Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma

Technology appraisal guidance
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## Contents

1 Recommendations .......................................................... 4
2 The technology .............................................................. 5
3 Evidence ........................................................................... 6
4 Committee discussion ...................................................... 7
   Current clinical management of Hodgkin lymphoma .......... 7
   Clinical effectiveness ....................................................... 9
   Cost effectiveness .......................................................... 12
   Innovation ....................................................................... 18
   End-of-life considerations ............................................... 19
   Committee's conclusions ................................................ 19
   Summary of appraisal committee's key conclusions ............ 20
5 Implementation .................................................................. 26
6 Appraisal committee members and NICE project team ......... 27
   Appraisal committee members ....................................... 27
   NICE project team ........................................................ 27
   Update information ........................................................ 28

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1 Recommendations

1.1 Nivolumab is recommended, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and treatment with brentuximab vedotin, when the company provides nivolumab according to the commercial arrangement.
## 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 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 June 2017). The company has a commercial arrangement. This makes nivolumab 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. |
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 the NICE technology appraisal guidance on brentuximab vedotin for Hodgkin lymphoma is the only NICE guidance on Hodgkin lymphoma, and that the guidance was published during the course of this appraisal. 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, and for relapsed disease following autologous stem cell transplant in patients who have not previously had brentuximab vedotin. 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 is potentially curative in around 60% of patients who have 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. It understood from the clinical experts and patient organisations 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 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, but 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 (see table 1). The investigator-assessed objective response rates and progression-free survival are also available for both trials, but the company plan to publish the results before the end of 2017 and therefore consider these to be academic in confidence, and so they cannot be reported here.

Table 1 Clinical data from CheckMate 205 and CA209-039

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<tr>
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<th>CheckMate 205 cohort B</th>
<th>CheckMate 205 cohort C</th>
<th>CA209-039</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>80</td>
<td>98</td>
<td>15</td>
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<tr>
<td>Median follow-up</td>
<td>15.7 months</td>
<td>8.9 months</td>
<td>23.3 months</td>
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<tr>
<td>Objective response rate (95% CI)</td>
<td>67.5% (54) (57.2, 77.8)</td>
<td>73.0% (73) (64.3, 81.7)</td>
<td>60% (9)</td>
</tr>
<tr>
<td>Progression-free survival*, median (95% CI)</td>
<td>14.78 months (11.33, NA)</td>
<td>11.17 months (8.51, NA)</td>
<td>12.65 months (5.91, NA)</td>
</tr>
<tr>
<td>Overall survival at 6 months** (95% CI)</td>
<td>96.1% (92.0, 100)</td>
<td>94.0% (89.1, 98.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>
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 indirect treatment 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 reflected 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 may not reflect UK practice, particularly regarding subsequent rates of allogeneic stem cell transplant. The committee noted that in response to consultation, the company had explored UK standard-of-care data from the Haematological Malignancy Research Network and surveyed clinicians actively treating relapsed or refractory classical Hodgkin lymphoma in the UK. The committee considered that both the network data and the clinician survey somewhat supported the Cheah study as reflecting UK practice, but it
recognised that the data were limited. The committee concluded that the Cheah study was the best available evidence for standard of care and considered it appropriate for its decision-making, but overall the clinical effectiveness of nivolumab compared with standard of care was highly uncertain because the comparator data may not fully represent UK clinical practice.

4.8 The committee noted that the company’s indirect treatment comparison excluded results from patients who had investigational agents in the Cheah study. It heard from the company that including 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 company that use of investigational agents tended to be restricted to large centres and that they could not therefore be considered current NHS practice. The committee acknowledged that the investigational agents used in the study could have included treatments not available in the UK, but noted that there was little detail about which specific therapies were defined as ‘investigational agents’. 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 so it considered that the overall population should be used for comparator data. The committee considered that selectively excluding potentially the fittest patients from the Cheah dataset could bias the results of the indirect treatment comparison more than including some treatments that may not be used in UK current practice. The committee concluded therefore 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 the standard-of-care data from the overall population in the Cheah study for progression-free and overall survival (results are academic in confidence because the company plan to publish them before the end of 2017, and so they cannot be reported here). The committee noted that in the company’s original submission, the results of the indirect treatment comparison were obtained from an unadjusted or ‘naive’ comparison, but that it had also presented the results of a matched-adjusted indirect comparison as a scenario analysis. The committee was aware that a matched-adjusted indirect comparison took account of different distributions of prognostic factors and effect modifiers arising from any differences in baseline characteristics of
patients in the trials. It concluded that a matched-adjusted indirect comparison would produce more robust results, but considered that the unadjusted comparison used in the company’s base-case analysis was similar and so was acceptable for its decision-making. Furthermore, the committee acknowledged that the company had used the results of the matched-adjusted comparison in its revised cost-effectiveness analysis submitted in response to consultation.

