

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab 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.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using pembrolizumab 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: 29 March 2018

Third appraisal committee meeting: 22 May 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 The committee is minded not to recommend pembrolizumab as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin.
- 1.2 The committee requests that the company provides a cost-comparison with nivolumab for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin.
- 1.3 Pembrolizumab is not recommended as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who cannot have autologous stem cell transplant and have had brentuximab vedotin.
- 1.4 These recommendations are not intended to affect treatment with pembrolizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There is no evidence directly comparing pembrolizumab with current standard care for relapsed or refractory classical Hodgkin lymphoma in people who have had autologous stem cell transplant followed by brentuximab vedotin, or who have had brentuximab vedotin but could not have autologous stem cell transplant. Indirect analyses suggest that having pembrolizumab after brentuximab vedotin may lead to longer progression-free survival than current treatment. This would increase the number of people who can have curative allogeneic stem cell transplant.

Modelling has been done to predict how many people having pembrolizumab will be able to have allogeneic stem cell transplant and their long-term outcomes, compared with those having standard care. However, these models can't be used to identify the

most plausible estimates of cost effectiveness. This is because of uncertainties in the assumptions which have not been fully explored, and because the modelled survival estimates for standard care do not match either the clinical evidence or the claim that end-of-life criteria are met.

Nivolumab is now recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and brentuximab vedotin. The committee heard from clinical experts that the clinical effectiveness of pembrolizumab and nivolumab are likely to be similar in this population. Therefore, a cost-comparison between pembrolizumab and nivolumab in this population is requested.

There is an unmet need for treatment for disease that has relapsed after brentuximab vedotin in people who cannot have autologous stem cell transplant. However, pembrolizumab cannot be recommended for this population because there is too much uncertainty in the company's estimates of cost effectiveness.

2 Information about pembrolizumab

Marketing authorisation indication	Pembrolizumab (Keytruda, Merck Sharp & Dohme) has a marketing authorisation as monotherapy 'for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV'.
Dosage in the marketing authorisation	200 mg every 3 weeks by intravenous infusion, until disease progression or unacceptable toxicity.
Price	A 100-mg vial costs £2,630 excluding VAT (British national formulary online, accessed February 2018) The company has a commercial access agreement with NHS England. This makes pembrolizumab available at a reduced cost. The financial terms of the agreement are commercial in confidence.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Merck, Sharp & Dohme and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Pembrolizumab is a potentially important treatment option

3.1 The marketing authorisation for pembrolizumab includes 2 subpopulations of people with relapsed or refractory classical Hodgkin lymphoma: people who have had brentuximab vedotin and autologous stem cell transplant (population 1), and those who have had brentuximab vedotin but cannot have autologous stem cell transplant (population 2). These subpopulations have different treatment options available to them. For population 1, NICE technology appraisal guidance recommends [nivolumab](#). The clinical expert stated that the use of nivolumab has increased since the publication of this guidance. For population 2, [brentuximab vedotin](#) is recommended within the Cancer Drugs Fund for relapsed or refractory disease after at least 2 previous therapies, in people who cannot have autologous stem cell transplant or multi-agent chemotherapy. The clinical expert explained that there is considerable need for effective treatment in population 2 who relapse following brentuximab vedotin, and that the aim is to achieve sufficient disease response to enable allogeneic stem cell transplant to be done, which may cure the disease. The committee concluded that pembrolizumab is a potentially important treatment option for people with relapsed or refractory classical Hodgkin lymphoma after treatment with brentuximab vedotin, particularly if they have not had autologous stem cell transplant.

Clinical evidence

Pembrolizumab is clinically effective based on response rates but the effect on overall survival is unknown

3.2 Clinical-effectiveness data for pembrolizumab came from the most recent data cut from KEYNOTE-087, an ongoing single-arm, open-label trial. This included people with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin (population 1), or after salvage chemotherapy and brentuximab vedotin but no autologous stem cell transplant (population 2). The committee considered objective response rates and progression-free survival

assessed by blinded, independent central review from the most recent data cut (March 2017) from KEYNOTE-087 (table 1). It noted that overall survival data from the trial are not mature.

