months to 34 months with investigational agents reporting a median OS of 47.7 months. As discussed above, the CS considered that some of the investigational agents were likely to be nivolumab and so chose to use the patients not receiving investigational agents. Clarification from the Cheah study authors suggests this is not the case and the ERG considers the company should have used the overall population from Cheah. The ERG notes that by choosing the population not receiving investigational agents, the model produces results that are more favourable to nivolumab.

The company fit survival curves for the patients not receiving investigational agents by adapting the Kaplan-Meier data for the overall population according to the median OS observed from the two populations. NICE and the ERG requested that the company provide data for additional SoC survival models, which the company provided (Clarification question B5). The ERG considered that the exponential survival curve fitted for the overall population was appropriate (Table 31).

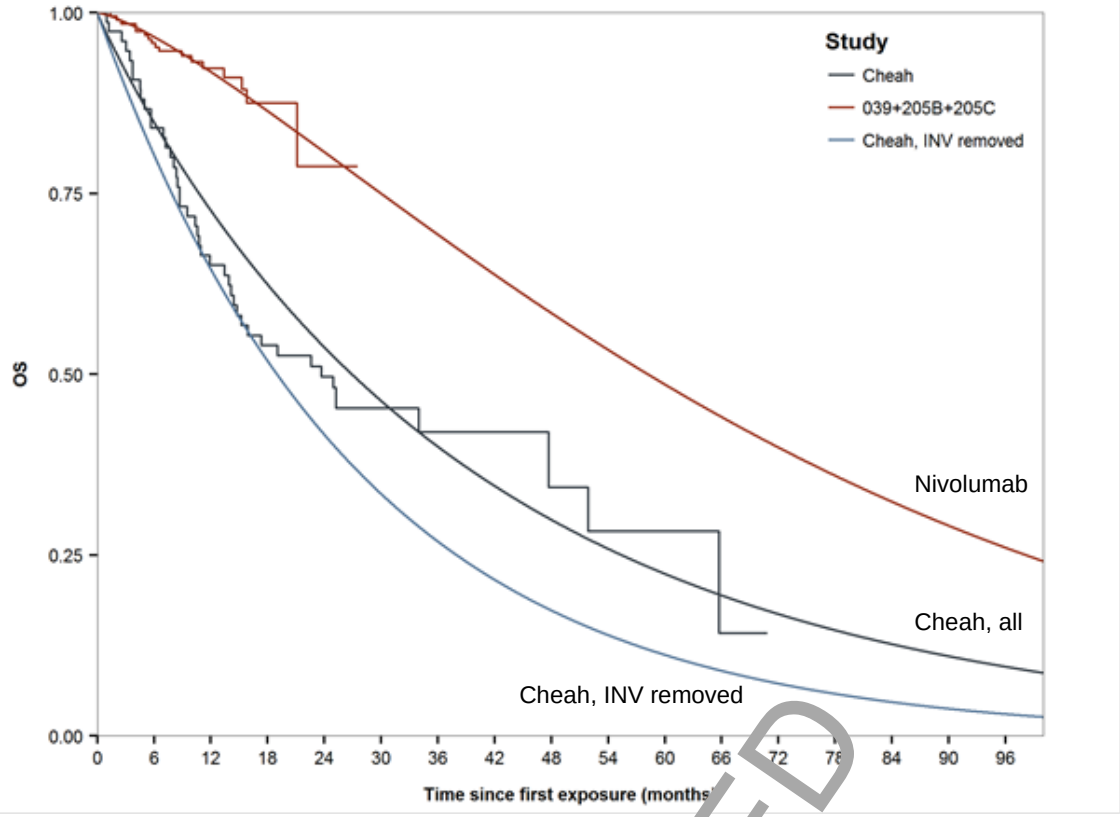


Figure 13 Overall survival: SoC, (CS, Figure 30)

4.3.5.2 Response rates

The response rates or best overall response (BOR) rates, within this submission, have no direct impact on progression or survival, in the economic model. This is due to the use of survival data that implicitly incorporates any impact on patients' survival. However, response rates are used to estimate utility values (details in section 4.3.6). Response rates are also applied in stopping rules and switching to subsequent therapies such as allo SCT.

Within the company model, the response rates used for nivolumab are derived from investigator-assessments from the two nivolumab studies and the impact of applying IRRS-derived response rates are assessed in sensitivity analyses. Response rates for the SoC arm are derived from the Cheah study after adjustment for exclusion of patients receiving investigational agents. Table 32, summarises the response rates applied within the base case analysis of the economic model.

Table 32 Treatment response: base case analysis (CS, Table 43)

Treatment	CR		PR		Source population
	Value	Standard error	Value	Standard error	
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	Eligible population from CheckMate 205 (B and C) and CA209-039
SoC	15.7%	5.09	23.5%	5.94	Cheah 2016[2] (excluding investigational agents)

CR, complete response; PR, partial response; SD, stable disease; SoC, standard of care.

4.3.5.3 Time to treatment discontinuation

The structure of the economic model assumes that patients in both nivolumab and SoC arms switch to subsequent treatment following progression (BSC for the base case). Nivolumab treatment is maintained until progression or discontinuation due to other reasons, while the SoC arm uses the recommended duration of SoC treatment which varies between 1 and 7 months, depending on the treatment (Table 42).

Patients discontinue treatment due to disease progression, AEs or other reasons such as patient preference. Table 33 shows the clinical data used to inform the parametric functions for time to treatment discontinuation. The approach taken in the economic model is for patients to discontinue treatment due to disease progression using the PFS curves described above and additionally for patients to discontinue treatment for reasons other than progression. The discontinuation rate for reasons other than progression is assumed to be the same for the nivolumab and SoC arms.

Table 33 Discontinuation due to any reason: nivolumab (CS, App.6 Table 9)

Parameter	N	Median follow-up (months)	6 Months	12 Months	Median Time on Treatment (months)
Overall, discontinuation any reason	193	12.1	76.7%	59.5%	20.0
Overall, excluding discontinuation due to progression	193	11.1	84.1%	74.2%	23.9

The survival function parameters and the Akaike and Bayesian Information Criteria for discontinuation curves are presented in Table 34 and the long-term survival functions presented in

Figure 14. The company concludes that the most appropriate distribution is the lognormal and the parameters for this are shown in Table 35. The ERG notes that there is a discrepancy in the description of the derivation of the survival function used in Appendix 6 and the survival function used in the economic model. Both functions are shown in Table 35.

Table 34 Discontinuation (excluding discontinuations due to progression) (CS, App.6, Table 12)

Parameters		Akaike Information Criteria	Bayesian Information Criteria	Median Time to Discontinuation (months)
Exponential	lambda: 0.01605	258.6	261.9	43.2
Weibull	Shape: 1.378 Scale: 37.75	257.4	263.9	29.0
Log-logistic	Shape: 1.437 Scale: 33.47	257.7	264.3	33.5
Lognormal	mu: 3.708 sigma: 1.383	256.5	263.1	40.8
Gompertz	Shape: 0.07401 Rate: 0.01021	257.7	264.2	24.3
G Gamma	mu: 3.558 sigma: 1.801 Q: -0.7575	258.3	268.1	56.9

Figure 14 Discontinuation (excluding discontinuation due to progression): nivolumab (CS, App.6 Figure 34)

Table 35 CheckMate 205 discontinuation: nivolumab and SoC (CS, Table 44)

	Discontinuation Parameter, economic model	Discontinuation Parameter, described in appendix 6[a]
Fitting	Lognormal	Lognormal
μ	3.283	3.708
σ	1.252	1.383

[a] CS, App.6 – Table 13.

4.3.5.4 Adverse events

AEs applied in the economic model affect costs and benefits accrued by patients in both arms. To identify AEs and assess the safety profile of nivolumab the company used pooled overall data from both the CheckMate 205 (including Cohort A patients who do not meet the decision problem criteria) and the CA209-39 studies (full sample which includes 8 patients who do not meet the decision problem criteria). The company used the incidence of treatment-related grade 3-4 AE rates,

converted to monthly equivalents based on follow-up times, and applied them to all patients in the model in all cycles. The nivolumab AEs rates are presented in Table 36.

The monthly incidence of AEs for SoC was calculated in a similar way using studies cited within the BCSH guidelines. These rates were then combined into a set of weighted mean chemotherapy monthly AE rates (CS, Table 46) using the proportions receiving each treatment from Cheah (2016). Table 36 presents the AE rates for SoC. The ERG notes that generally the adverse event profile for nivolumab is better than for SoC and in particular [redacted]

Table 36 Adverse Event rates: nivolumab and SoC (CS, Table 45, Table 47)

Adverse events	Weighted monthly rate, nivolumab	Weighted monthly rate, SoC
Anaemia	[redacted]	8.2%
Diarrhoea	[redacted]	0.5%
Dyspnoea	[redacted]	0.1%
Fatigue	[redacted]	0.6%
Leukopenia	[redacted]	13.6%
Nausea	[redacted]	2.0%
Neutropenia	[redacted]	14.2%
Pyrexia	[redacted]	0.3%
Thrombocytopenia	[redacted]	16.8%
Vomiting	[redacted]	2.3%

4.3.5.5 All-cause mortality

The company states that due to the young age of the population enrolled in the clinical trials, the economic model includes age and gender adjusted mortality from the UK life tables. These values are included in every model cycle and are applied multiplicatively. While the company acknowledges some form of double counting, they state that this only occurs in the first few years, due to the low baseline age, and this effect applies equally to all comparators, and therefore is likely to have a minimal impact on predicted survival and cost-effectiveness. The ERG agrees that this approach is unlikely to have a significant impact on the cost-effectiveness results.

4.3.5.6 AlloSCT

In the base case analysis, there is no consideration of patients who receive alloSCT. The CS states the company conducted scenario analyses that explored alternative treatment pathways including alloSCT. Patients were allocated to alloSCT according to evidence describing the use of alloSCT in the Perrot and colleagues (2016) study[40] (Section 4.3.10.2, for details). AlloSCT is allocated according to the proportion of patients in each response category. AlloSCT is associated with morbidity and mortality in the short-term but could be considered potentially curative over the long-term. Scenarios considering the use of alloSCT were modelled using the Kaplan-Meier data describing OS and PFS in the post-alloSCT population from the Cheah study. The description of the PFS and OS parameters used in the scenario analyses are presented in Table 37 and the alloSCT scenario analyses are presented in Section 4.3.10.2.

Table 37 Parameters describing PFS and OS for alloSCT (CS, Table 72)

Parameter	alloSCT
OS	Lognormal; μ: 9.252 σ: 3.551
PFS	Exponential λ: 0.037

The ERG notes that in the nivolumab trials and the Cheah study, a small proportion of patients received alloSCT. Therefore the survival for these studies already includes patients receiving alloSCT.

Summary

One of the main weaknesses of this appraisal is the lack of head-to-head evidence between nivolumab and SoC and the paucity of evidence in patients with relapsed or refractory Hodgkin lymphoma (post-ASCT, post-BTX setting). Therefore, the clinical pathway for Hodgkin lymphoma patients is subject to considerable uncertainty and heterogeneity. Given this, the clinical effectiveness for both the intervention and the comparators is based on assumptions and clinical plausibility. The ERG considers the company should have used the overall population from the Cheah study, rather than the excluding patients who received investigational agents. On balance, we found that the survival models used by the company in the base case were the most appropriate extrapolation choices for nivolumab and SoC.

