

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma

Technology appraisal guidance

Published: 3 September 2018

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

- 1.1 Pembrolizumab is not recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin.
- 1.2 Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had brentuximab vedotin and cannot have autologous stem cell transplant, only if:
- pembrolizumab is stopped after 2 years of treatment or earlier if the person has a stem cell transplant or the disease progresses and
 - the conditions in the [managed access agreement](#) for pembrolizumab are followed.
- 1.3 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

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 and those who have had brentuximab vedotin but cannot have autologous stem cell transplant.

There is no evidence directly comparing pembrolizumab with current standard care in either of the subpopulations. 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. It is uncertain 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 and this is a key driver of cost effectiveness.

NICE recommends nivolumab 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. The company did not provide a cost-comparison between pembrolizumab and nivolumab and so the committee based its decision on the cost effectiveness of pembrolizumab compared with standard care before the introduction of nivolumab.

Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life.

Because of uncertainties in the clinical effectiveness and the modelling, the cost-effectiveness estimates are uncertain. Because of this, pembrolizumab cannot be recommended for routine use in the NHS.

There is an unmet treatment need for people who have had brentuximab vedotin and cannot have autologous stem cell transplant. There are no licensed immunotherapies for this subpopulation. Pembrolizumab has plausible potential to be cost effective for people who cannot have autologous stem cell transplant. Further data collection may reduce the uncertainty about the cost effectiveness. Therefore pembrolizumab is recommended for use in the Cancer Drugs Fund for people who have classical Hodgkin lymphoma that has relapsed after, or not responded to, brentuximab vedotin and who cannot have autologous stem cell transplant.

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	<p>£2,630 per 100-mg vial (excluding VAT; company submission).</p> <p>The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.</p>

3 Committee discussion

The appraisal committee ([section 6](#)) 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 the clinical expert explained that there is considerable need for effective treatment for disease that relapses after, or doesn't respond to, 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). Comments received during consultation from patients and clinicians also highlighted an unmet need for treatment in this population. 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 cannot have 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) was the best available data for standard care at the time of the company's submission, particularly for population 1, but UK data are now available for standard care in population 2

- 3.3 No data providing direct 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 relatively good health (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 \(TA462\)](#). 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) might be a useful source of additional comparator data, because it provides data for standard care in a UK population rather than in the US (as in Cheah et al.). The company highlighted concerns about the use of data from the Eyre study. This included differences in the population, which was more heavily pre-treated in KEYNOTE-087 than in Eyre. The company also highlighted the small sample size in the Eyre study and the need to use estimates from digitised published survival curves. The company considered Cheah et al. to represent the most comparable population to the whole KEYNOTE-087 population, but it provided results of naive-indirect comparisons between Eyre et al. and KEYNOTE-087 (population 2) data for both overall and progression-free survival for the first 24 weeks after starting treatment. The company commented that the hazard ratio for overall survival produced from this comparison (which is academic in confidence) is similar to the hazard ratio of 13.13 derived from a comparison of KEYNOTE-087 (whole population) and Cheah et al. data, which was used in the updated 24-week model (see [section 3.7](#)). However the ERG cautioned against using this exploratory analysis to validate the use of this hazard ratio in the company's model. 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. The committee welcomed the exploratory analyses based on Eyre et al. that the company provided for the third committee meeting, but noted that the company and ERG had concerns about using this study as a source of evidence for standard care.

Indirect treatment comparisons

Pembrolizumab increases progression-free survival and objective response rate, but the size of the benefit and long-term outcomes are uncertain

- 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 a 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 are not 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 it 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' economic models

The assumption about timing of allogeneic stem cell transplants in the company's original model is not appropriate

- 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. 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 original 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 not appropriate. However it noted that the company subsequently provided models that assume 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 incremental cost-effectiveness ratios (ICERs) by around £2,000 per quality-adjusted life year (QALY) gained.