Table 1 Clinical data from KEYNOTE-087

		KEYNOTE-087 population 1	KEYNOTE-087 population 2
Number of patients		69	81
Progression-free survival, median (95% confidence interval [CI])		16.7 months (11.2 to not reached)	11.1 months (7.6 to 13.7)
Best overall response (95% CI)	Complete remission (CR)	27.5% (17.5 to 39.6)	24.7% (15.8 to 35.5)
	Partial remission (PR)	47.8% (35.6 to 60.2)	42% (31.1 to 53.5)
	Objective response (CR+PR)	75.4 (63.5 to 84.9)	66.7% (55.3 to 76.8)

The committee concluded that pembrolizumab is clinically effective based on response rates and progression-free survival data but the effect on overall survival is not known.

Comparator data

Cheah et al. (2016) is the best available data source for population 1, but UK data are now available for standard care in population 2

3.3 No data providing direct comparative evidence for the clinical effectiveness of pembrolizumab compared with current standard care are available. The company used Cheah et al. (2016), a retrospective observational study done in the US that reported data from a mixture of chemotherapy regimens, as a source of data for standard care. However, the company did not include any comparisons with best supportive care because there were insufficient data available. The committee heard from a clinical expert that the study was done in a single specialist centre, and included patients with a relatively good performance status. Around 70% of the total study population had had autologous stem cell transplant (population 1), and 30% had not (population 2). The committee noted that the Cheah study was used to provide comparator data in NICE’s

technology appraisal guidance on [nivolumab for treating relapsed or refractory classical Hodgkin lymphoma](#). It heard from the ERG that although the study was not a particularly good match for population 2, it was not aware of a more appropriate source of data for standard care at the time of reviewing the company submission. However, it heard from the clinical expert that a recent UK study (Eyre et al. 2017) has data relevant for this population, and that this might be a useful source of additional comparator data. The company considered that only a subgroup of patients in the Eyre study are relevant to the decision problem and they did not have sufficient detail on patient characteristics or outcomes for this subgroup to include it in their analysis. The ERG commented that despite these limitations, the Eyre study is likely to be a relevant source of data for population 2. The committee concluded that the Cheah study was the best available evidence for standard care at the time of the company's submission, particularly for population 1, but may not fully represent UK clinical practice. In addition, it considered that more appropriate standard-care data for population 2 are now available. The committee would have preferred the company's additional analysis to have explored the use of data from the Eyre study, compared with Cheah, and to provide justification for the data used to model standard care in this population.

Indirect treatment comparisons

Pembrolizumab has a beneficial effect on progression-free survival and objective response rate, but there is considerable uncertainty over the size of the effect and long-term outcomes

3.4 To provide estimates of relative treatment effectiveness, the company separately compared population 1 and population 2 from KEYNOTE-087 with standard care (using the whole population from Cheah et al. 2016). Both naive indirect comparison and matched-adjusted indirect comparisons were used. The company plans to publish these data and therefore considers the results to be academic in confidence, so they cannot be reported here. The committee noted that these comparisons

showed a beneficial effect for pembrolizumab for both of the outcomes included in the company's analysis (progression-free survival and objective response rate). It also noted that these beneficial effects were generally higher in the matched-adjusted indirect comparison than in the naive indirect comparison. It heard from the ERG that it considers neither method to be robust, but that on balance the naive comparison is more appropriate because it provides a more conservative estimate. The committee noted that the indirect comparisons may have underestimated the effect of pembrolizumab in population 2, because they compared the KEYNOTE-087 populations with the total population in the Cheah study. The Cheah study was predominantly population 1, who are likely to have a better prognosis than people in population 2. The committee heard from the company that it had not been possible to provide separate comparisons for each population, because they did not have access to the individual patient data from the Cheah study. The committee concluded that the indirect comparisons suggest that pembrolizumab has a beneficial effect on progression-free survival and objective response rate, but there is considerable uncertainty over the size of the effect and long-term outcomes.