4.3.6 Health related quality of life

The company conducted a literature search for utility values for adult patients with Hodgkin lymphoma. The search included Embase, Medline In-process, the Cochrane library and EconLit. The inclusion criteria specified generic QoL instruments or direct elicitation in adult patients with Hodgkin lymphoma, who may or may not have been treated previously. Twenty nine studies were included (CS Appendix 5, Table 11). The CS does not discuss the results of the literature search of the relevance of the studies identified. Of the studies included, the economic model uses values from the study by Swinburn and colleagues for the SoC arm.[41]

Swinburn and colleagues[41] reported utility values for patients with relapsed and refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma elicited from members of the public in several countries (including the 100 people from the UK) using the time trade off method. The study reported utility values for the pre-progression and post-progression health states.

HRQoL is incorporated in the model using utility estimates dependent upon the patients' disease state. A disutility is applied for adverse events and age-dependent utility decrements are applied.

The health state utility values used in the model are shown in Table 38 (CS Table 51, p. 122). The utility values for patients treated with nivolumab were based on the CheckMate 205 study. The EQ-5D questionnaire was completed by patients within CheckMate 205 at several time points: baseline (prior to first dose), week 9, every 8 weeks up to week 25, week 33 and every 12 weeks thereafter; following discontinuation, questionnaires were completed at two subsequent follow-ups. The EQ-5D questionnaire used the UK EQ-5D 3L tariff.

Table 38 Summary of utility values for the cost-effectiveness analysis (CS Table 51, p. 122)

State	Utility value: mean (standard error)	Reference
Health state utilities		
Nivolumab: pre-progression	[redacted]	Based on CheckMate 205 data
Nivolumab: post-progression	[redacted]	
SoC: pre-progression	0.76	HL response-specific utilities, Swinburn and colleagues.[41]
SoC: post-progression	0.38	

The EQ-5D utility values from CheckMate 205 were stratified by response for the pre-progression health state. In the base case analysis, the economic model uses the same utility values for patients in the pre-progression health state, i.e. does not use different utility values for those in CR, PR or SD.

The health state utility values from CheckMate 205 and Swinburn and colleagues are shown in Table 39 (CS Appendix 7, Table 1). The CS commented that the utility associated with CR in nivolumab-treated patients is slightly lower than that described in Swinburn and colleagues, while that for PR and SD are higher. The values for post-progression are considerably lower for Swinburn and colleagues (0.39) than for CheckMate 205 ([redacted]).

Table 39 Summary of nivolumab-specific utilities compared to those from Swinburn (CS Table 50, page 122)

Health-state	Response	Nivolumab-specific utility	Swinburn 2015[41]
Pre-progression	CR	[redacted]	0.91
	PR	[redacted]	0.79
	SD	[redacted]	0.71
	Overall	[redacted]	-
Post-progression		[redacted]	0.39

CR, complete response; PR, partial response; SD, stable disease.

In the base case analysis, the economic model uses pre-progression utility values from the CheckMate 205 study for patients treated with nivolumab and from Swinburn and colleagues for patients receiving SoC. This equates to a difference in utility of [redacted] between the arms. The ERG does not consider that this difference in utility between these patients has been proven and considers a more consistent approach would be to estimate the pre-progression utility values for patients on SoC from CheckMate 205. Applying the response-specific utilities from CheckMate 205 (Table 32) to the SoC treatment response proportions (Table 40) generates a pre-progression utility of [redacted], whilst applying response-specific utilities to nivolumab results in a utility of [redacted].

Table 40 Response weighted utility values for nivolumab and SoC

Health State	% in state, Nivolumab	% in state SoC	Swiftburn 2015	Nivolumab utility data
Complete Remission	[redacted]	15.69%	0.910	[redacted]
Partial Remission	[redacted]	23.53%	0.790	[redacted]
Stable Disease	[redacted]	60.78%	0.710	[redacted]
Nivolumab utility (weighted average)			0.801	[redacted]
SoC utility (weighted average)			0.760	[redacted]

The CS acknowledges that the large difference in utility for post-progression patients in the nivolumab and SoC arms may be considered counter-intuitive; however the company suggests that nivolumab has a unique mechanism of action that stimulates the patient's immune system and this would extend into benefits in quality of life in the post-progression phase, even though patients have discontinued treatment. The ERG is sceptical whether this large difference in utility is realistic.

The ERG identified a study by Ramsey and colleagues[42] that reported EQ-5D values for patients with relapsed or refractory Hodgkin lymphoma post-ASCT for patients receiving brentuximab vedotin vs. placebo. The study shows utility values for progressed disease for the placebo group to be between 0.85 (after 3 months) to 0.7 (after 24 months). Therefore, we suggest that the results from Swinburn and colleagues[41] are outliers and may not be realistic. The Swinburn study used TTO methodology using estimates from the general public and it may be that their perception of the disease is not consistent with EQ-5D valuation. In summary, therefore we conclude that our preferred approach is for the economic model to use the post-progression utility values from the CheckMate 205 study for the patients treated with nivolumab and with SoC. The ERG investigates the effect of changing these utility values in the ERG analyses reported in section 4.4.

Age dependent disutility

Age dependent disutility has been applied to patients according to patient age, based on the estimated health utility of the general population (Ara and Brazier[43]). The age-dependent decrement is calculated using the difference in utility between patients' age-related utility and the age-related utility at the age of patients at baseline. The ERG is unable to match the age related disutility to the study by Ara and Brazier and suggests the data is from the report by Kind and colleagues.[44]

Adverse event disutility

Disutilities were included in the model for grade 3-4 treatment-related AEs and are shown in Table 41 (CS Table 49, p. 121). The AE disutility values were based on those applied in the NICE appraisal for pixantrone for refractory aggressive non-Hodgkin's lymphoma (TA306)[45] and are listed in Table 41. In answer to a clarification question (B12), the company stated that the adverse event disutility is assumed to be applied as a one-off disutility in the monthly cycle.

Table 41 Adverse event disutilities (CS Table 49, p. 121)

Adverse event	Disutility	Standard Error	Source
Anaemia	0.090	0.0021	Beusterian 2010[46]
Diarrhoea	0.080	0.0021	Beusterian 2010[46]
Dyspnoea	0.050	0.0120	Doyle 2008[47]
Fatigue	0.073	0.0185	Nafees et al 2008[48]
Leukopenia	0.090	0.0154	Assumed as for neutropenia
Nausea	0.048	0.0162	Nafees et al 2008[48]
Neutropenia	0.090	0.0154	Nafees et al 2008[48]
Pyrexia	0.110	0.0021	Beusterian 2010[46]
Thrombocytopenia	0.108	0.0108	Tolley 2013[49]
Vomiting	0.048	0.0162	Nafees et al 2008[48]

4.3.7 Resource use and costs

The company conducted a literature search for resource use in Hodgkin lymphoma. The inclusion criteria specified that studies had to report resource use and/or costs associated with the management of Hodgkin lymphoma at the patient level where the study had been conducted in the UK or EU. The review identified 10 studies (shown in Appendix 5, Table 16). The ERG notes that the CS reports a different number of identified studies (i.e 12 studies, p. 124). The CS does not discuss the studies found or comment on whether any of them are relevant to this appraisal.

The nivolumab dosing schedule is stated in CS Table 52, p. 125. The recommended daily dose for nivolumab for patients with Hodgkin lymphoma is 3mg/kg by IV every 2 weeks, administered over 60 minutes. The dosage schedule is consistent with that used in the CheckMate 205 study. The unit cost for nivolumab is £1,097 for a 10 ml vial (10mg/mL) and £439 for 4ml vial. The cost per cycle is £5,724 per month, assuming wastage and a patient weight of 80kg. The administration costs are

£389.41[50] for the first administration and £326.41 for subsequent administrations. Nivolumab has been provided by the company with a patient access scheme discount of [redacted].

The cost calculation of SoC, comprised of chemotherapy, brentuximab vedotin retreatment and bendamustine, is based upon the proportion of patients who received each treatment in the Cheah and colleagues study. The dosage schedules of the treatments for SoC are shown in CS Table 57, p. 127. This table also shows the proportions of each treatment that comprise SoC (received by NICE and the ERG in response to a clarification question, B6). The proportions of patients that received bendamustine and brentuximab vedotin were specified in the Cheah and colleagues study. The CS calculated the proportions of patients on bendamustine and brentuximab vedotin using these data but excluded patients receiving investigational agents, ASCT and 'other'. For the chemotherapy agents, the company assumed an equal proportion of patients received each regimen. These regimens were chosen according to BCSH guidelines.[1] Clinical advice to the ERG suggested that mini-BEAM or DexaBEAM are not commonly used salvage regimens for Hodgkin lymphoma in the UK. The ERG therefore suggests that SoC should not contain these regimens. We investigate the effects of changing the SoC costs in the ERG analyses (section 4.4).

The unit costs and dose frequency for treatments comprising SoC and the proportion of patients receiving them are shown in Table 42. The monthly cost of SoC is as follows: £4,729 month 1, £4,141 month 2, £3,057 month 3, £2,251 month 4, £2,219 month 5, £1,913 month 6, £332 month 7, £0 month 8+.

Table 42 SoC costs and dosing schedule (CS Table 55, p. 126)

Regimen	Cost per cycle	Dosing instructions	Cycle length	Number of cycles	Proportion received
ICE	£1,993.51	every 14 d for two cycles	14	2	4.15%
IVE	£2,833.51	21 day cycle; 2 cycles	21	2	4.15%
MINE	£1,683.20	every 28 days; 2 courses	28	2	4.15%
IVOx	£3,128.47	21 day cycle; 3 cycles	21	3	4.15%
IGEV	£3,703.72	21 day cycle; 4 cycles	21	4	4.15%
GEM-P	£2,198.83	28 day cycle; three cycles	28	3	4.15%
GDP	£1,484.32	21 days; 2 cycles	21	2	4.15%

GVD	£3,020.85	21 days; 2 cycles	21	2	4.15%
Mini-BEAM	£11,221.91	28 day cycle; three cycles	28	3	4.15%
DexaBEAM	£11,355.50	28 day cycle; 2 cycles	28	2	4.15%
ESHAP	£1,056.87	every 21- 28 d for 4 cycles	28	4	4.15%
ASHAP	£1,058.87	Assumed 28 day cycle; 3 cycles	28	3	4.15%
DHAP	£1,204.27	every 21 days for two cycles	21	2	4.15%
DHAOx	£2,004.77	21 day cycle; 4 cycles	21	4	4.15%
Bendamustine	£2,096.91	every 28d for 6 cycles	28	6	27.91%
BTX	£7,889.41	3 week cycle for 9 cycles	21	9	13.95%

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BTX: brentuximab vedotin; DexaBEAM: dexamethasone, carmustine, etoposide, cytarabine, melphalan; DHAOx: dexamethasone, cytarabine, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; 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; Mini-BEAM: carmustine, etoposide, cytarabine, melphalan.

