NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using nivolumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 3 April 2017

Second appraisal committee meeting: 12 April 2017

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 The committee is minded not to recommend nivolumab, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma.

1.2 The committee recommends that NICE requests from the company for the second appraisal committee meeting revised probabilistic cost-effectiveness analyses comparing nivolumab with standard of care, which incorporate the committee's preferred assumptions regarding method of indirect comparison, costs and utilities. The analyses should also explore the use of UK data for standard of care (for example, from the Haematological Malignancy Research Network) and a range of subsequent allogeneic stem cell transplant rates for both nivolumab and standard of care that are higher than those used in the Cheah and Perrot studies and are from UK data.

2 The technology

Description of the technology	Nivolumab (Opdivo, Bristol-Myers Squibb) is a human monoclonal antibody that blocks an immune checkpoint protein receptor called programmed cell death protein 1 (PD-1) to promote anti-tumour response.
Marketing authorisation	Nivolumab has a marketing authorisation in the UK for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin.
Adverse reactions	The most common adverse reactions with nivolumab in clinical trials were diarrhoea, nausea, fatigue, pyrexia, rash (occurring in at least 10% of people). For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	3 mg/kg given intravenously every 2 weeks.
Price	The list price is £439 per 40 mg vial or £1,097 per 100 mg vial (excluding VAT; 'British national formulary' [BNF])

	The company has agreed a patient access scheme with the Department of Health. If nivolumab had been recommended, this scheme would provide a simple discount to the list price of nivolumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the evidence review group. See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of nivolumab, having considered evidence on the nature of classical Hodgkin lymphoma and the value placed on the benefits of nivolumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Current clinical management of Hodgkin lymphoma

4.1 The committee noted that there was currently no NICE technology appraisal guidance on Hodgkin lymphoma. It understood that current practice is first chemotherapy with or without radiotherapy. If this fails to lead to long-term remission, people may have high-dose chemotherapy followed when possible by autologous stem cell transplant. Brentuximab vedotin is currently available on the Cancer Drugs Fund following at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option. Up to half the people who have had autologous stem cell transplant develop progressive disease with a mean life expectancy of less than 3 years. The committee heard from the clinical experts that people whose disease has relapsed may be offered

further, usually single-drug chemotherapy, including brentuximab vedotin, gemcitabine, bendamustine or cisplatin, as salvage therapy. This aims to control the disease, and if possible, elicit a disease response to enable allogeneic stem cell transplant.

4.2 The committee understood that allogeneic stem cell transplant is the treatment of choice after autologous stem cell transplant has failed, provided there is a suitable donor and a good response to systemic therapy. The committee heard that allogeneic stem cell transplant is offered to relatively fit patients whose disease achieves a partial or complete response to salvage therapy following failure of autologous stem cell transplant. The committee heard from the clinical experts that allogeneic stem cell transplant was potentially curative in around 60% of patients who had it. The committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy after autologous stem cell transplant fails, and heard from clinical experts that nivolumab had the potential to act as salvage therapy to enable allogeneic stem cell transplant after both autologous stem cell transplant and brentuximab vedotin.

4.3 The committee considered the experience of people with relapsed or refractory Hodgkin lymphoma following autologous stem cell transplant. It heard from the patient experts that the side effects of existing chemotherapy treatments affect their quality of life and can dissuade people from allogeneic stem cell transplant (if transplant becomes possible). It heard from the clinical experts that treatment with nivolumab was generally well tolerated because it has more manageable side effects than existing treatments, and that it can significantly improve patients' quality of life.

4.4 The committee considered the groups of people with Hodgkin lymphoma which reflected the marketing authorisation for nivolumab (that is, for

treating relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin). The committee noted that the population in the marketing authorisation could be subdivided into 3 groups, based on the position of brentuximab vedotin in the treatment pathway for Hodgkin lymphoma:

- Adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin, when brentuximab vedotin is used as salvage therapy to enable an autologous stem cell transplant.
- Adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin, when brentuximab vedotin is used as salvage therapy to enable an allogeneic stem cell transplant (after autologous stem cell transplant fails).
- Adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin, when brentuximab vedotin is used both as salvage therapy to enable an autologous stem cell transplant and as salvage therapy to enable an allogeneic stem cell transplant (after autologous stem cell transplant fails).