The company's 'week 12' models

The assumption about timing of allogeneic stem cell transplants in the company's original model is inappropriate

3.5 The company's original model included a structural assumption that all allogeneic stem cell transplants would be done 12 weeks after starting treatment. This was modelled as a decision tree at week 12 when patients with partial or complete response, or stable disease, had the option of allogeneic stem cell transplant. The committee heard from the company that this was based on the mean number of administrations of pembrolizumab before allogeneic stem cell transplant in KEYNOTE-087, and on responses to a clinician survey that it had done. The committee heard from a clinical expert that a decision about whether to go ahead

with allogeneic stem cell transplant will typically be made around 2.5 to 3 months after starting treatment. However the arrangements for the transplant, such as establishing donor availability and arranging an inpatient stay for the procedure, usually cause some delay. The committee considered that a 12-week transplant model structure could potentially favour pembrolizumab because more people treated with pembrolizumab will have allogeneic stem cell transplant compared with standard care, and earlier transplant allows them to benefit from an earlier point in time. The ERG highlighted that this uncertainty could not be explored in the model because the fixed time point of 12 weeks could not be adjusted. The committee concluded that the 12-week timing for allogeneic transplant in the model is inappropriate. However it noted that the company subsequently provided a model that assumes all transplants happen at 24 weeks, to allow it to explore this uncertainty.

The omission of a progressed-disease state after allogeneic transplant in the company's original model is not clinically plausible

3.6 The company's original 12-week model for the post-allogeneic stem cell transplant population included only 2 states (alive or dead) and did not consider that disease could progress. The committee heard from the ERG that this lacks external validity because data from Lafferty et al. (2017) reported a progression-free survival of 54% at 1 year after allogeneic stem cell transplant. A clinical expert confirmed that not all allogeneic stem cell transplants are curative and that disease may return and progress. The committee concluded that the company's approach was not appropriate and that the omission of a progressed-disease state after allogeneic transplant is not clinically plausible. An updated 12-week model submitted by the company included a progressed-disease state after allogeneic stem cell transplant, and the committee agreed that this was more clinically appropriate. It noted that the inclusion of the progressed-disease state increased the ICERs by around £2,000 per quality-adjusted life year (QALY) gained.

The company's 'week 24' model

The difference in overall survival between pembrolizumab and standard care is overestimated at week 24

3.7 The committee considered a revised model provided by the company, which assumed that all allogeneic stem cell transplants were done 24 weeks after starting treatment. It noted that several parameters and assumptions had been updated in the company's model when changing the time at which allogeneic stem cell transplant occurs from week 12 to week 24. Unlike the 12-week models, the updated 24-week model did not assume equivalent overall survival for pembrolizumab and standard care in the period before allogeneic stem cell transplant (that is, a hazard ratio of 1) for populations 1 and 2. Instead, a hazard ratio of 13.13 (95% confidence interval [CI] 3.07 to 56.04) was used in the base case, and the impact of assuming no difference was explored in a scenario analysis. The company explained that this value was produced from a naive comparison between an earlier data-cut of KEYNOTE-087, which pooled data from both subpopulations, and the Cheah study. However, the company did not provide information to allow the ERG to confirm this estimate. The committee noted that at week 24 in the Cheah study, 88% of the standard-care population were alive. Using a hazard ratio of 13.13 estimated that only 78% (population 1) or 72% (population 2) of the standard-care population were alive, and using a hazard ratio of 1 estimated a value of 98%. The committee concluded that the difference in overall survival at week 24 is likely to have been overestimated in the model and that this uncertainty had not been adequately explored, particularly with regards to validating the estimates against published data for standard care.

The choice of parametric overall and progression-free survival curves used to model the pre-allogeneic transplant period introduces additional uncertainty

3.8 The ERG commented that using alternative parametric models for overall and progression-free survival in the period before allogeneic stem cell

transplant can affect the results of the model. The committee heard that different parametric models for progression-free survival in the pre-allogeneic stem cell transplant period had been used in the 24-week model, compared with the 12-week models, and some of these had poor statistical fit with the Kaplan–Meier curve from KEYNOTE-087. It questioned why parametric models had been used for modelling when observed survival data are available for both the 12-week and 24-week time points. The committee concluded that the choices made by the company to model progression-free and overall survival in the 24-week model pre-allogeneic stem cell transplant period introduced considerable uncertainty, which had not been fully investigated. The committee considered that the use of Kaplan–Meier data in the pre-allogeneic stem cell transplant period in the model would have been preferable.