We conferred with clinical experts who confirmed that mini-BEAM and DexaBeam would not be expected to be used in the UK. In light of this, we have calculated alternative costs that exclude these treatments. Table 43 reports these treatment costs.

Table 43 SoC costs excluding mini-BEAM and DexaBeam

Parameter	SoC (£) CS base case	SoC (£) ERG estimate
Month 1	4,729.43	3710.21
Month 2	4,141.92	3204.80
Month 3	3,037.50	2652.61
Month 4	2,251.40	2251.40
Month 5	2,218.97	2218.97
Month 6	1,913.31	1913.32
Month 7	331.52	331.52
Month 8+	0.00	0

Resource use estimated for the health states were derived from those previously used for the NICE appraisal of brentuximab vedotin,[51] shown in CS Table 59, p. 132. The company assumed the same resource use for the pre-progression and post-progression health states. The resources used were 10.4 outpatient attendances per year with blood tests and 3 CT scans per year. Fifty per cent of the CT scans included a PET scan. The costs for these resources are shown in Table 44 (CS Table 59, p. 132). The monthly costs of pre-progression and post-progression health states are £190.

Table 44 Pre- and post-progression resource use applied in the economic model (CS Table 59, p. 132)

Resource	Item	Value	Source
Outpatient attendance	Rate	10.40	BTX STA,[51]
	Cost (£)	150.38	NHS reference costs 2014-15[50] Clinical Haematology 303
	Total (£)	1,563.94	-
Blood count	Rate	10.40	BTX STA,[51]
	Cost (£)	3.01	NHS reference costs 2014-15[50] Haematology DAPS05
	Total (£)	31.26	-
Biochemistry	Rate	10.40	BTX STA,[51]
	Cost (£)	1.19	NHS reference costs 2014-15[50] Clinical Biochemistry DAPS04
	Total (£)	12.37	-
CT scan (with assumption that 50% will include PET scan)	Rate	3.00	BTX STA,[51]
	Cost (£)	224.44	NHS reference costs 2014-15[50] RD26Z; RN03A
	Total (£)	673.33	-
Overall cost	Annual (£)	2,280.91	-
	Monthly (£)	190.08	-

BTX, brentuximab vedotin.

The costs of treating treatment-related adverse events are shown in CS Table 60, page 133. These are taken from NICE appraisals for Pixantrone for non-Hodgkin's lymphoma (TA306)[45] and dasatinib, nilotinib and imatinib for chronic myeloid leukaemia (TA251)[52] and inflated to 2014-2015 costs. The company clarified (in answer to a clarification question, B14) that the adverse event costs from TA306 are from the ERG report for the TA306 NICE appraisal, rather than from the manufacturer submission.

In the company's base case, patients did not receive alloSCT. The ERG considers that the company should have included costs for alloSCT within the base case analysis because some patients in the nivolumab and SoC arms received alloSCT. The company conducted a scenario analysis where a proportion of patients received alloSCT at six months; the probability of receiving alloSCT was dependent on treatment respons. In this scenario, there were costs included for the alloSCT and subsequent immunosuppresion therapies. The company assumes that the proportion receiving alloSCT is based on the response category, derived from Perrot and colleagues,[40] where the proportion receiving alloSCT is 22.2% for CR, 14.1% for PR and 5.56% for SD. Patients receive immunosuppression therapies (ciclosporin and mycophenolate mofetil) and haematology outpatients appointments every 3 months. The cost of alloSCT is £21,672[50] and the monthly cost of immunosuppression therapies and outpatient appointments are £91.69.[53] The company varies the assumption around the costs and proportion of patients receiving alloSCT in scenario analyses.

The company conducts a scenario analysis using a cost of alloSCT of £110,374 as reported by Radford and colleagues[54] who conducted a retrospective analysis on resource use in 5 centres for patients with relapsed or refractory Hodgkin lymphoma post-ASCT. The ERG notes that the cost of alloSCT used in the appraisal of brentuximab vedotin was £108,052 based upon a study by the BMT Unit at the Beatson West of Scotland Cancer Centre.[51] We suggest that the company is therefore underestimating the cost of alloSCT and suggest that the cost of £110,374 should be used to be consistent with the NICE appraisal for brentuximab vedotin.

4.3.8 Model validation

Internal consistency

The company commissioned a technical review of the cost-effectiveness model conducted by an independent consultant. The technical review was designed to validate the modelling approach, illuminate areas of disagreement to be resolved prior to generating model results, and enable pre-emption of issues that reimbursement agencies and model critics may raise. The company also indicated that quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculations, formulae and visual basic code.

The company conducted additional internal validation assessing the fit of modelled survival to observed trial outcomes. These comparisons showed that modelled survival and observed survival closely matched. The results of these assessments of fit are reported in Table 45.

Table 45 Comparison of clinical trial inputs and modelled outputs (CS Table 65, p. 139)

Parameter	Nivolumab	SoC	Incremental
Overall survival in years			
Survival curve median (mean)	4.8 (5.9)	1.6 (2.3)	3.3 (3.6)
Model output median (mean)	4.0 (5.0)	1.5 (2.1)	2.6 (2.9)
Progression-free survival in years			
Clinical trial (Median)	1.4	0.4	1.0
Survival curve median (mean)	1.4 (2.6)	0.4 (0.5)	1.0 (2.1)
Model output median (mean)	1.1 ([redacted])	0.3 (0.4)	0.8 ([redacted])
Modelled output			
QALYs	[redacted]	0.93	[redacted]
Life year	5.01	2.11	2.90

QALY, quality-adjusted life year; SoC, standard of care.
No formal validation reports or procedures were reported.

The ERG replicated model outputs, checked inputs and outputs for consistency, and checked model code. Whilst the model was ostensibly in Excel; however, health state transitions and the utilities and costs associated with them are all calculated within and output from the VBA as values. The core outputs of the model are completely reliant on execution of VBA code — the model is more of a VBA model in an Excel graphical interface than a true spreadsheet model. The company conducted 58 scenario analyses, in total. Scenario analyses were manually run by the ERG to the extent that scenarios were sufficiently described. Some scenarios did not have sufficient explanation for their methods whilst others did not produce the results reported in the CS. The company's response to clarification question B9 enabled further scenario analysis checking. We identified discrepancies between the CS description of CS Analysis 26 and the parameters shown in the model provided for checking. When the ERG ran the analysis with parameters as reported, the ICER was £23,608 per QALY rather than £12,452 per QALY. Additionally, the reduction in the ICER reported by the company is illogical, as decreasing costs for SoC should not decrease the ICER of nivolumab. We were unable to identify the precise nature of the error, as the models provided in response to clarification did not produce the CS result, and had parameter discrepancies.

The ERG conducted additional validation of the company's alloSCT scenario 2 to verify that the numbers of people having alloSCT were consistent with those in the trials. Briefly, the alloSCT

scenarios implement a transition at six months to alloSCT as a new treatment for a proportion of patients with CR, PR and SD. To validate the use of Perrot and colleagues we multiplied the proportion of patients in each response state (CR, PR, SD) at the start of the model by the proportions of patients that Perrot and colleagues estimated would have alloSCT in each of these respective response states.[40] Table 46 compares the proportion of patients in each treatment who have alloSCT using the Perrot algorithm compared to the observed results of the treatment effectiveness trials. We note that the proportion of patients receiving alloSCT is underestimated in the economic model compared to observed alloSCT procedures in the studies. We investigate the effect on the model results of using the observed proportion of patients receiving alloSCT in the ERG analyses (section 4.4).

Table 46 Modelled versus observed proportion of patients receiving alloSCT

Source	Proportion observed with alloSCT	Proportion predicted using Perrot and colleagues
Nivolumab trials	[redacted]	[redacted]
SoC (Cheah and colleagues)	17.72%	[redacted]

alloSCT, Allogeneic stem cell transplant; SoC, Standard of Care.

Additionally, we have compared the predicted survival in the model to predicted survival from observed data and from parametric curves for both nivolumab and alloSCT. We found that there was substantial variation in the data, primarily concerning whether SoC patients received the benefits of investigational therapies. Table 47 shows the results of these comparisons on mean and median survival. It should be noted, that there is substantial uncertainty with regards to long term survival in this patient population because data are immature for nivolumab and derived from a small population that may not be representative for SoC. There is substantial uncertainty around overall survival for nivolumab. Experts consulted by the ERG stated that there were insufficient data to estimate nivolumab OS, but that the recently published Younes and colleagues study estimate of 10 months median PFS seemed plausible.[4]

Table 47 Comparison of company survival models

Analysis	Nivolumab median (mean) years OS	SoC median (mean) years OS
Survival curve estimate	4.8 (5.9)	1.6 (2.3)
CS base case output	4.0 (5.0)	1.5 (2.1)
CS Analysis 20 (alloSCT Scenario 2, CS p. 153)	[redacted]	[redacted]

OS: overall survival; PFS: progression-free survival; SoC: standard of care.

External consistency

There is a lack of data on the patient population for patients who have failed brentuximab vedotin and ASCT with classical Hodgkin lymphoma. A NICE Technology Appraisal for brentuximab vedotin after the failure ASCT in classical Hodgkin lymphoma is in progress at the time of submission of this report.[51] As noted in the CS for nivolumab, the population in the brentuximab vedotin STA is at an earlier stage of the disease with greater expected survival, making the two STA populations not comparable.

The results presented were consistent with the data presented. Unfortunately, neither the company nor the ERG were able to identify a suitable model for external validation.

4.3.9 Cost effectiveness results

The results from the economic model are presented as incremental cost per QALY gained (CS Section 5.7, pp. 136-140). The company presented results for the base case analysis, with and without a PAS. Results for one-way sensitivity analyses, probabilistic sensitivity analyses, and the 58 scenario analyses reported by the company were conducted with the confidential PAS included.

The results of the list price base case analysis are reported in Table 48. Total costs for nivolumab were [redacted] whilst total costs for SoC were £21,090 [redacted] incremental). Total QALYs for nivolumab were [redacted] whilst total QALYs for SoC were 0.932 ([redacted] incremental QALYs). The base case ICER for nivolumab at list price was [redacted] per QALY compared to SoC. Base results with a [redacted] discount for nivolumab are reported in Table 49. The ICER for nivolumab (with PAS) compared to SoC was £19,882 per QALY.

Table 48 Base case cost-effectiveness results (list price)

Parameter	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
SoC	£21,090	-	0.932	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 49 Base case cost-effectiveness results (with PAS)

	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
SoC	£21,090	-	0.932	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,882

ICER, Incremental cost-effectiveness ratio; SoC, Standard of Care; QALY, Quality-adjusted life year.

4.3.10 Assessment of uncertainty

4.3.10.1 One-way sensitivity analyses

The company conducted a range of one-way sensitivity analyses (CS Section 5.8.2, pp. 144 to 146). The following parameters were varied in one-way deterministic sensitivity analyses:

- Rates of discounting
- Time horizon
- Baseline patient age
- Proportion male
- Health state costs: complete remission
- Health state costs: partial remission
- Health state costs: stable disease
- Health state costs: progressed disease (initial month)
- Health state health state utility: CR
- Health state health state utility: PR
- Health state health state utility: SD
- Health state health state utility: post-progression
- Pre-progression therapy costs: nivolumab
- Pre-progression therapy costs: SoC
- Pre-progression therapy costs: BSC
- Pre-progression therapy costs: BSC

Figure 15 shows the effect of the analyses on the ICERs. The most influential parameters were shortening the time horizon to 5 or 10 years, raising or lowering nivolumab pre-progression therapy costs by 20%, followed by lowering or raising post-progression utility by 20%. No analyses raised the ICER above £30,000 per QALY. The ICER of nivolumab, in comparison to SoC, appears robust to the alternative parameter assumptions in one-way sensitivity analyses. We considered that the choice of parameters for one-way sensitivity analyses were adequate.