The company's 'week-24' economic model

The difference in overall survival between pembrolizumab and standard care is likely to be overestimated at week 24 using results from the naive-indirect comparison of data from Cheah and KEYNOTE-087

- 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%. Further analysis provided by the company used alternative hazard ratios for overall survival in weeks 0 to 24, which were calibrated to match observed survival data for standard care from Cheah et al. (hazard ratios of 8.01 for population 1 and 5.18 for population 2). The ERG had concerns about the use of a methodology that matched overall survival estimates to those at a single point, because this does not follow conventional curve-fitting methodology and may result in the curve being a poor fit to the data at other time points. However, because data were not provided to validate the use of the 13.13 hazard ratio and a hazard ratio of 1.0 lacked face validity, the ERG had a slight preference for using the alternative hazard ratios in the week-24 economic model. The ERG commented that because of uncertainty about the most appropriate value to use, the results of the week-24 model should be interpreted with caution, and should only be considered as a scenario analysis. The committee concluded that the difference in overall survival at week 24 is subject to uncertainty, but is likely to have been overestimated in the model using a naive-indirect comparison between Cheah and KEYNOTE-087.

There is uncertainty about the parametric overall and progression-free survival curves used to model the pre-allogeneic transplant period

- 3.8 The ERG commented that the choice of parametric model 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. A subsequently updated 24-week model used the same parametric models for progression-free survival as the 12-week model. The committee 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 observed survival 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 provide suboptimal 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, rather than observed, transplant 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

It is appropriate to assume that people will have pembrolizumab for up to 24 months

- 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

There is uncertainty about the time to allogeneic stem cell transplant, which is a key driver of the cost-effectiveness estimates

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 occurred 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 relative to standard care in population 1 is highly uncertain

3.14 After the committee concluded at its second meeting that a plausible ICER for population 1 could not be accurately estimated using the company's 12-week or 24-week model, the company provided updated 12-week and 24-week analyses for the third appraisal committee meeting. These included an updated commercial access agreement and changes to the parametric distributions used for progression-free and overall survival in the models. The company also presented further scenario analyses to explore some of the uncertainties the committee had highlighted in the consultation document. For population 1, the updated base-case ICERs were £42,123 (24-week model) and £49,058 (12-week model) per QALY gained. The ERG implemented their preferred assumptions in the updated models and produced ICERs of £45,829 (24-week model) and £54,325 (12-week model) per QALY gained. The ERG commented that there is still substantial uncertainty associated with the model results, particularly for the 24-week model (see [section 3.7](#) and [section 3.8](#)). The committee recalled its conclusion that the most plausible ICER is likely to fall between the values predicted by models using a fixed time of transplant of 12 and 24 weeks ([section 3.13](#)). It noted that the range of ICERs produced by the company's and ERG's 24-week and 12-week models are between £42,100 and £54,300 per QALY gained, but that these results are highly uncertain because of the total life-years predicted by the model (see [section 3.17](#)), the uncertainties associated with the 24-week model, uptake rate and timing of allogeneic stem cell transplant (see [section 3.9](#) and [section 3.13](#)). The committee concluded that because of the substantial uncertainty associated with the model results, the ICERs for population 1 remain highly uncertain.

A requested cost-comparison with nivolumab for population 1 was not provided

3.15 The committee noted that NICE technology appraisal guidance recommends [nivolumab](#) for use in population 1 (TA462), and that the committee in that appraisal concluded that the most plausible ICER is likely to be around £30,000 per QALY gained. The ERG commented that the committee's and ERG's preferred analyses in TA462 used the same cost of allogenic stem cell transplant (from Radford et al. 2017) as used in the current appraisal. 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 company's models for the current appraisal of pembrolizumab are higher than those generated for standard care in TA462. It noted a statement from NHS England that, compared with nivolumab, pembrolizumab may have clinical and cost benefits because it is administered less frequently. The committee further noted that nivolumab's marketing authorisation had recently changed to fixed-dosing, rather than dosing based on body weight. 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 results compared with the nivolumab model, a cost-comparison between the 2 technologies may address these uncertainties for the NHS. It requested that this should be provided by the company. The company did not provide a cost-comparison for the third committee meeting. The committee heard from the company that based on a naive comparison, results from single-arm trials are more favourable for pembrolizumab and that there are insufficient comparative data to confirm that the clinical effectiveness of the 2 drugs is similar. The company also commented that the 2 drugs differ in chemical structure. The committee noted that the company had not provided evidence to demonstrate different clinical efficacy between nivolumab and pembrolizumab, or provided a convincing explanation as to why the treatment effects would be likely to differ. The committee concluded that, in the absence of a cost-comparison with nivolumab, it can only base its estimate of cost effectiveness for pembrolizumab in population 1 on the analyses comparing it with standard of care and that the results of these analyses are highly uncertain.