Rate of allogeneic stem cell transplants

The uptake rate of allogeneic stem cell transplant is uncertain

3.9 To estimate the uptake of allogeneic stem cell transplant, the company combined results from 2 surveys of clinicians. Data from KEYNOTE-087 were not used by the company, because uptake of allogeneic stem cell transplant was low in the study and they did not consider it to be representative of UK practice. The committee considered that survey results are weak evidence to inform parameter estimates and heard from the ERG that the same clinicians could have been included in both surveys, potentially resulting in double-counting in the combined results. The ERG also stated that the results represented expected transplant rates and not observed rates. The committee noted that the sample size of the survey was small and heard from a clinical expert that this was to be expected because only a small number of clinicians treat this disease in the UK. Combining the 2 surveys resulted in a higher predicted rate of allogeneic stem cell transplants than in the single survey carried out by the company. The committee heard from a clinical expert that in their opinion the number of people with a complete or partial response to

treatment who would have an allogeneic stem cell transplant is higher than the estimates from the company's survey alone (which were 57% for complete response and 44% for partial response), and closer to the combined overall mean (values are academic in confidence and cannot be reported here). The committee concluded that there is considerable uncertainty about whether the rates of allogeneic stem cell transplant used in the models are an accurate reflection of transplant rates in UK clinical practice. The committee concluded that combining the results of the 2 surveys did increase the number of responses, although the combined number of responses was still small. However, there remained uncertainty about the validity and reliability of clinical predictions, as well as the potential duplication of clinicians in the combined survey.

It is appropriate to assume that people with progressed disease would not have allogeneic stem cell transplant

3.10 The company's models assume that patients with progressed disease do not have allogeneic stem cell transplant. The committee heard from the ERG that some clinicians included in the company survey had suggested that some patients with progressed disease may go on to have a transplant. A clinical expert stated that this was not done in current practice, and noted that guidelines from the British Committee for Standards in Haematology advise against transplants for people with progressive disease. The committee concluded that it is appropriate to assume that patients with progressed disease do not have allogeneic stem cell transplants.

Stopping rule

The assumption that people will be treated with pembrolizumab for up to 24 months in the model is appropriate

3.11 The company's models assume that treatment with pembrolizumab continues for up to 24 months as in the trial protocol for KEYNOTE-087, unless unacceptable toxicity occurs. The committee was aware that a

24-month stopping rule is not included in the summary of product characteristics and it questioned how long pembrolizumab treatment would be continued in clinical practice, particularly for people unable to have allogeneic stem cell transplant. It noted a submission received from NHS England, which stated that an assumption of discontinuation at 24 months is appropriate and is supported by the current evidence base. The committee therefore concluded that stopping treatment with pembrolizumab at a maximum of 24 months in the models is appropriate.

Utility values in the economic models

There is considerable uncertainty about the utility value for progressed disease

3.12 The committee considered the utility values used in the company's and the ERG's base-case analyses. The company aims to publish utility data from KEYNOTE-087 and therefore considers the results to be academic in confidence, so they cannot be reported here. The committee noted that the company used utility data from KEYNOTE-087 from week 12 only, and that they had estimated the utility for progressed disease by applying a decrement from Swinburn et al. (2015). It heard from the company that this was because EQ-5D data were only collected in KEYNOTE-087 for up to 30 days post-progression, and any longer-term effects of progression will therefore not have been captured. The committee noted that the company's utility values decreased substantially when disease progressed and it considered that the size of the decrease, relative to the other health states in the model, is implausible. In its base-case analysis of the company's original model, the ERG had used utility values from KEYNOTE-087 alone. It preferred to use a mixed-effects model provided by the company, incorporating all available EQ-5D data from KEYNOTE-087, rather than using only the 12-week data. The committee noted that this results in a far smaller decrease in utility when disease progresses than estimated by the company. The committee heard from a clinical expert that symptoms caused by progressed disease will not immediately

appear, but are expected to worsen over time, although receiving the diagnosis of disease progression alone could have a substantial effect on the patient. Consequently it is plausible that the utility for progressive disease was too high in the ERG's base case, but it is unlikely to be as low as the value proposed by the company. The committee therefore concluded that there is considerable uncertainty about the utility decrease that occurs when disease progresses, and that the actual value is likely to be between the company's and the ERG's base-case values.