4.10 In conclusion, the committee acknowledged that nivolumab was clinically effective, but noted that the available evidence was highly uncertain because the data were immature and from single-arm studies. The committee noted that the company’s indirect comparison with standard of care had compared pooled outcomes from the nivolumab trials with outcomes from the Cheah et al. study. The committee considered that Cheah et al. may not fully reflect UK current practice, but it acknowledged that the published evidence for comparator treatments used in the UK was limited. When considering the new evidence received from the company in response to consultation, it acknowledged that Cheah et al. was currently the best available evidence for standard of care and considered it appropriate for decision-making. The committee concluded that there was a large degree of uncertainty in the clinical evidence.

Cost effectiveness

4.11 The committee discussed the company's economic model and modelling assumptions, which it received in response to consultation. Overall, it accepted the structure of the model as representing the treatment pathway for relapsed or refractory Hodgkin lymphoma and considered it appropriate for decision-making. The committee recognised that the company had presented a revised base-case analysis incorporating some of the committee's preferred assumptions, and a number of scenario analyses that explored alternative sources of UK standard-of-care data and rates of subsequent allogeneic stem cell transplant:

- A revised base case incorporating the committee's preferred assumptions relating to the method of indirect treatment comparison, costs and utilities, including costs and outcomes of subsequent allogeneic stem cell transplant (using rates taken from the nivolumab trials and the Cheah study).

- A revised base case incorporating the committee's same preferred assumptions but excluding costs and outcomes of subsequent allogeneic stem cell transplant.
• A scenario analysis using the results from the clinician survey as standard-of-care data, and including costs and outcomes of subsequent allogeneic stem cell transplant (using rates taken from the survey).

• A scenario analysis using the results from the clinician survey as standard-of-care data (expected overall and progression-free survival) but excluding costs and outcomes of subsequent allogeneic stem cell transplant.

• A scenario analysis as per the revised base case but using rates of allogeneic stem cell transplant taken from the survey.

The committee noted that in each of the new analyses that used standard-of-care data from the Cheah study, the company had presented results from both the overall population and the subpopulation excluding patients who had investigational agents. It recalled that it preferred to use the overall population in its decision-making (see section 4.8) and therefore discounted results obtained from a comparison with the Cheah dataset that excluded patients who had investigational agents. It also noted that for the analyses that included costs and outcomes of subsequent allogeneic stem cell transplant, the company had presented results for 2 different sources of cost data. The committee recalled that it preferred to use the costs of allogeneic stem cell transplant obtained from Radford et al. (2016, see section 4.16) for its decision-making and therefore discounted results that did not use allogeneic stem cell transplant costs from the Radford paper. It considered the scenario analysis that used the results of the clinician survey as standard-of-care data, but concluded that because this evidence was limited and of low quality the Cheah data were a more reasonable representation of UK standard of care and should be used for its decision-making. The committee ultimately concluded that the company’s revised base case (including the costs and outcomes of subsequent allogeneic stem cell transplant) and the scenario analysis that replicated the revised base case but used rates of subsequent allogeneic stem cell transplant from the clinician survey, were the most relevant analyses for its decision-making.

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 matched-adjusted indirect treatment comparison of nivolumab compared with the treatments in the Cheah study (see section 4.6). It 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 (investigator-assessed) 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. 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. It concluded that all the parametric curves fitted to the data had a reasonable fit, but that they needed to be considered alongside survival modelling that included the long-term survival benefit of subsequent allogeneic stem cell transplant.