The company did not make any conclusions with regards to the one-way sensitivity analyses except in the company's overall conclusions on sensitivity analyses.

Figure 15 Univariate sensitivity analysis, ICERs (PAS price)(CS Figure 38, p. 145)

4.3.10.2 Scenario Analysis

A total of 58 scenario analyses were conducted (CS Section 5.8.3, pp. 147-165). For this section of the report we will break the section into the following categories:

- A. Alternative parameterisations of both PFS and OS nivolumab survival (16 analyses)
- B. Alternative parameterisations of SoC OS (2 analyses)
- C. Analyses with alternative treatment sequences (5 analyses)
- D. Analyses with alternative comparator arm treatment composition (3 analyses)
- E. Analyses using alternative synthesis methods for indirect treatment comparisons (18 analyses)
- F. Analyses with alternative baseline age (2 analyses)
- G. Explorations of treatment stopping rules (4 analyses)
- H. Explorations of alternative utility values (4 analyses)
- I. Analyses testing other modelling assumptions (4 analyses)
    - A scenario with no adverse events modelled (1 analysis)
    - A scenario doubling resource use in the post-progression health state (1 analysis)
    - A scenario that applies IRRC-assessed endpoints for nivolumab (1 analysis)
    - Analysis without half-cycle correction (1 analysis)

To maintain a consistent flow and allow convenient referencing between analyses, we have numbered the scenario analyses conducted by the company from 0-58. Analysis 0 corresponds to the company base case.

A. Alternative parameterisations of both PFS and OS nivolumab survival

The company ran a wide variety of alternative survival analyses for PFS and OS in nivolumab patients (see CS Figure 25 and CS Figure 26, pp. 106-107). The alternative survival curves tested for nivolumab in the model included the following: exponential, Weibull, lognormal, and log-logistic. Generalised gamma and Gompertz curves were assessed for goodness of fit in survival modelling, but not utilised in any cost-effectiveness model parameterisations. Analyses 1 to 15 assess alternative parametric forms, whilst Analysis 16 applies Kaplan-Meier curves during the trial follow-up and extrapolates using the survival models selected for the base case.

Table 50 Alternative nivolumab survival models (PAS Price)

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case Lognormal PFS Weibull OS	[redacted]	[redacted]	£21,090	0.932	£19,882
1	Exponential PFS Exponential OS	[redacted]	[redacted]	£21,090	0.932	£13,764
2	Weibull PFS Exponential OS	[redacted]	[redacted]	£21,090	0.932	£12,199
3	Log-logistic PFS Exponential OS	[redacted]	[redacted]	£21,090	0.932	£13,202
4	Lognormal PFS Exponential OS	[redacted]	[redacted]	£21,090	0.932	£13,642
5	Exponential PFS Weibull OS	[redacted]	[redacted]	£21,090	0.932	£20,132
6	Weibull PFS Weibull OS	[redacted]	[redacted]	£21,090	0.932	£17,984
7	Log-logistic PFS Weibull OS	[redacted]	[redacted]	£21,090	0.932	£19,264
8	Exponential PFS Log-logistic OS	[redacted]	[redacted]	£21,090	0.932	£14,842
9	Weibull PFS Log-logistic OS	[redacted]	[redacted]	£21,090	0.932	£13,252
10	Log-logistic PFS Log-logistic OS	[redacted]	[redacted]	£21,090	0.932	£14,245
11	Lognormal PFS Log-logistic OS	[redacted]	[redacted]	£21,090	0.932	£14,697
12	Exponential PFS Lognormal OS	[redacted]	[redacted]	£21,090	0.932	£12,015
13	Weibull PFS Lognormal OS	[redacted]	[redacted]	£21,090	0.932	£10,718
14	Log-logistic PFS Lognormal OS	[redacted]	[redacted]	£21,090	0.932	£11,562
15	Lognormal PFS Lognormal OS	[redacted]	[redacted]	£21,090	0.932	£11,926
16	Kaplan-Meier over trial, with lognormal PFS and Weibull OS extrapolation (as in base case)	[redacted]	[redacted]	£21,090	0.932	£19,994

ICER, Incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; SoC: standard of care; QALY, Quality-adjusted life year.

[a] For Analyses 1 to 15, parameters from CS Figure 25 and CS Figure 26 (CS pp.106-107), Results from CS Table 67 (CS p. 148). [b] For Analysis 16, results derived from CS Table 70 (CS p. 150); Kaplan-Meier data was not provided with the CS, but was provided in the answers to clarification questions.

Analysis of goodness of fit for the various survival models showed that there was little difference between the models for PFS on the Akaike Information Criterion and the Bayesian Information Criterion. Figure 11 shows the assessments of survival model fits for PFS and OS.

In the scenario analyses conducted by the company, the survival model chosen for OS was a key driver of cost effectiveness. Alternative models for PFS had a modest impact on ICERs. Analyses 1 to 16 produced ICERs between £10,718 per QALY and £20,132 per QALY. The company stated that the survival curves utilised for the base case could be considered the least beneficial to nivolumab's cost-effectiveness but the most clinically plausible. We found that the choices made by the company in the base case were appropriate extrapolation choices as noted in Section 4.3.5.

B. Scenarios evaluating alternative models for SoC OS

The company conducted two analyses that tested the high and low estimates for OS using the exponential curve from data in Cheah and colleagues excluding investigational agents. Table 51 reports the alternative survival curves used and the results of the analysis.

Table 51 Alternative SoC survival models (PAS Price) (CS Table 69, p. 149)

#	Analysis parameters	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)	Source
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882	Table 63 (p. 136)
17	High SoC OS from Cheah 2016 (exponential model) λ: 0.0204	[redacted]	[redacted]	£25,287	1.468	£22,742	Table 69 (p. 149)
18	Low SoC OS from Cheah 2016 (exponential model) λ: 0.07296	[redacted]	[redacted]	£17,135	0.528	£18,613	

OS: overall survival; SoC: standard of care.

C. Analyses with alternative treatment sequences

The company conducted several analyses where alloSCT was modelled as a 'special transition case'. In this case, a proportion of patients transitioned at six months to a new alloSCT treatment arm. This treatment arm was identical whether patients transitioned from SoC or nivolumab. In the base case, patients' survival after initial therapy is determined by the survival curve for their initial therapy. In the special transition case, the proportion of patients that receive alloSCT have a new

survival curve that is not based on initial treatment. This new survival curve for patients receiving alloSCT was modelled based on data from Cheah and colleagues[2] using the parameters in Table 37. Patients who progressed after alloSCT were assumed to have costs, utilities and survival comparable to the SoC arm, regardless of initial therapy.

Whilst alloSCT survival was derived from Cheah and colleagues,[2] the probability of having an alloSCT was externally derived and applied to both arms using data from Perrot and colleagues,[40] under two assumptions. The first assumption based proportions of patients on probability of alloSCT by the level of response in Perrot and colleagues, whilst the second assumption assumed patients who had complete remission and partial remission had an equivalent probability of alloSCT. The second assumption is based on pooling response across patients with a complete or partial remission in Table 52, resulting in 18.6% of complete and partial responders receiving alloSCT.

Table 52 Patients receiving alloSCT in the model based on response category (CS Table 74, p. 153)

Parameter	Proportion who received alloSCT in CS Scenario Analyses 19 and 20 (Perrot 2016)[40]	Proportion who received alloSCT in CS Scenario Analyses 21 and 22 (pooled CR and PR)
CR	18/81 (22.1%)	27/145 (18.6%)
PR	9/64 (14.1%)	27/145 (18.6%)
SD	1/18 (5.56%)	1/18 (5.56%)

AlloSCT, allogenic stem cell transplant; CR, complete remission; PR, partial remission: SD: stable disease.

The cost of alloSCT was estimated in two ways: using pooled NHS Reference Costs (as in Analyses 19 and 21), and using costs estimated by Radford and colleagues (as in Analyses 20 and 22).[54] Details of the Reference Cost based calculation are reported in Table 53. Radford and colleagues estimated that the cost of alloSCT was £110,374. Under both alloSCT cost assumptions, the monthly cost of treatment after the alloSCT procedure is £91.69, as calculated in TA241.[55] We present further analysis of the cost of alloSCT in Section 4.3.7.

Table 53 Estimation of ongoing drug and monitoring costs after alloSCT (CS Table 73, p. 153)

Resource	Mean	Source	
AlloSCT	£21,672.64	National Schedule of Reference Costs 2014-15 - Total HRGs: weighted average of total adult bone marrow transplantation costs [codes: SA19A, SA20A, SA21A, SA22A, SA23A].[50]	
Monthly cost of AlloSCT	£91.69	Derivation based on Assessment Group method NICE TA241[55] set out below	
Unit	**Unit cost**	**Source**	**Monthly cost**
Quarterly specialist appointment			
Clinical Haematology consultant-led outpatient attendance	£150.38 per appointment	NHS Reference Costs 2014-15[50]	£50.13
Immunosuppressive therapies			
Ciclosporin 50 mg twice daily plus prednisolone 20 mg once daily (60% of patients)	Ciclosporin: 30 x 50 mg capsules £25.50 Prednisolone: 100 x 5 mg tablet £2.20	MIMS[53]	£54.42
Mycophenolate mofetil 1g twice daily plus prednisolone 20 mg once daily (40% of patients)	Mycophenolate mofetil: 50 x 500 mg tablets £8.05 Prednisolone: 100 x 5 mg tablet £2.20	MIMS[53]	£22.28
Total management costs			
Quarterly specialist appointment plus weighted average of two immunosuppressive regimens			£91.69

Resource costs: AlloSCT, allogenic stem cell transplant.

Drug and monitoring costs: Length of month assumed to be 30.475 days

National Schedule of Reference Costs 2014-15 – Consultant-led outpatient attendance: Clinical Haematology; Currency code: WF01A; Service code: 303

In addition to scenario analyses modelling alloSCT as a separate treatment, the company modelled pre-progression therapy (after discontinuation) using an alternative method. In the base case analysis, it is assumed that patients with progression or discontinuation switch to BSC, comprised of several therapies including chemotherapy and palliative care, dependent on progression status. The company argues that this is a simplification, and in clinical practice, patients are likely to receive chemotherapy in the pre-progression phase if it is clinically feasible. Based on this, the company conducted a scenario analysis where patients discontinuing therapy (either nivolumab or SoC) in the pre-progression phase receive subsequent SoC, subject to the same assumptions and costs as the initial therapy line; BSC is still received as the post-progression therapy.

Table 54 presents the results of the analyses with alternative treatment sequences. In Section 4.4 we have undertaken analyses using Analysis 20, as we believe that this scenario is most representative of the expected costs of alloSCT.