The committee noted that brentuximab vedotin's UK marketing authorisation does not explicitly exclude retreatment, however, retreatment was not permitted through the Cancer Drugs Fund. The committee therefore did not consider the final group because brentuximab vedotin retreatment is not currently used in clinical practice in England. The committee concluded that based on current clinical practice, nivolumab would be used in patients who have had autologous stem cell transplant and brentuximab vedotin, when brentuximab vedotin has been used as salvage therapy to either enable an autologous stem cell transplant or to enable an allogeneic stem cell transplant following failure of autologous stem cell transplant.

Clinical effectiveness

4.5 The committee noted that the evidence for nivolumab in this population came from 2 non-comparative single-arm trials: CheckMate 205 (cohorts B and C) and CA209-039. The trials included patients who had brentuximab vedotin after autologous stem cell transplant (CheckMate 205 cohort B and CA209-039), patients who had brentuximab vedotin either before or after autologous stem cell transplant, or both (CheckMate 205 cohort C). The committee noted that CheckMate 205 cohort C included 8 people who had brentuximab vedotin retreatment. The primary outcome measure for CheckMate 205 and CA209-039 was objective response rate, defined as the proportion of patients with a best overall response of complete or partial response. Progression-free and overall survival were secondary outcome measures. The objective response rates and progression-free survival reported are as assessed by the Independent Radiologic Review Committee. The investigator-assessed objective response rates and progression-free survival are also available for both trials but the company consider these to be academic-in-confidence and so they cannot be reported here (see table 1).

Table 1 Clinical data from CheckMate 205 and CA209-039

	CheckMate 205 cohort B	CheckMate 205 cohort C	CA209-039
Number of patients	80	98	15
Median follow-up	15.7 months	8.9 months	23.3 months
Objective response rate (95% CI)	67.5% (54) (57.2, 77.8)	73.0% (73) (64.3, 81.7)	60% (9)
Progression-free survival, median (95% CI)	14.78 months (11.33, NA)	11.17 months (8.51, NA)	12.65 months (5.91, NA)
Overall survival, at 6 months* (95% CI)	96.1% (92.0, 100)	94.0% (89.1, 98.8)	NA
* Median overall survival was not reached.			

CI, confidence interval; NA, not available.

The committee was concerned that the single-arm design of the trials, the small number of patients included and short follow-up meant that the results were potentially biased. The committee accepted that the results from the latest data cut-off for both trials (April 2016 for CheckMate 205 and August 2015 for CA209-039) showed that nivolumab was clinically effective based on response rates but agreed that there was a large degree of uncertainty in the clinical evidence.

Indirect treatment comparison of nivolumab with standard of care

4.6 The committee was aware that there were no data providing direct comparative evidence for the clinical effectiveness of nivolumab compared with current practice (standard of care), because nivolumab for Hodgkin lymphoma had only been studied in single-arm trials. It noted that the company had done an unadjusted indirect comparison of nivolumab compared with standard of care by comparing the pooled outcomes from the nivolumab trials with standard of care. The outcomes for standard of care came from Cheah et al. (2016), a retrospective real-world study done in the US. The study aimed to determine progression-free survival and overall survival in patients with Hodgkin lymphoma following disease relapse after brentuximab vedotin therapy; a secondary outcome was the efficacy of subsequent treatments.