**Subsequent allogeneic stem cell transplant**

4.13 The committee considered those patients who had a partial or complete response to nivolumab and went on to 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), and 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 transplant. It was aware that the survival modelling used in the company's original 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 this 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. The committee noted that in its revised cost-
effectiveness analyses received in response to consultation, the company had
censored overall survival data for patients having nivolumab who went on to
have subsequent allogeneic stem cell transplant. It considered that censoring
data in only 1 arm of a model introduced a more substantial bias than a small
amount of double counting, and was not therefore methodologically
appropriate.

4.14 The committee noted that the company had used data from a UK study to model
long-term survival after allogeneic stem cell transplant in its revised cost-
effectiveness analyses. The committee considered the UK study of 13 patients
with classical Hodgkin lymphoma having allogeneic stem cell transplant after
3 previous therapies (Laffety et al. 2017), and noted the small number of
patients included in the study. It agreed that any modelling of long-term overall
survival beyond the median trial follow-up of approximately 28 months would
therefore be subject to significant uncertainty. It noted that the company had
fitted a Gompertz parametric curve to the data from the Laffety study to
extrapolate long-term overall survival but that this projected an infinite median
survival for patients having allogeneic stem cell transplant (all-cause mortality
excluded), which the committee considered implausible. It therefore considered
that the lognormal and Weibull parametric curves used by the ERG in its new
exploratory analysis were more clinically plausible because these curves did not
predict infinite median survival.

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 original 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 who 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 considered the results of the company's clinician survey, which it received in response to consultation. It noted that the response-specific proportions of patients expected to have subsequent allogeneic stem cell transplant, as reported by clinicians working in the UK, were significantly higher than those used in the original analyses by both the company and ERG. However, because these rates were expected rather than actual, and the results of the survey included a wide range of expected transplant rates (which were very different from the actual rates reported in the nivolumab trials and Cheah study), the committee agreed that rates of allogeneic stem cell transplant in the UK remained uncertain. The committee was also aware from supportive evidence provided by the company in response to consultation that caution may be warranted about using allogeneic stem cell transplant following treatment with nivolumab or another PD-1 inhibitor, because of the potential for increased risk of complications from transplant linked to PD-1 inhibitors' immunomodulatory mechanism of action. The committee also heard that recent NHS referrals for allogeneic stem cell transplant were lower than those reported in the survey. The committee concluded that UK rates of allogeneic stem cell transplant may lie somewhere between the high rates reported in the results of the survey, and the considerably lower rates of actual transplants reported in the nivolumab trials and Cheah study.

**Treatment costs**

4.16 The committee recognised that some patients in the nivolumab trials and the Cheah study had subsequent allogeneic stem cell transplant, and that because the survival benefit from allogeneic stem cell transplant was captured in the survival data for both arms of the model, the costs should also be included. It recognised that the company had used 2 different sources to calculate costs of allogeneic stem cell transplant: a weighted average of NHS reference costs and the costs included in the Radford et al. (2016) paper. The committee agreed that the Radford costs were more appropriate for its decision-making because they were consistent with the costs used for allogeneic stem cell transplant in guidelines currently in development. The committee 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.

4.19 The committee noted the ERG's identification of an error in the company's revised analyses received in response to consultation, whereby utility values for patients who discontinued treatment and transitioned to best supportive care reflected the company's original base case and not the committee's preferred assumptions about pre- and post-progression utilities (see sections 4.17 and 4.18). The committee was aware that the ERG had corrected this in its new exploratory analysis and agreed that this was appropriate.

**Results of cost-effectiveness analyses**

4.20 The committee noted that the company had presented deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) in its revised base-
case analysis provided in response to consultation. For nivolumab compared with standard of care, including the confidential discount agreed for nivolumab, the company’s deterministic base-case ICER was £15,181 per quality-adjusted life year (QALY) gained and the probabilistic ICER was £17,826 per QALY gained.

