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

Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

ERRATUM

Replacement pages for factual inaccuracies in Evidence Review Group report

06 February 2017

Produced by Southampton Health Technology Assessments Centre (SHTAC)

[CheckMate 205 Cohort B n=80 (median follow-up 15.7 months); CheckMate 205 Cohort C n=98 (median follow-up 8.9 months); CA209-039 n=15 (median follow-up 23.3 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:

[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 unadjusted 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] obtained for the subgroup of SLR-identified studies that reported outcomes separately for post-ASCT and post-brentuximab vedotin patients or where >70% of the patients matched that criterion. 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. IRRC-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 100 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.

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 40 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 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 [redacted] 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).

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

1.1 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% chance of achieving a good enough remission for transplant.

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 69% to 87%.

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 0 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): 8.9 months.
- Post-ASCT/brentuximab vedotin patients from CA209-039 (n = 15); median follow-up (OS):

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 8.92 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 15.7 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)**	66 (66.0)	9 (60)	**13 (87)**
(95% CI)	**(57.2, 77.8)**	[redacted]	**(64.3, 81.7)**	(56.7, 75.3)	[redacted]	
Additional endpoints						
Duration of response: events	[redacted]	[redacted]	[redacted]	9/66		

Median duration of response, months	[redacted]	[redacted]	[redacted]	4.17	[redacted]	[redacted]
Median time to response, months					[redacted]	[redacted]
CR, n (%)[a]	6 (7.5)	[redacted]	17 (17.0)	26 (26.0)	0	2 (13)
PR, n (%)[a]	48 (60.0)	[redacted]	56 (56.0)	40 (40.0)	9 (60)	11(73)
SD, n (%)[a]	17 (21.3)	[redacted]	17 (17.0)	24 (24.0)	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]	[redacted]	[redacted]	[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 13 (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). IRRC-derived response rate data are used in a sensitivity analysis (ERG Table 64).

[redacted]

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

[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]
[redacted]		[redacted]	[redacted]

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

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

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

[redacted]

[redacted]

The objective response rate was 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 8.92 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.

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 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 [redacted]

There is uncertainty about the effectiveness of nivolumab 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]

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 the impact of half-cycle correction is included as a sensitivity analysis. The company included half-cycle correction in the base case analysis.

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.

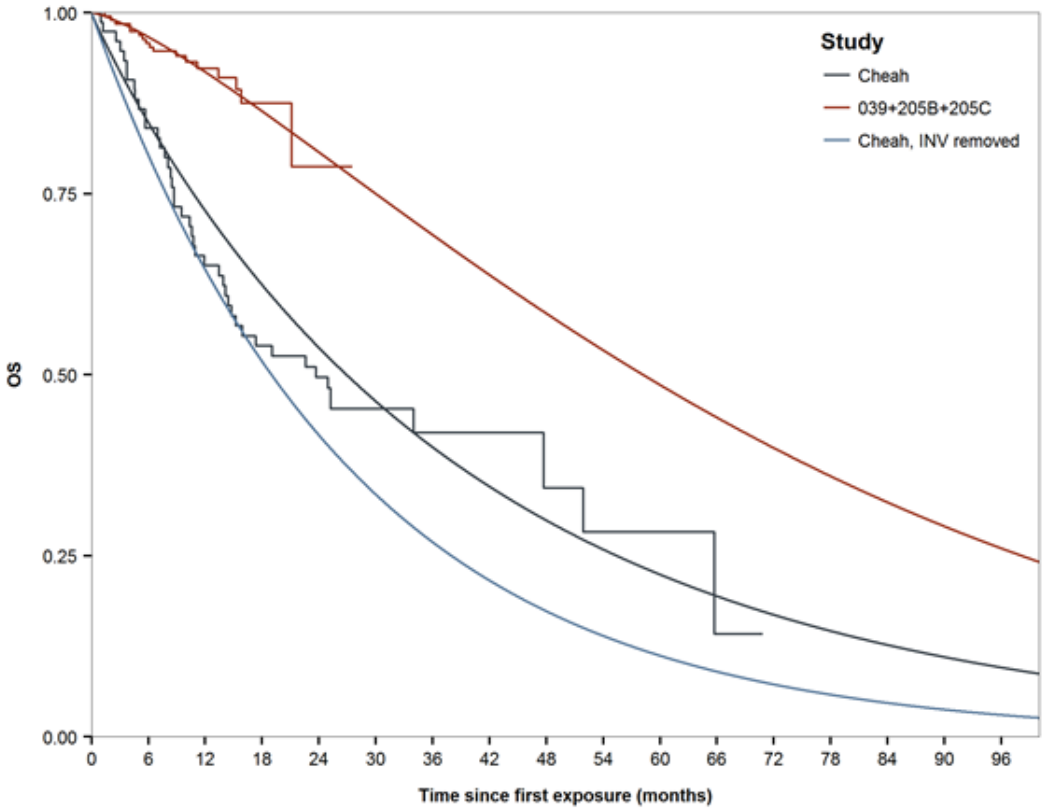

Figure 13 Overall survival: SoC, (CS, Figure 30)

1.1.1.1 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 alloSCT.

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 IRRC-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 40 Response weighted utility values for nivolumab and SoC

Health State	% in state, Nivolumab	% in state SoC	Swinburn 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]

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)
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.

	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 71 (p. 151)
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), Table 92 (p. 166)

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-

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