4.7 The committee considered whether the population and composition of treatments in the Cheah study was reflective of clinical practice in the UK. The committee noted that the study population partially matched the population of interest because around 70% of patients had previous autologous stem cell transplant and brentuximab vedotin. The committee noted a lack of detail on the precise combinations of chemotherapies given as standard of care in the study, and the inclusion of platinum-based therapies and 'other alkylators'. It considered that the study did not reflect UK practice, particularly regarding subsequent rates of allogeneic

stem cell transplant. The committee recognised that the Cheah study was the best available evidence for standard of care from the evidence presented, and concluded that the clinical effectiveness of nivolumab compared with standard of care was highly uncertain because the data for the comparator did not represent UK clinical practice. It concluded that data from the UK was needed in order to assess the clinical effectiveness of nivolumab compared with standard of care in the UK, and that the company should provide analyses that explores the data available from the UK (for example, from the Haematological Malignancy Research Network).

4.8 The committee noted that the company's unadjusted indirect comparison excluded results from the population who had investigational agents in the Cheah study. It heard from the company that the inclusion of investigational agents could have confounded the results because they increased survival benefit above that expected from treatments used in current practice, and that the investigational agents were likely to include PD-1 inhibitors, one of which is nivolumab itself. It also heard from the clinical experts that the investigational agents used in the study could include treatments that were not available in the UK. The committee noted that there was little detail about which specific therapies were defined as 'investigational agents' in the Cheah study. It heard from the evidence review group (ERG), who had contacted the authors of the study, that only 'a couple' of patients in the study had a PD-1 inhibitor, and therefore the ERG considered that the overall population should be used for comparator data. The committee considered that the patients in the Cheah study having investigational agents may have differed from people seen in clinical practice more in terms of their fitness to have such treatments rather than the treatments themselves. It agreed that the overall population of the Cheah study, including those having investigational agents, would better match the population in the nivolumab trials because patients in trials tend to be fitter. The committee concluded

that the overall population of the Cheah study was the most appropriate dataset for standard of care to use in the indirect comparison.

4.9 The committee was aware of the results of the company's comparison of the pooled nivolumab data with standard of care data from the overall population in the Cheah study for progression-free survival and overall survival (results are academic-in-confidence and cannot be reported here). The committee noted that these results were obtained from an unadjusted, or 'naïve', indirect treatment comparison and therefore did not take account of differences in the baseline characteristics of patients in the trials. The committee was aware that a matched-adjusted indirect treatment comparison would account for different distributions of prognostic factors and effect modifiers arising from any differences in baseline characteristics and therefore would produce more robust results. It noted that the company had done a matched-adjusted indirect comparison but had presented the results as a scenario analysis in its economic modelling and not included them in the base-case analysis. The committee agreed that it would have preferred to have seen the matched-adjusted indirect comparison or an alternative indirect comparison method that took account of different distributions of prognostic factors and effect modifiers, included in the company's base-case analysis.

4.10 In conclusion, the committee noted that the available evidence for the clinical effectiveness of nivolumab was highly uncertain because the data were immature and from single-arm studies. It acknowledged that the published evidence for comparator treatments was limited, but considered that Cheah et al. did not represent UK practice. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted this could potentially be addressed by additional comparative analysis with UK sources of comparator data.

Cost effectiveness

4.11 The committee discussed the company's economic model and modelling assumptions. Overall, it accepted the structure of the model as representative of the treatment pathway of patients with relapsed or refractory Hodgkin lymphoma and considered it appropriate for decision-making, but acknowledged its divergence from UK clinical practice in terms of comparator treatments (see section 4.7) and especially rates of allogeneic stem cell transplant (see section 4.15).

Modelling survival data

4.12 The committee noted that to model progression-free survival and overall survival, the company used the outcome data from the unadjusted indirect treatment comparison of nivolumab compared with the treatments in the Cheah study (see section 4.6). The committee considered that the results of the matched-adjusted indirect treatment comparison should have been used in the base-case analysis because it accounted for differences in the baseline characteristics of the patients in the trials (see section 4.9).