Table 54 Parameters and results from analyses of alternative treatment sequences

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
19	Scenario 1: likelihood of alloSCT from Perrot 2016[107] and costs from NHS reference costs,[104] utility = 0.856	[redacted]	[redacted]	£22,866	1.076	£18,587
20	Scenario 2: likelihood of alloSCT from Perrot 2016[107] and costs derived from Radford 2016,[108] utility = 0.856	[redacted]	[redacted]	£24,880	1.076	£20,433
21	Scenario 3: likelihood of alloSCT from Perrot 2016[107], but nivolumab patients with CR and PR assumed equivalent; costs from NHS reference costs,[104] utility = 0.856	[redacted]	[redacted]	£22,866	1.076	£18,479
22	Scenario 2: likelihood of alloSCT from Perrot 2016[107], but nivolumab patients with CR and PR assumed equivalent; costs derived from Radford 2016,[108] utility = 0.856	[redacted]	[redacted]	£24,880	1.076	£20,489
23	Patients receive chemotherapy pre-progression after discontinuing treatment (nivolumab or SoC)	[redacted]	[redacted]	£21,988	0.930	£22,095

alloSCT, allogenic stem cell transplant; CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results derived from CS Table 63 (CS p. 136).
[b] Parameters and results derived from CS Table 75 (CS p. 153).

D. Analyses with alternative comparator arm treatment composition

The company conducted several analyses evaluating alternative compositions of SoC treatment. In the base case, OS was modelled with investigational agents excluded. Analysis 24 used digitised Kaplan-Meier data from Cheah and colleagues to fit survival curves for SoC. The company assumed that a lognormal parametric curve was the best model for PFS and Weibull was the best model for OS. They assumed this based on the assumption that a high number of patients in Cheah would have been taking nivolumab. As stated earlier, contact with the authors of Cheah and colleagues revealed that few patients received nivolumab.

An analysis was also conducted that compared nivolumab to SoC wherein SoC consisted only of BSC treatment. The company identified no evidence supporting the efficacy of BSC, so assumed that all patients would enter the model with stable disease and OS derived from the lowest reported by Cheah and colleagues for chemotherapies (exponential parametric fit; λ: 0.07296).[2] PFS was assumed equivalent to base case SoC PFS. Utilities for BSC were derived based on Swinburn and colleagues,[41] weighted to assume 100% occupancy of the stable disease response rate (utility = 0.71). Adverse events and discontinuation were assumed to be zero with patients remaining on BSC until death.

An additional analysis was undertaken where the make-up of SoC, and corresponding costs, were derived from the in-progress STA of brentuximab vedotin.[52] Efficacy was assumed to be equivalent to survival for the entire Cheah and colleagues population (including investigational agents). PFS was modelled using a lognormal curve (μ: 1.074, σ: 0.728) and OS was modelled using a Weibull curve (Scale: 39.438; Shape: 0.959). The make-up of chemotherapy in the brentuximab vedotin appraisal is reported in Table 55.

Table 55 Chemotherapy composition during brentuximab vedotin appraisal (CS Table 81, p. 157)

Component	Usage
GEM-Ox: gemcitabine and oxaliplatin	15%
GEM-P: gemcitabine ,cisplatin, methylprednisolone	15%
BEACOPP: Cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisolone, vincristine, bleomycin	10%
DHAP: dexamethasone, cytarabine, cisplatin	10%
Bendamustine	20%
Investigational agents	5%
ChIVPP: chlorambucil, vinblastine, procarbazine, prednisolone	25%

Adverse events for the alternative SoC make-up in Analysis 26 were derived from the brentuximab vedotin appraisal (see Table 56). Costs accorded to the new SoC treatment composition are reported in Table 57.

Table 56 Rate of adverse events for SoC, derived from brentuximab vedotin appraisal (CS Table 82, p. 157)

Adverse event	Rate
Anaemia	0.052852
Diarrhoea	0.014965
Dyspnoea	0.0000374
Fatigue	0.002373
Leukopenia	0.12179
Nausea	0.031132
Neutropenia	0.11337
Pyrexia	0.00032
Thrombocytopenia	0.147947
Vomiting	0.054733

Table 57 Costs of SoC in Analysis 26, derived from brentuximab vedotin appraisal (CS Table 83, p. 158)

Month	Monthly cost (£)
Month 1	2041.17
Month 2	1932.93
Month 3	1780.49
Month 4	1508.09
Month 5	1027.86
Month 6	512.19
Month 7	38.91
Month 8+	0

Table 58 reports the results of Analyses 24-26, in which alternative treatment compositions for SoC are examined. The ERG found an error in CS Analysis 26. When we input the parameters described by the company (CS pp. 155-156), the analysis produced an ICER of £23,608 per QALY not the value reported in Table 58. Examining further models provided by the company in response to clarification questions produced no further insight as to why total SoC costs more than double from the CS base case in an analysis that lowers the cost of SoC.

Table 58 Analyses using alternative SoC treatment composition

#	Analysis parameters	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)	Source
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882	Table 63 (p. 136)
24	Including investigational interventions (naive ITC): SoC survival, PFS = Lognormal; μ: 1.074 σ: 0.728 OS = Weibull; Scale (A): 39.438 Shape (B): 0.959 Utilities for response and preprogression reflect Cheah whole population.	[redacted]	[redacted]	£18,988	1.204	£22,855	Table 79 (p. 156)

25	Best Supportive Care only OS Exponential λ: 0.07296 Utility (SoC) 0.71 No AE or discontinuation.	[redacted]	[redacted]	£7,630	0.528	£21,580	Table 80 (p. 157)
26	SoC composition and AE equivalent to ongoing BTX TA SoC survival PFS = Lognormal; μ: 1.074 σ: 0.728 OS = Weibull; Scale (A): 39.438 Shape (B): 0.959 AE derived from BTX appraisal	[redacted]	[redacted]	£45,274	1.204	£12,452	Table 84 (p. 158), the reported value is incorrect. The correct value is £23,608 per QALY

BTX, brentuximab vedotin; OS, overall survival; PFS, progression-free survival; SoC: standard of care; QALY, Quality-adjusted life year.

E. Analyses using alternative synthesis methods for indirect treatment comparisons

The company conducted analyses modelling SoC based on indirect treatment comparisons described in Section 3.1.7. Table 59 reports parameters and results for analyses for studies in a post-ASCT, post-BTX population, whilst Table 60 reports parameters and results for studies with post-ASCT populations. Analyses adjusted PFS, OS, and composition of treatment response for SoC. As utility scores are based on treatment response, this also changes pre-progression utilities for SoC.

For the purposes of this assessment, the group of studies that is derived from a population that have not necessarily had brentuximab vedotin (Table 60), is not the most relevant population. ICERs for the alternative indirect treatment comparisons ranged between £20,885 per QALY and £24,361 per QALY. We believed that of the analyses conducted in this section, CS Analysis 30 is the most relevant. CS Analysis 30 is derived from the subgroup of studies where 70% of patients or more have had ASCT and brentuximab vedotin, better accounts for uncertainty by using a random effects model, and includes investigative agents in the estimates of efficacy. For these reasons, we have used CS Analysis 30 (in combination with CS Analysis 20) for some scenario analyses in our investigation of uncertainty in Section 4.4.

Table 59 Alternative ITC comparisons (CS Table 85, p. 160) Post-ASCT, Post-brentuximab vedotin studies, SoC parameters and results

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
27	Unadjusted ITC, all studies, fixed effects. PFS = λ: 0.1134 OS= λ: 0.0204 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£23,379	1.532	£24,277
28	Unadjusted ITC, all studies, random effects PFS = λ: 0.1134 OS= λ: 0.0204 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£23,379	1.540	£24,361
29	Unadjusted ITC, subgroup,[c] fixed effects PFS = λ: 0.1576 OS= λ: 0.0261 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£20,149	1.229	£22,626
30	Unadjusted ITC, subgroup,[c] random effects PFS = λ: 0.1576 OS= λ: 0.0261 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£20,149	1.236	£22,686
31	MAIC ITC, all studies, fixed effects. PFS = λ: 0.1169 OS= λ: 0.0222 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£22,554	1.435	£23,605
32	MAIC ITC, all studies, random effects PFS = λ: 0.1169 OS= λ: 0.0222	[redacted]	[redacted]	£22,554	1.442	£23,681

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
	Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]					
33	MAIC ITC, subgroup,[c] fixed effects PFS = λ: 0.1602 OS= λ: 0.0277 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£19,651	1.170	£22,298
34	MAIC ITC, subgroup,[c] random effects PFS = λ: 0.1602 OS= λ: 0.0277 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£19,651	1.177	£22,357
35	MAIC ITC, Cheah (overall) PFS = λ: 0.2064 OS= λ: 0.0292 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£18,349	1.086	£22,079
36	MAIC ITC, Cheah (no investigational agents) PFS = λ: 0.1673 OS= λ: 0.0387 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£17,338	0.886	£20,885

ICER, Incremental cost-effectiveness ratio; MAIC ITC, matching-adjusted indirect comparisons Indirect treatment comparison; OS, overall survival; PFS, progression-free survival SoC: standard of care; QALY, Quality-adjusted life year.

[a] Results for the base case from CS Table 63 (CS p. 136)

[b] Parameters and results for CS Analyses 27-36 derived from CS Table 85 (CS p. 159)

[c] Subgroup of SLR studies based on those studies where subgroup of post-ASCT post-BTX population is reported or where >70% of patients match this criteria; this includes efficacy of investigational agents.

Table 60 Alternative ITC comparisons (CS Table 85, p. 160) Post-ASCT studies, SoC parameters and results

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
37	Unadjusted ITC, all studies, fixed effects PFS = λ: 0.0640 OS= λ: 0.0246 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£23,970	1.456	£23,204
38	Unadjusted ITC, all studies, random effects PFS = λ: 0.0640 OS= λ: 0.0246 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£23,970	1.462	£23,262
39	Unadjusted ITC, subgroup,[c] fixed effects PFS = λ: 0.0928 OS= λ: 0.0305 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£20,953	1.163	£21,733
40	Unadjusted ITC, subgroup,[c] random effects PFS = λ: 0.0928 OS= λ: 0.0305 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£20,953	1.167	£21,764
41	MAIC ITC, all studies, fixed effects. PFS = λ: 0.0615 OS= λ: 0.0239 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£24,384	1.500	£23,477

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
42	MAIC ITC, all studies, random effects PFS = λ: 0.0615 OS= λ: 0.0239 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£24,384	1.506	£23,540
43	MAIC ITC, subgroup,[c] fixed effects PFS = λ: 0.0881 OS= λ: 0.0294 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£21,400	1.206	£21,918
44	MAIC ITC, subgroup,[c] random effects PFS = λ: 0.0881 OS= λ: 0.0294 Complete response= [redacted] Partial response= [redacted] Utility (pre-progression)= [redacted]	[redacted]	[redacted]	£21,400	1.209	£21,951

ICER, Incremental cost-effectiveness ratio; MAIC ITC, matching-adjusted indirect comparisons Indirect treatment comparison; OS, overall survival; PFS, progression-free survival SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results for the base case from CS Table 63 (CS p. 137)
[b] Parameters and results for CS Analyses 37-44 derived from CS Table 85 (CS p. 158)
[c] Subgroup of SLR studies based on those studies where subgroup of post-ASCT population is reported or where >70% of patients match this criteria, this includes efficacy of investigational agents.