4.21 The committee was aware that the company's revised base case included the committee's preferred assumptions about using the overall population from the Cheah study for the standard-of-care data (see section 4.8), the method of indirect treatment comparison (see section 4.9), costs (see section 4.16) and utilities (see sections 4.17 to 4.18), and incorporated subsequent allogeneic stem cell transplant overall survival data (see section 4.13). However, the committee considered that this revised base-case analysis was flawed because of errors in the utility values for best supportive care (see section 4.19) and inappropriate censoring of nivolumab overall survival data (see section 4.13). The committee noted that when the ERG corrected these errors, the company's revised base-case ICER increased to £26,664 per QALY gained. The committee also noted that the company's revised base case had extrapolated long-term survival after allogeneic stem cell transplant using a Gompertz curve, which it had considered implausible (see section 4.14). It was aware that the ERG’s new exploratory analyses using the lognormal and Weibull curves increased the ICER to £30,366 and £31,031 per QALY gained respectively. However, the committee was also aware that these analyses included the high rates of allogeneic stem cell transplant from the clinician survey; because the committee considered that actual rates may be lower (see section 4.15), it concluded that the most plausible ICER was likely to be around £30,000 per QALY gained. But this ICER was associated with a large degree of uncertainty because of the immaturity of the nivolumab trial data, the lack of comparator data fully relevant to UK practice, and uncertain outcomes and rates of subsequent allogeneic stem cell transplant in the UK.

**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 and was aware that before the marketing authorisation was granted, nivolumab was available for people in the NHS through the early access to medicines scheme. 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 that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. However, the committee also considered the data from the Haematological Malignancy Research Network provided by the company in response to consultation, which showed shorter survival and suggested that the Cheah study may have been optimistic. The committee acknowledged that nivolumab did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply. It therefore agreed that on balance, nivolumab met the criterion for short life expectancy, and that it would take this into account in its decision-making.

4.24 The committee also discussed whether there was sufficient evidence to show that the treatment offers an extension to life 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, it concluded that based on the evidence presented, nivolumab met the criterion for extending life by at least an additional 3 months.

Committee's conclusions

4.25 The committee was aware that an ICER of around £30,000 per QALY gained required certainty about the assumptions underpinning the ICER in order to be
considered a cost-effective use of NHS resources. It considered that in this case, significant uncertainty remained because of the immaturity of the nivolumab trial data, the lack of comparator data fully relevant to UK practice, and uncertain outcomes and rates of subsequent allogeneic stem cell transplant in the UK. However, the committee also took into account the poor prognosis of people with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin, and the case for nivolumab meeting the end-of-life criteria (see sections 4.23 and 4.24), and concluded that there was sufficient justification for recommending nivolumab as a cost-effective use of NHS resources.

4.26 The committee understood that there were some people with relapsed or refractory Hodgkin lymphoma who were at the last line of treatment after failure of allogeneic stem cell transplant. It agreed that, although the analysis presented did not include this group, there was no biological reason why they would not benefit from treatment with nivolumab, and so they should not be disadvantaged. The committee therefore concluded that the recommendation should also cover these people.

Summary of appraisal committee's key conclusions

<table>
<thead>
<tr>
<th>TA462</th>
<th>Appraisal title: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Key conclusion</td>
<td></td>
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</table>

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Nivolumab is recommended, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and treatment with brentuximab vedotin, when the company provides nivolumab according to the commercial arrangement.

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 the committee could not be certain that the data used for standard of care fully represented UK current practice.

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. When accounting for the high rates of subsequent allogeneic stem cell transplant included in this analysis, the committee considered that the most plausible ICER was around £30,000 per QALY gained. Although significant uncertainty remained about the assumptions underpinning the cost-effectiveness analysis, the committee took into account the poor prognosis of people with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin, and the case for nivolumab meeting the end-of-life criteria, and concluded that there was sufficient justification for recommending nivolumab as a cost-effective use of NHS resources.