4.13 The committee was concerned that a large proportion of the survival benefit of nivolumab compared with standard of care was based on extrapolation rather than on trial data, because the trial data were very immature. It was aware that the company had extrapolated beyond the trial follow-up for nivolumab by fitting a lognormal curve to progression-free survival data and a Weibull curve to overall survival, and that for standard of care, exponential curves had been fitted to the progression-free and overall survival data from the Cheah study (excluding the population who had investigational agents in that study). The committee heard from the ERG that the extrapolation curves used were plausible, but it also considered the plausibility of the Gompertz curve fit to the nivolumab overall survival curve, which represented a more pessimistic assumption about long-term survival. The committee concluded that the Gompertz curve may not be clinically probable, but it was not at all clear

that the outcomes would be as favourable as the company's estimates. However, it noted that all the parametric curves fitted to the data had a reasonable fit and concluded that more data were needed to assess which fit was the most realistic.

Subsequent allogeneic stem cell transplant

4.14 The committee considered those patients who had a partial or complete response to nivolumab and went onto have a potentially curative allogeneic stem cell transplant, and how these patients may have affected overall survival in the model. The committee recalled that allogeneic stem cell transplant was potentially curative (see section 4.2). It was aware that the survival modelling used in the company's base-case analysis included both patients who had allogeneic stem cell transplant and those who had not, in both treatment arms, but that the company had only modelled the effect of subsequent allogeneic stem cell transplant on long-term survival in a scenario analysis. The committee noted that in its scenario analysis, the company had used non-UK data from the Cheah study to project long-term survival for patients who had subsequent allogeneic stem cell transplant. The committee understood that the survival data for subsequent allogeneic stem cell transplant had been extrapolated independently from the overall survival extrapolation used in the base case. It acknowledged that there would be some double-counting because the overall survival extrapolation used in the base case included some patients who had allogeneic stem cell transplant, but agreed that it was an acceptable approach.

4.15 The committee considered the proportion of patients who were likely to have an allogeneic stem cell transplant in the UK, if their disease had partially or completely responded to treatment after autologous stem cell transplant failed. The committee was aware that in its scenario analyses, the company had obtained response-specific proportions of patients having subsequent allogeneic stem cell transplant (22.2% of those with complete response, 14.1% with partial response and 5.56% with stable

disease) from a study in France (Perrot et al., 2016), and applied them to the response rates seen in the nivolumab and Cheah studies to generate transition probabilities for each treatment arm for use in the model. The committee understood that the ERG had assumed the proportion of patients having subsequent allogeneic stem cell transplant would be equivalent to the proportion that had subsequent allogeneic stem cell transplant in the nivolumab and Cheah studies, which was overall slightly higher than the proportions in the Perrot study. However, it heard from the clinical experts that UK rates of allogeneic stem cell transplant were much higher than those in the US. The committee concluded that a range of subsequent allogeneic stem cell transplant rates for both nivolumab and standard of care that are higher than those used in the Cheah and Perrot studies and are derived from UK data were needed in order to more accurately predict long-term survival and other outcomes in these patients in the cost-effectiveness analyses.

Treatment costs

4.16 The committee was aware that the company's base case excluded the costs of subsequent allogeneic stem cell transplant, but it recognised that some patients in the nivolumab trials and the Cheah study had subsequent allogeneic stem cell transplant. Because the survival benefit from allogeneic stem cell transplant was captured in the survival data for both arms of the model, the committee considered that the costs should also be included. It also considered the costs of comparator treatments, and agreed with the ERG that the costs of mini-BEAM (carmustine, etoposide, cytarabine and melphalan) and DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine and melphalan) should be excluded because they are not used in UK clinical practice, and their benefits would not significantly affect the progression-free or overall survival projections.

Utility values

4.17 The committee was aware that CheckMate 205 (cohort B) collected health-related quality of life data for patients having nivolumab using the EQ-5D, which were then converted to utility data. It was also aware that utility data for patients having standard of care were taken from published literature (Swinburn et al., 2015). The committee recognised that response-specific utility values from CheckMate 205 and Swinburn et al. diverged, and that the ERG had instead used the response-specific utility values from CheckMate 205 to estimate utility values for standard of care. The committee agreed that this was a more consistent approach but heard from the clinical experts that pre-progression quality of life was likely to be better with nivolumab than with existing treatments because of nivolumab's potential to improve quality of life (see section 4.3). The committee recognised that the pre-progression utility values used by the ERG in its base case maintained a difference between the treatment arms and concluded that they were therefore more appropriate for its decision-making.