Cost-effectiveness estimates

The time to allogeneic stem cell transplant is a key driver of cost-effectiveness estimates and there is considerable uncertainty about the true value

3.13 The committee noted that how allogeneic stem cell transplant is incorporated in the models is a major driver of incremental QALYs for pembrolizumab compared with standard care. The company's submission stated that the average time to transplant is likely to be between 12 and 24 weeks after starting treatment. The committee noted its previous consideration that it is unrealistic to assume that all allogeneic stem cell transplants would have occurred by week 12 (see section 3.5). It considered that, in practice, allogeneic stem cell transplants are likely to occur between weeks 12 and 24. It also heard from a clinical expert that all allogeneic stem cell transplants are likely to have been done by week 24. The most plausible ICER is therefore likely to fall between the values predicted by models using a fixed time of transplant of 12 and 24 weeks.

The cost effectiveness of pembrolizumab in population 1 is highly uncertain and a plausible ICER cannot be accurately estimated using the company's 12-week or 24-week model. An alternative cost-comparison approach is recommended.

3.14 The committee considered the cost-effectiveness estimates from each of the company's models for population 1 (that is, people with relapsed or

refractory classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin):

- in the original model, deterministic ICERs ranged from £43,511 per QALY gained in the company's base case to £61,705 per QALY gained in the ERG's base case
- in the updated 12-week model, the company's deterministic base-case ICER was £45,033 per QALY gained
- in the updated 24-week model, the company's deterministic base-case ICER was £39,880 per QALY gained.

The ERG's preferences could not be fully implemented in the company's updated models, but it estimated that this would increase the ICERs by about £14,000 per QALY gained if its preferred amendments were made to the model. However there is greater uncertainty for the 24-week model than the 12-week model, because of the changes made to structure and parameters. The probabilistic sensitivity analyses highlighted that the results are subject to substantial uncertainty. The committee noted that, despite using the same study to provide comparator data for standard care (Cheah et al. 2016), the total QALYs and costs generated by modelling standard care for population 1 in the original model for the current appraisal were about double those generated for standard care in NICE's guidance on [nivolumab for treating relapsed or refractory classical Hodgkin lymphoma](#). It noted a statement from NHS England that, compared with nivolumab, pembrolizumab may have clinical and cost benefits because it is administered less frequently and has fixed-rate dosing. A clinical expert commented that the clinical effectiveness of pembrolizumab and nivolumab in this population is likely to be similar. The committee therefore concluded that because of the uncertainties in the company's modelling for this population, and the substantial differences in its outputs compared with the nivolumab model, a cost-comparison between the 2 technologies may address these uncertainties for the NHS.

The cost effectiveness of pembrolizumab in population 2 is highly uncertain, and a plausible ICER cannot be accurately estimated using the company's 12-week or 24-week models.

3.15 The committee considered the cost-effectiveness estimates from each of the company's models for population 2 (that is, people who have had salvage chemotherapy and brentuximab vedotin, but no autologous stem cell transplant):

- in the company's original model, deterministic ICERs ranged from £48,571 per QALY gained in the company's base case to £73,594 per QALY gained in the ERG's base case
- in the updated 12-week model, the company's deterministic base-case ICER was £50,353 per QALY gained
- in the updated 24-week model, the company's deterministic base-case ICER was £39,714 per QALY gained.

The ERG's preferences could not be fully implemented in the company's models for this population but it estimated that if its preferred base-case amendments were made to the model this could increase the ICERs to above £50,000 per QALY gained, although this was very difficult to predict. The committee noted its previous consideration that the uncertainties about how the company had altered the model to change the time at which allogeneic stem cell transplant occurs from week 12 to week 24 had not been fully explored (see sections 3.7 and 3.8). The committee concluded that because of its concerns about the models, a plausible ICER could not be accurately estimated using the company's 12 or 24 week models for population 2.