The most plausible ICER for pembrolizumab in population 2 is highly uncertain

3.16 The committee noted its conclusions from the first and second appraisal

meetings; that the cost effectiveness of pembrolizumab in population 2 is highly uncertain, and that a plausible ICER could not be accurately estimated using the company's 12-week or 24-week models. The committee noted that the company had provided updated 12-week and 24-week scenario analyses for the third appraisal committee meeting (see [section 3.14](#)). For population 2, the updated base-case ICERs are £36,950 (24-week model) and £55,628 (12-week model) per QALY gained. The ERG implemented their preferred assumptions in the updated models provided for the third committee meeting, which produced ICERs of £42,501 (24-week model) and £62,527 (12-week model) per QALY gained. The ERG commented that there is still substantial uncertainty associated with the model results, particularly for the 24-week model (see [section 3.7](#) and [section 3.8](#)). The committee concluded that because of the substantial uncertainty associated with the model results, including the total life-years generated by the model (see [section 3.14](#) and [section 3.17](#)) it is unable to predict the most plausible ICER for population 2, but the extreme values from the company's and ERG's 24-week and 12-week models (that is, between £37,000 and £62,500 per QALY gained) reflected a plausible range in which the true ICER may fall. The committee concluded that the estimates of cost effectiveness are too uncertain to recommend pembrolizumab for routine use.

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

3.17 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 2 life-years were estimated for standard care in the company's base-case models. The company explained 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 company highlighted that Eyre et al. reported a median overall survival of 12.2 months (95% CI 8.1 to 18.3) for people who were transplant naive and were unable to

have a stem cell transplant after treatment with brentuximab vedotin, in a UK population. The committee concluded that there is lack of face validity between the modelled survival estimates for standard care and the clinical evidence, and company's assertion that end-of-life criteria are met, which further adds to the uncertainty about the results produced by the models.

Innovation

Pembrolizumab's benefits are captured in the measurement of QALYs

- 3.18 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 not responded or 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 committee agreed that, on balance, pembrolizumab meets the end-of-life criteria

- 3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [guide to the methods of technology appraisal](#). 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 2 life-years were estimated for standard care in the company's models, which is inconsistent with the company's claim and the published literature. However, the committee noted the company's explanation for the higher number of life-years produced by the models (see [section 3.17](#)). It also noted the conclusion of the NICE technology appraisal committee for nivolumab ([TA462](#)), in which models using Cheah data for standard care predicted overall survival of more than 24 months for the comparator treatment arm. The committee concluded that while pembrolizumab did not unequivocally meet the criterion for short life

expectancy, it is plausible that the criterion could apply. The committee concluded that on balance, pembrolizumab meets the criterion for short life expectancy.

Pembrolizumab offers an extension to life of at least 3 months

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

Cancer Drugs Fund

The committee considered pembrolizumab as an option for use in the Cancer Drugs Fund

3.21 Having concluded that pembrolizumab could not be recommended for routine use (see [section 3.16](#)) the committee considered if it could be recommended for use within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#).

The company proposed pembrolizumab for the Cancer Drugs Fund for population 2

3.22 The company commented that it has no further plans to collect data on pembrolizumab for treating relapsed or refractory Hodgkin lymphoma in population 2. It requested that the committee consider pembrolizumab for inclusion in the Cancer Drugs Fund for this population to allow further data collection, which may reduce the uncertainty.

3.23 It suggested data that could be feasible for collection in the Cancer Drugs Fund:

- proportion of people who have an allogeneic stem cell transplant
- timing of allogeneic stem cell transplant
- duration of pembrolizumab treatment before allogeneic stem cell transplant.