4.18 The committee considered the post-progression utility values and noted the large difference in values between the nivolumab and standard of care treatment arms. It heard from the clinical experts that this large difference was not clinically plausible. The committee preferred the ERG's assumption that post-progression utility values were the same across all treatments.

Results of cost-effectiveness analyses

4.19 The committee noted that the company had presented deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) in its base-case analysis. Including the confidential discount agreed for nivolumab, the company's deterministic base-case ICER was £19,882 per quality-adjusted life year (QALY) gained for nivolumab compared with standard of care, and the probabilistic ICER was £19,165 per QALY gained The

ERG's deterministic base-case ICER was £36,525 per QALY gained. The committee would have preferred to use probabilistic ICERs in its decision-making.

4.20 The committee preferred the ERG's base-case assumptions for comparator data (see section 4.8), costs (see section 4.16) and utility values (see sections 4.17 and 4.18). It also agreed that because nivolumab could be used as salvage therapy to enable allogeneic stem cell transplant, the modelling should include the projected long-term survival benefit of subsequent allogeneic stem cell transplant (although the ERG included this in its base case, the committee preferred the company's method for long-term extrapolation used in its scenario analysis; see section 4.14). The committee considered that incorporating the long-term survival benefit of allogeneic stem cell transplant as subsequent therapy should improve the cost effectiveness of nivolumab (if its use led to more people having a potentially curative allogeneic stem cell transplant), but it noted that this made little difference to the company's base-case ICER. It heard from the ERG that this was because the company's base case already captured the benefits, because some patients in the nivolumab trials had gone on to have allogeneic stem cell transplants, and that the added costs of allogeneic stem cell transplant were not offset by the benefits accrued. The committee considered this to be counterintuitive because the added costs of allogeneic stem cell transplant, although large, would also be offset by stopping nivolumab treatment in those who had a transplant. It also considered that the benefits of subsequent allogeneic stem cell transplant might not be fully captured because the proportion of patients assumed to have an allogeneic stem cell transplant did not match the proportions expected to have a transplant in the UK. The committee discussed the potential effect on the long-term extrapolation of including subsequent allogeneic stem cell transplant in the survival modelling. It noted that approximately 60% of patients having allogeneic stem cell transplant were cured, which meant

that only about 30% of the total population of patients having nivolumab in the trials would have long-term survival, but that the different prognosis for these patients might affect the survival curves significantly had follow-up been longer. Overall, the committee concluded that the effect of incorporating the projected long-term survival benefit of allogeneic stem cell transplant on the cost-effectiveness results was uncertain. It further concluded that an analysis using a range of subsequent allogeneic stem cell transplant rates that more closely matched UK practice was needed to address this uncertainty.

Committee's conclusions

4.21 The committee considered that the most plausible ICER was likely to be higher than the company's base case because of the uncertainty around the immature nivolumab data and the relevance of the comparator data. It accepted the ERG's base case as being potentially plausible because it incorporated some of its preferred assumptions, but noted that it had not seen a cost-effectiveness analysis that contained all of its preferred assumptions. It noted that the analysis using a Gompertz curve to project long-term overall survival for nivolumab increased the ICER to £122,825, which demonstrated the degree of uncertainty arising in such immature data. However, with the possible long-term survival benefit of subsequent allogeneic stem cell transplant the most plausible ICER was likely to be lower than this figure. The committee concluded that because of the high central estimate and wide confidence intervals around the ICER as a result of the immaturity of the nivolumab trial data, the lack of comparator data relevant to UK practice and of rates of subsequent allogeneic stem cell transplant in the UK, it could not recommend nivolumab as a cost-effective use of NHS resources without further analyses to address these uncertainties. The committee recommends that NICE requests further analyses from the company, as specified in section 1.2, which should be made available for the second appraisal committee meeting.