A full critique of the alternative synthesis methods used in Analysis 27-44 is reported in Section 3.1.7. In brief, the MAIC methods lacked sufficient power and it was unclear how the matching criteria were chosen or whether only the most relevant criteria were included. Additionally, all survival analyses assume an exponential curve, which was insufficiently justified.

F. Analyses with alternative baseline age

The company undertook two analyses to represent the bimodal age distribution of classical Hodgkin lymphoma. The parameters of these cohorts and the results of the analyses are reported in Table 61.

Table 61 Alternative baseline age (CS Table 86, p. 162)

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
45	Age 20, alloSCT likelihood of alloSCT from Perrot 2016 and costs from NHS reference costs	[redacted]	[redacted]	£22,193	1.101	£18,037
46	Age 70, BSC assumed to be the most appropriate comparator, (OS derived from the lowest reported by Cheah 2016 for chemotherapies (exponential parametric fit; λ: 0.07296); PFS was assumed to be equivalent to the PFS applied in the base case for SoC, due to the evidence supporting comparable PFS for non-investigational agent)	[redacted]	[redacted]	£7,561	0.518	£23,226

alloSCT, allogenic stem cell transplant; ICER, Incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results for the base case from CS Table 63 (CS p. 137).
[b] Parameters and results for CS Analyses 45-46 derived from CS Table 86 (CS p. 162).

G. Explorations of treatment stopping rules

In the base case analysis, it is assumed that patients in both treatment arms discontinue therapy at the time of progression or due to the rate of discontinuation, which was derived from nivolumab patient-level data. This is likely to reflect clinical practice in most patients and with most therapies, and also provides a conservative assessment of incidence of discontinuation due to AEs during SoC. However, clinical practice may vary, particularly with the use of nivolumab, where treatment may be continued following progression due to the novel mechanism of action. Additionally, clinicians may wish to stop treatment in patients responding at one year.

The following scenario analyses were conducted:

- Patients in the nivolumab arm achieving CR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.
- Patients in the nivolumab arm achieving CR or PR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.
- Patients in the nivolumab arm no longer switch treatment at progression. Additionally, the nivolumab patient-level data-derived treatment discontinuation curve was adjusted to include

discontinuation due to all causes, including progression, with the intent of reflecting potential nivolumab use in clinical practice (lognormal curve; μ: 2.732; σ: 1.057)

- Patient discontinuation for reasons other than death or progression was assumed to be zero; on progression, patients were assumed to switch to therapies in line with base case assumptions.

It should be noted that these analyses assume that the clinical benefit of nivolumab remains the same when applying these assumptions around treatment duration; the company argued that this can be considered conservative, as treatment guidelines and clinicians are unlikely to use these treatment durations where efficacy is impacted. Results from these analyses are detailed in Table 62.

Table 62 Alternative assumptions around treatment duration (stopping rules) (CS Table 87, p.163)

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
47	Patients in the nivolumab arm achieving CR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.	[redacted]	[redacted]	£21,090	0.932	£17,436
48	Patients in the nivolumab arm achieving CR or PR and remaining on initial therapy at 12 months cease to receive therapy costs and incur AEs until discontinuation or progression.	[redacted]	[redacted]	£21,090	0.932	£13,632
49	Patients in the nivolumab arm no longer switch treatment at progression. Additionally, the nivolumab patient-level data-derived treatment discontinuation curve was adjusted to include discontinuation due to all causes, including progression, with the intent of reflecting potential nivolumab	[redacted]	[redacted]	£21,090	0.932	£16,186

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
	use in clinical practice (lognormal curve; μ: 2.732; σ: 1.057)					
50	Patient discontinuation for reasons other than death or progression were assumed to be zero; on progression, patients were assumed to switch to therapies in line with base case assumptions.	[redacted]	[redacted]	£21,090	0.932	£29,573

AE, adverse events; CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SoC: standard of care; QALY, Quality-adjusted life year.
[a] Results for the base case from CS Table 63 (CS p. 137)
[b] Parameters and results for CS Analyses 47-50 derived from CS Table 87 (CS p. 163)

H. Explorations of alternative utility values

Table 63 provides alternative utility parameters and the results of analyses using these parameters. The ERG considered that Analysis 51 presents the most realistic representation of post-progression utility for SoC. In ERG scenario analyses conducted in Section 4.4 we assume that SoC post-progression utility is equivalent to that of nivolumab, as in Analysis 51.

Table 63 Alternative utility scores (CS Table 88, p. 164)

#	Analysis parameters[a,b]	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
51	Comparator post-progression utility set equal to nivolumab post-progression utility Post progression = [redacted]	[redacted]	[redacted]	£21,090	1.503	£24,983
52	Nivolumab post-progression utility set equal to comparator post-progression utility Post progression = 0.38	[redacted]	[redacted]	£21,090	0.932	£33,167
53	Swinburn 2015 used to derive utility for pre- and post-progression in both arms	[redacted]	[redacted]	£21,090	0.932	£34,332

	Pre-progression = 0.76 Post-progression = 0.38					
54	Response-specific pre-progression utilities applied Nivolumab CR = [redacted] PR = [redacted] SD = [redacted] post-progression = [redacted] SoC CR = 0.91 PR = 0.79 SD = 0.71 post-progression = 0.38	[redacted]	[redacted]	£21,090	0.932	£19,930

CR, complete response; ICER, Incremental cost-effectiveness ratio; PR, partial response; SD, stable disease; SoC, standard of care; QALY, Quality-adjusted life year

[a] Results for the base case from CS Table 63 (CS p. 137).

[b] Parameters and results for CS Analyses 51-54 derived from CS Table 88 (CS p. 164).

I. Analyses testing other modelling assumptions

Several analyses that did not fall under other classifications were conducted by the company. Analysis 55 presents results without half-cycle correction. Analysis 56 assumes that neither SoC nor nivolumab have adverse events. The company postulated that available utilities may already account for the toxicity of therapies, which might make utilising disutilities for adverse events double counting, so conducted Analysis 56. Analysis 57 doubles post-progression costs. Analysis 58 applies IRRC-assessed endpoints for nivolumab. Table 64 reports the results of these analyses.

Table 64 CS Analyses testing other modelling assumptions

#	Analysis parameters	Nivolumab Costs	Nivolumab QALYs	SoC Costs	SoC QALYs	ICER (£/QALY)	Source
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882	Table 63 (p. 137)
55	No half-cycle correction	[redacted]	[redacted]	£23,732	0.960	£19,730	Table 70 (p. 150)
56	Assume that utility scores from studies include disutilities for AE, no AEs modelled	[redacted]	[redacted]	£19,233	0.951	£20,580	Table 89 (p.164)
57	Alternative post-progression costs: resource use doubles post progression	[redacted]	[redacted]	£24,978	0.932	£21,218	Table 90 (p.165)

58	Application of IRRC-assessed endpoints for nivolumab PFS μ: 2.656 σ: 1.121 Response rates CR: [redacted] PR: [redacted] Utilities Pre-progression: [redacted] Post-progression: [redacted]	[redacted]	[redacted]	£21,090	0.932	£17,617	Table 91 (p. 165)

AE, adverse events; CR, complete response; ICER, Incremental cost-effectiveness ratio; IRRC, independent regulatory review committee; PR, partial response; SoC: standard of care;

Summary

The company conducted a large number of scenario analyses. All 58 scenario analyses required manual modification of input parameters in order to run and validate analyses. The ERG was unable to replicate some analyses, which led to requests for clarification on how analyses were run and updated analysis parameters were received from the company. The company complied with the clarification requests, providing both unrounded input values and versions of the model that allowed running alternative analyses with full explanation of the methods. All analyses produced results under £50,000 per QALY (end-of-life cost-effectiveness threshold) and only two analyses produced results above £30,000 per QALY (Analysis 52 and Analysis 53), both analyses assessed alternative post-progression utility scores. In the CS exploratory analyses, Nivolumab appears robust to parameter uncertainty. There are some unresolved uncertainties that we explore in Section 4.4.

4.3.10.3 Probabilistic Sensitivity Analysis (PSA)

The company undertook assessment of joint parameter uncertainty using a PSA. All relevant parameters, including costs and survival, were included in the PSA. Costs were sampled using gamma distributions. Age was sampled using the normal distribution. Proportions and percentages were sampled using the beta distribution.

In general, each parameter included in the PSA is sampled independently; however, there are several exceptions to this approach. The model allows health state costs to be specified by treatment and response state; however, the base case analysis applies pre-progression and post-progression cost regardless of response or therapy arm. Thus, within the PSA, treatment arm-

specific and response-state specific health state costs are not sampled independently, but are linked so that health state costs are varied similarly.

Similarly, response and survival parameters are sampled differently to other parameters, due to the paucity of data around SoC. Mean PFS and OS associated with SoC are sampled according to a normal distribution based on the specified standard error level, due to a lack of confidence bounds on the fit. The mean PFS and OS data are then transformed to the exponential rate required for the parametric survival curve generation. When sampling SoC response rates, the inverse relative risk of response versus nivolumab is sampled according to a lognormal distribution, and then the nivolumab mean response rate is divided by this deviate to provide the SoC response rate sample.

The company conducted probabilistic sensitivity analyses under two sets of assumptions: one where unknown standard errors were assumed to be 10% of the parameter mean, and one where unknown standard errors were assumed to be 20% of the parameter mean. We believe that of these two sets of simulations, the simulation with 20% uncertainty is more realistic. However, we note that given the paucity of data in the treatment population even larger estimates of uncertainty may be appropriate. In general, the distributions chosen and assumptions for the PSA were reasonable.

Due to the considerable time (4 hours 40 minutes) needed to run the PSA, the ERG has not tested larger uncertainty assumptions. At a willing-to-pay of £30,000 per QALY, nivolumab was cost-effective in 94.8% (10% SE) to 96.6% (20% SE) of simulations. If the willingness-to-pay threshold is £50,000 per QALY, nivolumab is cost-effective in 100% of simulations. Probabilistic ICERs were not reported. Figure 16 shows cost-effectiveness planes for nivolumab compared to SoC.

Figure 17 shows cost-effectiveness acceptability curves (CEAC) for nivolumab compared to SoC.

Figure 16 Cost-effectiveness plane (CS Figure 36, p. 143)

Figure 17 Cost-effectiveness acceptability curve (CEAC) (CS Figure 37, p. 143)

4.4 Additional work undertaken by the ERG

There were a number of areas where the ERG considered the CS base case to be limited. It included the survival benefits of alloSCT, but none of the costs of alloSCT; the population for SoC did not include those patients that received; utility scores were not based on EQ-5D values for all interventions; response weighted utilities were not precisely calculated; and post-progression utilities produced exaggerated differences between nivolumab and SoC. The ERG believes that CS Analysis 20 (CS alloSCT Scenario B, p.153) addresses concerns about the costs of alloSCT not being adequately represented in the base case, but this analysis carries forward some issues of the base case and introduces other issues. CS Analysis 20 allows alloSCT as a treatment administered as a special transition at six months wherein patients have the full costs and benefits of alloSCT and survival modelled independently from the baseline treatment curve. We have used CS Analysis 20 as the structural basis for additional analysis by the ERG. In each analysis conducted in this section,

parameters within CS Analysis 20 are substituted for alternative values, resulting in analyses that are combinations of CS Analysis 20 and other data, including data from other company analyses.