There is a lack of face validity between modelled survival estimates for standard care and the clinical evidence, and for the company's assertion that end-of-life criteria are met

3.16 The committee was concerned that there was a lack of face validity between the modelled survival for standard care and the clinical evidence,

and for the company's assertion that end-of-life criteria are met, because more than 3 life-years were estimated for standard care in the company's models (see section 3.18). The committee heard from the company that it used aggregated data from the Cheah study in the model, because it did not have access to individual patient data from the study. Survival estimates for people who could not have allogeneic stem cell transplant are therefore likely to have been influenced by data from people who did have stem cell transplant. The committee heard from a clinical expert that they would expect overall survival, particularly for population 2, to be closer to that reported in the literature (median overall survival of between 17.1 and 19 months), as presented in the company's submission. The committee also noted that additional data on standard care for population 2 is now available (see section 3.3) and considered that it would like to see the incorporation of relevant data from this study, which could help to address the uncertainty in the cost-effectiveness estimates for population 2.

Innovation

Pembrolizumab's benefits are captured in the measurement of QALYs

3.17 The company considered pembrolizumab to be an innovative treatment. A clinical expert explained that there is an unmet need for treatment to allow people with disease that has relapsed after brentuximab vedotin, and who cannot have autologous stem cell transplant, to have allogeneic stem cell transplant, which is potentially curative. The committee concluded that pembrolizumab would be beneficial for patients, but that it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

End of life**The total life-years predicted by the company's models exceeds 24 months**

3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). The company made the case that pembrolizumab meets the criteria for life-extending treatments for people with a short life expectancy (normally less than 24 months) based on available literature estimates of median overall survival for people with relapsed or refractory classical Hodgkin lymphoma. The committee noted that more than 3 life-years were estimated for standard care in the company's models, which is inconsistent with the company's claim and the published literature (see section 3.16). The committee concluded that the company should have provided further explanation and justification for this discrepancy.

There is sufficient evidence to suggest that pembrolizumab compared with standard care offers an extension to life of at least 3 months

3.19 The committee considered that based on survival data from KEYNOTE-087 presented by the company, and also model results, there is sufficient evidence to indicate that pembrolizumab offers an extension to life of at least 3 months.

Conclusions**The committee is minded not to recommend pembrolizumab as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin**

3.20 Pembrolizumab is a clinically effective treatment, compared with standard care, for treating relapsed or refractory classical Hodgkin lymphoma, although there is uncertainty about the size of the effect (see section 3.4). The committee concluded that it could not use the models provided to identify the most plausible ICERs for population 1 because of

uncertainties that have not fully been addressed, and because of concerns about a lack of face validity between modelled survival estimates and clinical evidence, and the company's claim that end-of-life criteria are met. The committee noted its conclusion that a cost-comparison between nivolumab and pembrolizumab may address uncertainties about the use of pembrolizumab in population 1 for the NHS (see section 3.14). The committee therefore requests that a cost-comparison of pembrolizumab and nivolumab for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin is made available by the company. This further analysis should be made available for the third appraisal committee meeting.

Pembrolizumab is not recommended as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who cannot have autologous stem cell transplant and have had brentuximab vedotin

3.21 The committee noted that because nivolumab is not licenced for use in population 2 (that is, people who have had brentuximab vedotin and who cannot have allogeneic stem cell transplant), a cost-comparison approach could not be used for this population. It further noted that pembrolizumab is a potentially important treatment option for population 2 (see section 3.1). However, the committee concluded that, because of considerable concerns about the models provided by the company (see sections 3.15 and 3.16), it was unable to identify the most plausible ICER. The committee concluded that the uncertainty is too great for it to recommend pembrolizumab as cost-effective for use in population 2.

4 Proposed date for review of guidance

4.1 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.

Jane Adam
Chair, appraisal committee
March 2018

5 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 A](#).

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.

Thomas Walker

Technical Lead

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Project Manager

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