Innovation

4.22 The committee considered whether nivolumab was an innovative treatment. It noted that nivolumab had been awarded 'promising innovative medicine' designation by the Medicines and Health Products Regulatory Agency. It also heard from the clinical and patient experts that nivolumab was an important new option for people with relapsed or refractory Hodgkin lymphoma. The committee agreed that nivolumab was innovative and promising but that it had not been presented with any evidence of additional benefits that were not captured in the QALY measure.

End-of-life considerations

4.23 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The company made the case that nivolumab met the criteria for life-extending treatments for people with a short life expectancy, normally less than 24 months. The committee noted, however, that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. The committee acknowledged that it had not been presented with comparator data that reflected current standard of care in the UK, and concluded that the criterion for short life expectancy did not apply.

4.24 The committee also discussed whether there was sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The committee noted that the cost-effectiveness analysis from which the survival benefit of nivolumab could be inferred did not reflect the committee's preferred analysis, and that because of the immaturity of the trial data and the lack of UK comparator data, all the estimates were uncertain. However, the committee concluded that based on the evidence

presented, nivolumab did fulfil the criterion for extending life by at least an additional 3 months.

4.25 The committee concluded that based on the evidence presented, nivolumab did not fulfil all the criteria for life-extending treatments for people with a short life expectancy.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Nivolumab for relapsed or refractory classical Hodgkin lymphoma**	**Section**
Key conclusion		
The committee is minded not to recommend nivolumab, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma.		1.1
The committee recommends that NICE requests from the company for the second appraisal committee meeting revised probabilistic cost-effectiveness analyses comparing nivolumab with standard of care, which incorporate the committee's preferred assumptions regarding method of indirect comparison, costs and utilities. The analyses should also explore the use of UK data for standard of care (for example, from the Haematological Malignancy Research Network) and a range of subsequent allogeneic stem cell transplant rates for both nivolumab and standard of care that are higher than those used in the Cheah and Perrot studies and are from UK data.		1.2
Evidence for the clinical effectiveness of nivolumab was highly uncertain because the data were immature and from single-arm studies. In addition, the published evidence for comparator treatments was limited, and that presented did not represent UK practice.		4.10

The evidence review group's (ERG's) deterministic incremental cost-effectiveness ratio (ICER) for nivolumab compared with standard of care was more than £30,000 per quality-adjusted life year (QALY) gained, and the committee concluded that based on the evidence presented, nivolumab did not fulfil all the end-of-life criteria. The committee considered that because of the high central estimate and wide confidence intervals around the ICER as a result of the immaturity of the nivolumab trial data, the lack of comparator data relevant to UK practice and of rates of subsequent allogeneic stem cell transplant in the UK, it could not recommend nivolumab as a cost-effectiveness use of NHS resources without further analyses to address these uncertainties.		4.19 4.25 4.21
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee recognised that there is an unmet clinical need for patients whose disease does not achieve a partial or complete response to salvage therapy such as brentuximab vedotin, following failure of autologous stem cell transplant.	4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from clinical experts that treatment with nivolumab was generally well tolerated because it has more manageable side effects than existing treatments, and can significantly improve patients' quality of life. Nivolumab had been awarded 'promising innovative medicine' designation by the Medicines and Health Products Regulatory Agency. The committee agreed that nivolumab was innovative and promising.	4.3 4.22
What is the position of the treatment in the pathway of care for the condition?	The committee concluded that based on current clinical practice, nivolumab would be used in patients who have had autologous stem cell transplant and brentuximab vedotin, when brentuximab vedotin has been used as salvage therapy to either enable an autologous stem cell transplant or to enable an allogeneic stem cell transplant following failure of autologous stem cell transplant.	4.4
Adverse reactions	The most common adverse reactions with nivolumab in clinical trials were diarrhoea, nausea, fatigue, pyrexia and rash.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The evidence came from 2 non-comparative single-arm trials: CheckMate 205 (cohorts B and C) and CA209-039, with a total of 193 patients.	4.5