CS Analysis 20 uses response based estimates from Perrot and colleagues to assign the proportion of patients that have an alloSCT at six months. The model assumes that all alloSCTs happen at this time. In order for this assumption to be valid, the estimated proportion of patients receiving alloSCT treatment should be similar to that observed in the trials. As Section 4.3.8 shows, the estimates produced by Perrot and colleagues underestimate alloSCTs. Additionally, the company assumes that the post alloSCT survival can be defined by the post alloSCT survival in patients receiving alloSCT in the Cheah study. These data are based on 14 patients that are already included in OS data for SoC, so this is a form of double counting. Finally, the post-progression utility estimate for alloSCT is only 0.38. As we have discussed in Section 4.3.6, we would expect post-progression utility to be similar across all interventions, and an independent study found that utility values for brentuximab vedotin were similar to placebo after ASCT at all time points.[42]

Table 65 lists the analyses carried out by the ERG, along with their justifications, and how these analyses changed parameters from the CS. These analyses culminate in the ERG base case (ERG 10), which we believe is the most representative analysis for the cost-effectiveness of nivolumab compared to SoC.

In the company model for CS Analysis 20, only one survival curve may be applied at a time and this curve is applied to both interventions. In the CS Analysis 20, this curve is derived from Cheah and colleagues survival data for patients who have alloSCT (see Table 54). In order to analyse separate curves for each intervention (ERG6, ERG9, ERG17, ERG18) the model must be run twice, and the necessary results data (costs and QALYs) extracted and ICERs calculated.

The ERG base case (ERG10) uses data derived from all patients in Cheah and colleagues, including those who received investigational agents. We have chosen to use Cheah and colleagues data for our base case SoC efficacy data instead of data from the ITC because the other single-arm trials in the ITC (see Section 3.1.7) consist primarily of trials exploring purely investigational agents. This can be expected to bias the comparisons against nivolumab as current SoC consists of a mix of standard chemotherapies and investigational agents. We have investigated using efficacy data from the ITC in several scenario analyses (ERG9, ERG17, ERG18).

In ERG4, ERG9, ERG17, and ERG18, utilities are derived from EQ-5D data from CheckMate 205. Utilities are weighted by the proportions of people in each of the complete remission, partial remission and stable disease states for pre-progression utilities (see Section 4.3.6). In ERG9, ERG17, and ERG18, the health state weightings are derived from CS Analysis 30 (see Table 59). ERG9, ERG 17, and ERG18 also use parametric survival curves derived from CS Analysis 30 in combination with structural assumptions from CS Analysis 20 and other parameter estimates.

Table 65 Assumptions for ERG exploratory analyses subsequent to CS analysis 20 (alloSCT scenario B)

#	Analysis Description	Analysis 20 parameters	ERG analysis parameters	Justification
0	Base Case	See CS Table 63, p. 137	--	
20	CS alloSCT Scenario B (CS Table 75, p. 153)	See CS Table 75, p. 153	--	
ERG1	Alternative special transition case, alloSCT rates derived from trials	Both nivolumab and SoC have transitions based on Perrot 2016 Special transition case (all) Complete remission: 22.22% Partial remission: 14.06% Stable disease: 5.56%	Special transition case based on observed alloSCT in Cheah for SoC and in nivolumab trials for nivolumab Special transition case (nivolumab) All levels of response: [redacted] Special transition case (SoC) All levels of response: 17.72% (14/79)	The company analysis underestimates the proportion of patients receiving alloSCT compared to observed alloSCT procedures in the studies. (see Section 4.3.8)
ERG2	Alternative SoC survival population (including investigational agents)	PFS Exponential λ: 0.160 OS Exponential λ: 0.036	PFS Exponential λ: 0.0253 OS Exponential λ: 0.025	The company's base case does not include investigational agents. The ERG considered it more appropriate to use the overall population

#	Analysis Description	Analysis 20 parameters	ERG analysis parameters	Justification
				(including investigational agents) (section 4.3.5)
ERG3	Alternative nivolumab pre-progression utilities	[redacted]	[redacted]	The utilities based on the weighted average of response states are lower than the average value reported in the CS.
ERG4	Alternative SoC pre-progression utilities (CheckMate 205 utilities weighted by response in Cheah)	0.76	[redacted]	The Swinburn utility values were based on the Time Trade Off method and not derived from patients with HL. CheckMate 205 utilities are EQ-5D and derived from patients. Response weighting allows for showing treatment effect of nivolumab.
ERG5	SoC post-progression utility same as nivolumab post-progression utility	0.38	[redacted]	The difference in post-progression utility is not plausible (section 4.3.6).
ERG6	alloSCT survival modelled using original treatment OS curves instead of lognormal curve from Cheah	All Treatments OS Lognormal μ: 9.252 σ: 3.551	Nivolumab OS Weibull A (Scale): 76.742 B (Shape): 1.326 SoC OS Exponential λ: 0.025	Using the lognormal curve provides an estimate of survival that is significantly greater than the original estimates based on the trial data. As the original survival modelling included patients having alloSCT, there should not be a significant boost in projected survival. (see Section 4.3.5)
ERG7	Alternative post-progression utility for alloSCT intervention	0.38	[redacted]	This allows post-progression utility to be consistent between all treatments. (see Section 4.3.6)
ERG8	ERG calculated costs for SoC (omitting miniBEAM and dexaBEAM)	Section 4.3.7Table 43	Table 43	miniBEAM and dexaBEAM are expensive and not commonly used in UK clinical practice. Their inclusion is not likely to be appropriate (see Section 4.3.7)
ERG9	SoC pre-progression OS,	PFS Exponential λ: 0.160	PFS Exponential	As discussed in Section 3.1.7 and Section 4.3.10.2

#	Analysis Description	Analysis 20 parameters	ERG analysis parameters	Justification
	PFS, and response from CS Analysis 30, utilities weighted using CheckMate 205 values)	OS Exponential λ: 0.036 Response Complete Remission: [redacted] Partial Remission: [redacted] Pre-progression Utility [redacted]	λ: 0.158 OS Exponential λ: 0.026 Response Complete Remission: [redacted] Partial Remission: [redacted] Pre-progression Utility [redacted]	that ITC methods are appropriate, but are less representative of the composition of SoC than Cheah and colleagues. The primary purpose of this analysis is to explore methodological uncertainty, as the most appropriate method of extrapolation is not entirely clear for this population.
ERG10	ERG Base case combines ERG1 to ERG8	--	As above	As stated above

alloSCT, allogenic stem cell transplant; dexaBEAM, Dexamethasone, carmustine, etoposide, cytarabine and melphalan; miniBEAM, Carmustine, etoposide, cytarabine and melphalan; OS, overall survival; PFS, progression-free survival; SoC, standard of care

We identified a number of further areas of uncertainty that we have explored through sensitivity analyses carried out by modifying some parameters in the ERG base case (ERG10). The additional analyses are as follows:

- There is uncertainty in the cost of SoC. ERG11 examines the ERG base case with costs derived from CS Analysis 20. ERG12 uses costs derived from the brentuximab vedotin STA.
- We conducted additional analyses to investigate uncertainty in survival parameters post-alloSCT, as the data from the nivolumab studies were immature and the data for SoC were based on a small number of patients from an observational dataset. Four additional analyses (ERG13 to ERG16) were conducted that modified alloSCT OS assumptions to account for structural uncertainty in alloSCT OS. PFS was not altered by the ERG analyses undertaken subsequent to the ERG base case.
- As noted in ERG9, there is some uncertainty in the methods that are most appropriate for estimating efficacy. ERG17 and ERG18 analyse the impact on cost-effectiveness of using efficacy (survival, response, utility score) estimates derived from CS Analysis 30.

The assumptions and justifications for ERG Analyses 11-18 are reported in Table 66.

Table 66 Assumptions for ERG exploratory analyses subsequent to the base case

#	Analysis Description	Justification
ERG11	ERG Base case with SoC costs derived from CS	As above
ERG12	ERG Base case with SoC costs derived from brentuximab vedotin STA	As above
ERG13	ERG Base case, alloSCT survival from CS Scenario 20	See CS Table 75, p. 153
ERG14	ERG Base case, alloSCT survival from nivolumab	OS Weibull A (Scale): 76.742 B (Shape): 1.326
ERG15	ERG Base case, alloSCT survival from SoC including investigational agents	PFS Exponential (λ: 0.0253) OS Exponential (λ: 0.025)
ERG16	ERG Base case, SoC without investigational agents (including alloSCT)	SoC PFS (λ: 0.160) SoC OS (λ: 0.036) SoC alloSCT OS (λ: 0.036)
ERG17	ERG Base Case, SoC survival (PFS, OS before and OS after alloSCT) and response derived from CS Analysis 30, utilities reweighted as in ERG4	SoC PFS Exponential (λ: 0.158) SoC OS Exponential (λ: 0.026) SoC alloSCT OS (λ: 0.026) Response Complete Remission: [redacted] Partial Remission: [redacted] SoC Pre-progression Utility [redacted]
ERG18	As ERG17, SoC survival (PFS, OS before and OS after alloSCT) and response derived from CS Analysis 30; utilities reweighted as in ERG4; but post alloSCT survival from CS Analysis 30 for all interventions.	SoC PFS Exponential (λ: 0.158) SoC OS Exponential (λ: 0.026) All interventions alloSCT OS (λ: 0.026) SoC Response Complete Remission: [redacted] Partial Remission: [redacted] SoC Pre-progression Utility [redacted]

alloSCT, allogenic stem cell transplant; OS, overall survival; PFS, progression-free survival; SoC, standard of care

The results of all analyses conducted by the ERG are reported in Table 67. ICERs for the ERG analyses ranged between £18,174 per QALY and £42,226 per QALY with the ERG base case analysis (ERG10) producing an ICER of £36,525 per QALY. The ERG analyses that used alternative survival assumptions for alloSCT whilst maintaining other assumptions of the ERG base case produced ICERs ranging between £25,647 per QALY and £42,226 per QALY. All analyses produced ICERs below the £50,000 per QALY threshold for end-of-life treatments, but several

analyses, including the ERG base case produced ICERs above £30,000 per QALY, the upper bound of the NICE threshold range for cost-effectiveness.