The company noted that data collection should include long-term follow-up of all people having pembrolizumab, regardless of whether they subsequently have allogeneic stem cell transplant. The committee noted the considerable unmet need for

- treatment in population 2 (see [section 3.1](#)) and that there is considerable uncertainty about the most plausible ICER for this population, which is likely to be between £37,000 and £62,500 per QALY gained (see [section 3.16](#)). It noted that time to allogeneic stem cell transplant is a key driver of the cost-effectiveness estimates and there is considerable uncertainty about the true value (see [section 3.13](#)). There is also uncertainty about whether the rates of allogeneic stem cell transplant used in the models (which are based on clinician surveys) are an accurate reflection of transplant rates in UK clinical practice (see [section 3.9](#)). The committee concluded that these are appropriate outcomes to collect data on, and this would reduce uncertainty in the cost-effectiveness estimate for population 2. It considered that overall survival for people having pembrolizumab would be a useful long-term outcome to measure.

Pembrolizumab is recommended as an option for use in the Cancer Drugs Fund for population 2

- 3.24 The committee concluded that pembrolizumab meets the criteria to be considered for inclusion in the Cancer Drugs Fund for population 2. It therefore recommended pembrolizumab for use within the Cancer Drugs Fund as an option for adults with relapsed or refractory classical Hodgkin lymphoma who have had brentuximab vedotin and cannot have autologous stem cell transplant, if the conditions in the managed access agreement are followed.

Pembrolizumab is not recommended as an option for use in the Cancer Drugs Fund for population 1

- 3.25 The committee considered pembrolizumab for inclusion in the Cancer Drugs Fund for population 1. It noted that the company had not requested that this population should be considered in the Cancer Drugs Fund. It further noted that nivolumab is in routine use for this population, therefore people in this population already have access to immunotherapy. The committee was unable to resolve its uncertainties about the relative cost effectiveness of pembrolizumab and nivolumab because a requested cost-comparison was not provided. The committee did not recommend pembrolizumab for use within the Cancer Drugs Fund for population 1.

Conclusions

Pembrolizumab is not recommended as an option for population 1

3.26 Pembrolizumab is a clinically effective treatment, compared with standard care, for relapsed or refractory classical Hodgkin lymphoma, although there is uncertainty about the size of the effect (see [section 3.4](#)). Despite considerable uncertainty in the results of the model provided by the company for this appraisal (see [section 3.14](#) and [section 3.15](#)), the model results had to be used for decision-making because a requested cost-comparison with nivolumab for this population was not provided. The committee noted that the estimated ICERs in the current appraisal are substantially higher than the most plausible ICER in [TA462](#). The committee took into account the case for pembrolizumab meeting the end-of-life criteria (see [section 3.19](#) and [section 3.20](#)). However, because of the considerable uncertainty associated with the model results there is insufficient justification for recommending pembrolizumab as a cost-effective use of NHS resources in population 1.

Pembrolizumab is recommended for use in the Cancer Drugs Fund for population 2

3.27 The committee noted that because there is no licensed immunotherapy for population 2 (that is, people who have had brentuximab vedotin and who cannot have allogeneic stem cell transplant) there is a high unmet need for treatment (see [section 3.1](#)). The most plausible ICER for pembrolizumab in population 2 is highly uncertain (see [section 3.16](#)) and therefore it cannot be recommended for use in routine commissioning. However it is plausible that pembrolizumab could be cost effective in this population, and therefore it is recommended for use within the Cancer Drugs Fund. Further data collection through inclusion in the Cancer Drugs Fund will allow a more accurate estimate of the cost effectiveness of pembrolizumab in this population (see [section 5](#)).

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient with relapsed or refractory classical Hodgkin lymphoma has had brentuximab vedotin and cannot have autologous stem cell transplant, and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#).
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

5 Recommendations for data collection

5.1 Proposals for further data collection in the Cancer Drugs Fund include:

- proportion of people having pembrolizumab who have an allogenic stem cell transplant
- time to allogenic stem cell transplant
- duration of treatment with pembrolizumab before allogenic stem cell transplant
- long-term follow-up of people having pembrolizumab with or without subsequent allogenic stem cell transplant (in particular, collection of data on overall survival).

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 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.

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ISBN: 978-1-4731-3081-4

Accreditation