### Current practice

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>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, after autologous stem cell transplant fails.</th>
</tr>
</thead>
</table>

### The technology

<p>| 1.1, 4.10, 4.21, 4.25 | 4.2 |</p>
<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>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, and before the marketing authorisation was granted, it was available for people in the NHS through the early access to medicines scheme. The committee agreed that nivolumab was innovative and promising.</th>
<th>4.3, 4.22</th>
</tr>
</thead>
<tbody>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
<td>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. The committee understood there were some people with relapsed or refractory Hodgkin lymphoma who were at the last line of treatment after failure of allogeneic stem cell transplant, and considered that the recommendation should also cover this group.</td>
<td>4.4, 4.26</td>
</tr>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>The most common adverse reactions with nivolumab in clinical trials were diarrhoea, nausea, fatigue, pyrexia and rash.</td>
<td>2</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>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.</td>
<td>4.5</td>
</tr>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>The committee considered that data for the comparator may not represent UK clinical practice. However, when considering the new evidence received from the company in response to consultation, it concluded that the Cheah study was the best available evidence for standard of care.</td>
<td>4.7</td>
</tr>
<tr>
<td>Uncertainties generated by the evidence</td>
<td>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 effectiveness of nivolumab compared with standard of care because the data for the comparator may not fully represent UK clinical practice.</td>
<td>4.5, 4.7</td>
</tr>
<tr>
<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
<td>There are no clinically relevant subgroups for which there is evidence of differential effectiveness.</td>
<td>–</td>
</tr>
<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>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 uncertainty about the comparator's relevance to UK practice.</td>
<td>4.5, 4.10</td>
</tr>
</tbody>
</table>

**Evidence for cost effectiveness**

| Availability and nature of evidence | The company presented an economic model that the committee accepted as representing the treatment pathway for 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 fully relevant to UK practice, and uncertain outcomes and rates of subsequent allogeneic stem cell transplant in the UK.

There was substantial uncertainty around the long-term survival data because of the immaturity of the nivolumab trial data.

There was significant uncertainty around the long-term survival of people having allogeneic stem cell transplant because of the small number of patients in the relevant study, and short follow-up.

Rates of allogeneic stem cell transplant in the UK were uncertain.

### Incorporation of health-related quality-of-life benefits and utility values

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.

### What are the key drivers of cost effectiveness?

- Overall survival with nivolumab.
- Post-progression utility values.
<table>
<thead>
<tr>
<th>Most likely cost-effectiveness estimate (given as an ICER)</th>
<th>The committee noted that the company’s revised base-case ICER, when corrected by the ERG, was £26,664 per QALY gained. It was aware that this incorporated an overall survival extrapolation it deemed implausible. The ERG’s exploratory analysis using more plausible extrapolations increased the ICER to over £30,000 per QALY gained. However, the committee was aware that this analysis included high rates of allogeneic stem cell transplant, and because it considered that actual rates may be lower, it concluded that the most plausible ICER was likely to be around £30,000 per QALY gained.</th>
<th>4.21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional factors taken into account</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient access schemes (PPRS)</td>
<td>The company presented analyses that included the confidential patient access scheme for nivolumab.</td>
<td>–</td>
</tr>
<tr>
<td>End-of-life considerations</td>
<td>Nivolumab did not unequivocally meet the criterion for short life expectancy, but it was plausible that the criterion could apply, and therefore the committee agreed that on balance, nivolumab met the criterion for short life expectancy. Nivolumab met the criterion for extending life by at least an additional 3 months.</td>
<td>4.23, 4.24</td>
</tr>
<tr>
<td>Equalities considerations and social value judgements</td>
<td>No equalities issues were identified that could be addressed in the appraisal. The committee agreed that it was important to be clear that the recommendation would include people for whom there were no more treatment options (after autologous stem cell transplant and brentuximab vedotin). It therefore included a paragraph in the guidance relating to people who were at the last line of treatment, confirming that the recommendation should also cover these people. The equality impact assessment provides further information.</td>
<td>4.26</td>
</tr>
</tbody>
</table>
5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because nivolumab was made available in the NHS through the early access to medicines scheme, NHS England has indicated that this guidance will be implemented 30 days after final publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has classical Hodgkin lymphoma and the doctor responsible for their care thinks that nivolumab is the right treatment, it should be available for use, in line with NICE's recommendations.
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
Update information

Minor changes since publication

January 2019: The commercial access agreement has been replaced by a patient access scheme. Sections 1.1, 2 and 5 have been updated.

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Accreditation

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