Table 67 Results of ERG exploratory analyses

#	Analysis	Nivolumab		SoC		
		Costs	QALY	Costs	QALY	ICER
0	Base Case	[redacted]	[redacted]	£21,090	0.932	£19,882
20	CS alloSCT Scenario B (CS Table 75, p. 153)	[redacted]	[redacted]	£24,880	1.076	£20,433
ERG1	Alternative special transition case population	[redacted]	[redacted]	£27,692	1.184	£20,616
ERG2	Alternative SoC survival (including investigational agents)	[redacted]	[redacted]	£23,756	1.278	£22,348
ERG3	Alternative nivolumab pre-progression utilities	[redacted]	[redacted]	£24,880	1.076	£20,476
ERG4	Alternative SoC pre-progression utilities (CheckMate 205 utilities weighted by response in Cheah)	[redacted]	[redacted]	£24,880	1.101	£20,603
ERG5	SoC post-progression utility same as nivolumab post-progression utility	[redacted]	[redacted]	£24,880	1.633	£25,209
ERG6	alloSCT survival modelled using original treatment OS curves instead of lognormal curve from Cheah	[redacted]	[redacted]	£23,952	0.952	£21,517
ERG7	Alternative post-progression utility for alloSCT intervention	[redacted]	[redacted]	£24,880	1.212	£18,174
ERG8	ERG calculated costs for SoC (omitting miniBEAM and dexaBEAM)	[redacted]	[redacted]	£23,360	1.076	£20,950
ERG9	SoC OS, PFS, and response from CS Analysis 30, utilities weighted using CheckMate 205 values)	[redacted]	[redacted]	£28,806	2.227	£31,392
ERG10	***ERG Base case combines ERG1 to ERG8***	[redacted]	[redacted]	***£23,043***	***2.102***	***£36,525***
ERG11	ERG Base case with SoC costs derived from CS	[redacted]	[redacted]	£24,465	2.102	£35,684
ERG12	ERG Base case with SoC costs derived from BTX STA	[redacted]	[redacted]	£19,791	2.102	£38,451
ERG13	ERG Base case, alloSCT survival from Cheah for both arms	[redacted]	[redacted]	£24,027	2.363	£25,647
ERG14	ERG Base case, alloSCT survival from nivolumab	[redacted]	[redacted]	£23,233	2.150	£37,489

#	Analysis	Nivolumab		SoC		
		Costs	QALY	Costs	QALY	ICER
ERG15	ERG Base case, alloSCT survival from as SoC including investigational agents	[redacted]	[redacted]	£23,043	2.102	£42,226
ERG16	ERG Base case, SoC without investigational agents (including alloSCT)	[redacted]	[redacted]	£24,446	1.534	£26,712
ERG17	ERG Base Case, SoC survival (PFS, OS before and after alloSCT) and response derived from CS Analysis 30, utilities reweighted as in ERG4	[redacted]	[redacted]	£27,255	2.068	£33,370
ERG18	ERG Base Case, SoC survival (PFS, OS before and OS after alloSCT) and response derived from CS Analysis 30, utilities reweighted as in ERG5, post alloSCT survival from CS Analysis 30 for all interventions.	[redacted]	[redacted]	£27,255	2.068	£38,575

BTX, brentuximab vedotin; alloSCT, allogenic stem cell transplant; dexaBEAM, Dexamethasone, carmustine, etoposide, cytarabine and melphalan; ICER, ICER, Incremental cost-effectiveness ratio; miniBEAM, Carmustine, etoposide, cytarabine and melphalan; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; SoC, standard of care.

We compared survival curve estimated OS, CS estimates for OS and the estimates produced by the ERG analyses. As the CS base case did not include investigational agents in the SoC arm, we believe that the ERG base case (Analysis 10) is the closest to a direct estimate of survival from Cheah and colleagues relevant to the decision problem. Table 68 provides the results of the ERG's comparisons.

Table 68 Comparison of ERG analysis results

Analysis	Nivolumab mean years OS	SoC mean years OS
Survival curve estimate	5.9	2.3
CS base case output	5.0	2.1
CS Analysis 20 (alloSCT Scenario 2, p. 153)	[redacted]	[redacted]
ERG Analysis 2 (SoC survival with investigational agents)	[redacted]	[redacted]
ERG Analysis 10 (ERG base case)	[redacted]	[redacted]
ERG Analysis 13 (alloSCT survival as in CS Analysis 20)	[redacted]	[redacted]
ERG Analysis 14 (alloSCT survival with nivolumab OS curve for both interventions)	[redacted]	[redacted]

ERG Analysis 15 (alloSCT survival with SoC OS curve for both interventions)	[redacted]	[redacted]
ERG Analysis 16 (SoC without investigational agents, including on alloSCT)	[redacted]	[redacted]
ERG Analysis 17 (SoC survival, response from CS Analysis 30)	[redacted]	[redacted]
ERG Analysis 18 (SoC survival/response as in ERG Analysis 18, all interventions have SoC OS)	[redacted]	[redacted]

alloSCT, allogenic stem cell transplant; OS, overall survival; SoC, standard of care.

As can be seen, the CS base case produces significantly lower overall survival estimates for nivolumab than the survival curve estimate. For nivolumab survival, CS Analysis 20 produces a mean OS estimate closest to the survival curve estimate. As the data from the nivolumab study are immature, there is a large amount of uncertainty about extrapolation of overall survival. Clinical experts we consulted were not able to estimate overall survival for patients receiving nivolumab treatment. For SoC, the ERG base case (Analysis 10) should be considered the base comparison for estimating SoC survival as this survival curve includes investigational agents and is derived directly from Cheah and colleagues.

4.5 Conclusions of cost effectiveness

The company used a model structure commonly used for economic models of cancer treatments with health states for progression-free survival, progression and death. In addition, patients may discontinue treatment whilst in the progression-free state. The ERG considers the model structure to be appropriate for the decision problem.

The company used methods that are consistent with NICE methodological guidelines. The population, intervention and comparators used in the economic evaluation are consistent with the NICE scope.

The core clinical evidence for nivolumab was from single-arm studies and there are no direct head-to-head trials between nivolumvab and SoC. There is a paucity of evidence available for SoC for patients who have been previously treated with ASCT and brentuximab vedotin. The ERG considers the company has selected the most appropriate study for SoC but cautions that there is considerable uncertainty surrounding the comparison between nivolumab and SoC.

The SoC comparator has been based upon a study by Cheah and colleagues. Some patients within this study received investigational agents. The company has used the population excluding patients

receiving investigational agents. The ERG considers PFS and OS survival should be based upon the total population of Cheah and colleagues, including patients with investigational agents.

The results in the CS are presented with a patient access scheme discount. The CS base case analysis comparing nivolumab to SoC had an ICER of £19,888 per QALY gained. The company provides a large number of scenario analyses to test alternative modelling assumptions including the choice of survival parametric distributions used, utilities, treatment sequences and SoC composition. In general the results from the scenario analyses were robust with only two analyses producing results above £30,000 per QALY gained. The ERG preferred base case produced an ICER of £36,525 per QALY gained.

5 End of life

According to the NICE criteria for End of life, the following criteria should be satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company considers the two criteria for end of life. They state that ‘patients with relapsed or refractory classical Hodgkin lymphoma following ASCT had a median OS of 19-29 months, depending on therapies received and availability of brentuximab vedotin,[56,57] and this decreases further in patients who do not achieve an initial response following ASCT.[57] OS in relapsed or refractory patients who have received both ASCT and brentuximab vedotin is around two years for OS, but this is obscured by inclusion of the efficacy of clinical trial therapies (47.4 months).[2] When the efficacy of the investigational agents is removed, median OS is estimated to be around 19 months.

The CS states that based on CheckMate 205 or CA209-039 nivolumab is likely to increase survival substantially to an estimated median OS exceeding 42.9 months, although median OS was not reached during these studies.

Based upon this evidence, the company considers that nivolumab meets the criteria for end of life.

The ERG notes that the mean life years of the patients with SoC in the economic model is 2.3 years which is greater than the 24 months specified in the NICE end of life criteria. However, the company base case excludes investigational agents in patients treated with SoC. The ERG considers that the full population of Cheah (i.e. including those treated with investigational agents) to be more representative and for this population OS is 3.3 years. We agree that the results from CheckMate 205 and CA 209-039 are likely to increase the life expectancy of these patients by at least three months. Whilst there is uncertainty around the life expectancy of patients in the non-treated population, the ERG considers, based on the evidence provided by the company, that the NICE criteria for end of life has not been met.

6 Innovation

The CS highlights that the innovative nature of nivolumab has already been recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) which awarded nivolumab Promising Innovative Medicine (PIM) status (CS p. 15 and p. 20).

Nivolumab will also be the only treatment with European Medicines Agency (EMA) approval for patients with relapsed or refractory classical Hodgkin lymphoma who have received both ASCT and brentuximab vedotin. Treatment options for this group of patients are limited, and estimates of median PFS and OS are short (The CS indicates not more than 5 months for PFS or 19 months to 2 years for OS depending on whether investigative agents are included when estimating OS).

In comparison to the other chemotherapeutic treatment options for this patient group, which not all patients may tolerate, nivolumab has a fortnightly treatment schedule that patients may find convenient and which may be a well-tolerated therapeutic option.

There is also the potential for nivolumab to act as a bridge to alloSCT in eligible patients. Although there is a mortality risk with alloSCT, it can be a curative treatment option for some patients.

7 DISCUSSION

7.1 Summary of clinical effectiveness

Two relevant non-comparative single-arm studies of nivolumab were identified and described in the CS providing evidence on a total of 193 patients with classical Hodgkin lymphoma who had failed prior ASCT and brentuximab vedotin. Available follow-up extends to 15.7 months for 80 patients, 8.9 months for 98 patients and 23.3 months for the remaining 15 patients. Median overall survival has not yet been reached in either study.

To obtain an estimate of the comparative effectiveness of nivolumab in comparison to potential comparators indirect comparisons were conducted. A systematic review identified 12 studies reporting data for potential comparators but these data were limited in terms of quality and outcomes reported. Comparator studies were predominantly phase 1 or 2 single-arm studies and over half of them were only reported as conference abstracts.

The extent to which the benefits of nivolumab exceed those of potential comparator treatments is very uncertain due to absence of direct head-to-head comparisons and the immaturity of the evidence base both for nivolumab and for the potential comparator treatments.

No evidence was presented for people with relapsed or refractory classical Hodgkin lymphoma following at least two prior therapies when ASCT is not a treatment option.

7.2 Summary of cost effectiveness

The CS includes evidence on the cost-effectiveness of nivolumab compared to SoC in patients with refractory or relapsed Hodgkin lymphoma following ASCT and brentuximab vedotin. The model structure adopted for the economic evaluation is generally appropriate and consistent with the clinical disease pathway. The model contains health states of progression-free, progressed and death and uses survival curves based upon the clinical evidence. The clinical evidence comprises of single-arm studies. There is a paucity of evidence available for SoC for patients who have been previously treated with ASCT and brentuximab vedotin. The ERG considers that there is considerable uncertainty surrounding the comparison between nivolumab and SoC.

The CS presents results with a PAS discount for nivolumab. The CS model results produce an ICER of £19,888 per QALY for nivolumab compared to SoC. The company conducted deterministic

sensitivity analyses for the input parameters and a large number of scenario analyses varying model assumptions. The model results were robust to changes in input values and assumptions. The company's probabilistic sensitivity analyses showed there is a probability of 94.8% and 100% that nivolumab is cost effective at a willingness to pay of £30,000 and £50,000 respectively.

The ERG conducted sensitivity analyses evaluating alternative overall survival for SoC, utility estimates, lower costs for SoC, and including the effects and costs of alloSCT. The ERG's alternative base case analysis for nivolumab compared to SoC produces an ICER of £36,525 per QALY.

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