Relevance to general clinical practice in the NHS	The committee concluded that data for the comparator did not represent UK clinical practice, and requested additional analysis to assess the clinical effectiveness of nivolumab compared with standard of care, exploring the data available in the UK (for example, from the Haematological Malignancy Research Network).	4.7 1.2
Uncertainties generated by the evidence	The single-arm design of the trials, the small number of patients included and the short follow-up meant that there was a large degree of uncertainty in the clinical evidence for nivolumab. There was a large degree of uncertainty about the comparative effectiveness of nivolumab compared with standard of care because the data for the comparator did not represent UK practice.	4.5 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	There are no clinically relevant subgroups for which there is evidence of differential effectiveness.	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee was aware of the results of the company's unadjusted indirect treatment comparison of the pooled nivolumab data compared with standard of care data from the Cheah study for progression-free survival and overall survival. However, there is substantial uncertainty about the clinical effectiveness of nivolumab because of the nature of the evidence for nivolumab (non-comparative studies, small patient numbers and short follow-up) and the lack of comparator data relevant to UK practice.	4.9 4.10 4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The company presented an economic model that the committee accepted as representative of the treatment pathway of patients with relapsed or refractory Hodgkin lymphoma.	4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	The cost-effectiveness estimates were uncertain because of the immaturity of the nivolumab trial data (and long-term survival modelling), the lack of comparator data relevant to UK practice and of rates of subsequent allogeneic stem cell transplant from the UK.	4.21
	Outcome data from the unadjusted indirect treatment comparison were used to model progression-free survival and overall survival in the company's base-case analysis; the committee considered the results of a matched-adjusted indirect treatment comparison to be more robust.	4.12
	There was substantial uncertainty around the long-term survival data because of the immaturity of the nivolumab trial data.	4.13
	The committee concluded that the survival modelling should incorporate the outcomes from subsequent allogeneic stem cell transplant using different rates of allogeneic stem cell transplant that more closely matched UK practice.	4.20

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee did not find the company's utility values plausible and it preferred the ERG's alternative assumptions around utility. The committee was not presented with any evidence of additional benefits of nivolumab that were not captured in the QALY measure.	4.17 4.18 4.22
What are the key drivers of cost effectiveness?	• Overall survival with nivolumab. • Post-progression utility values.	4.13 4.18

Most likely cost-effectiveness estimate (given as an ICER)	The committee considered that the most plausible ICER was likely to be above the company's deterministic base-case of £19,882 per QALY gained because of the uncertainty around the immature nivolumab data and the relevance of the comparator data. It accepted the ERG's deterministic base-case of £36,525 was potentially plausible because it incorporated some of the committee's preferred assumptions. It noted that using a Gompertz curve to project long-term overall survival for nivolumab increased the ICER to £122,825. With the possible long-term survival benefit of subsequent allogeneic stem cell transplant the most plausible ICER was likely to be lower than this figure.	4.19 4.20 4.21
Additional factors taken into account		
Patient access schemes (PPRS)	The company presented analyses that included the confidential patient access scheme for nivolumab.	
End-of-life considerations	The committee considered that nivolumab did fulfil the criterion for extending life by at least an additional 3 months. However, it did not meet the end-of-life criterion for short life expectancy because the company's modelling predicated a mean overall survival in the comparator treatment arm of more than 24 months.	4.23 to 4.25

Equalities considerations and social value judgements	No equalities issues were identified that could be addressed in the appraisal. The equality impact assessment provides further information.	

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Andrew Stevens
Chair, appraisal committee C
March 2017

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Anna Brett
Technical lead

Nicola Hay
Technical adviser

Stephanie Yates
Project manager

ISBN: [to be added at publication]