NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy

1 Recommendations

1.1 Nivolumab is recommended as an option for treating recurrent or metastatic squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy, only if:

- the disease has progressed within 6 months of having chemotherapy and
- the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy (NICE technology appraisal guidance 490).

The new evidence includes data from 1 clinical trial and from people having treatment in the NHS, while this treatment was available in the Cancer Drugs Fund in England. The new evidence shows that people who have nivolumab are likely to live up to 9 months longer than those who have other treatments. But it is unclear how well nivolumab works compared with docetaxel, which is the most relevant comparator.

Issue date: September 2021

Nivolumab meets NICE's criteria to be considered a life-extending treatment at the end of life. Despite the uncertainty in the clinical evidence, the cost-effectiveness estimates are likely to be within the range NICE considers an acceptable use of NHS resources. So nivolumab is recommended.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol Myers Squibb) as monotherapy is indicated for 'the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price is £439 per 40-mg vial, £1,097 per 100-mg vial and £2,633 per 240-mg vial (excluding VAT; British National Formulary [BNF] online [accessed June 2021] and company submission). The company has a commercial access agreement. 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 Committee discussion

The appraisal committee considered evidence submitted by Bristol Myers Squibb, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

This guidance review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the

original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect updated efficacy data from the CheckMate 141 study. Data was also collected using the Systemic Anti-Cancer Therapy (SACT) dataset.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, page 8), and took these into account in its decision making. The committee discussed the following issues, which were outstanding after consultation:

- the generalisability of the trial population to NHS clinical practice
- the cost effectiveness in PD-L1 subgroups
- the choice of parametric models to predict overall survival
- the choice of parametric models to predict time to treatment discontinuation
- the 2-year stopping rule and the continued duration of treatment benefit if nivolumab is stopped at 2 years
- the choice of utility values
- if nivolumab meets the life-extending element of NICE's end of life criteria.

The condition and clinical management

Squamous cell carcinoma of the head and neck is a debilitating condition with an unmet need for effective treatment options

3.1 Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) that has progressed during or after platinum-based chemotherapy has a poor prognosis. The patient experts described SCCHN as a debilitating condition with multiple distressing symptoms such as disfigurement, a dry and sore mouth, weight loss and decreased appetite. They explained that the disease affects all aspects of life including mental wellbeing, social functioning, mobility and work. The clinical expert explained that people have limited treatment options and their disease is generally considered incurable at this stage. Existing treatments are taxane-based chemotherapies such as docetaxel or

paclitaxel, which can cause serious adverse reactions, and more recently pembrolizumab and cetuximab have become available (see section 3.2). The patient experts stated that the outlook is poor for patients with recurrent or metastatic SCCHN that has relapsed on or after platinum-based chemotherapy. The committee noted that improved quality of life both during and after treatment is most important to this patient group, as is extending life. The committee concluded that there is an unmet need for effective treatment options for people with recurrent or metastatic SCCHN that has progressed on or after platinum-based chemotherapy.

Docetaxel is the most appropriate comparator for people fit enough to have it

3.2 The committee noted that the treatment pathway for recurrent or metastatic SCCHN had changed since the publication of the original appraisal of nivolumab. This is because cetuximab combination therapy and pembrolizumab monotherapy have been recommended for treating recurrent or metastatic SCCHN (see NICE's technology appraisal guidance on cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck and pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma). Although no changes are permitted to the scope in a Cancer Drugs Fund review, the committee noted that there are potential implications for using nivolumab to treat SCCHN that has progressed within 6 months of platinum-based chemotherapy. It was aware that pembrolizumab is recommended by NICE for untreated metastatic or unresectable recurrent SCCHN in adults whose tumours express PD-L1 with a combined positive score of 1 or more. The clinical lead for the Cancer Drugs Fund explained that pembrolizumab is administered every 3 or 6 weeks whereas nivolumab is administered every 2 weeks. Therefore, when both drugs are indicated, pembrolizumab would be more likely to be chosen. They also explained that there are people whose PD-L1 status cannot be determined because of issues accessing tissue or assays not working,

and these people would likely get nivolumab because they are not eligible for pembrolizumab. The committee considered that, in NHS clinical practice, this could result in a large proportion of people having nivolumab when they have tumours with a PD-L1 score of less than 1 or indeterminate. This could be different to the proportion of those tumours seen in the clinical trial population. At the time of the original appraisal of nivolumab, treatment options in clinical practice in England included taxane-based chemotherapies (such as docetaxel and paclitaxel) or methotrexate. In the original appraisal, the clinical experts agreed that although there was no evidence of difference in efficacy between docetaxel and paclitaxel, docetaxel would be the standard single-agent chemotherapy used for recurrent or metastatic SCCHN that progressed during or after platinum-based therapy in the NHS (most often prescribed as a 3-weekly treatment regimen). They agreed that use of paclitaxel in clinical practice is limited. They also stated that methotrexate is normally only offered to people with a poor performance status who are not fit enough to have a taxane, or as subsequent therapy for people who have had a single-agent taxane. The committee concluded in the original appraisal that docetaxel would be the most appropriate comparator for people fit enough to have it. For this review, the committee concluded that docetaxel was still the most appropriate comparator for its decision making.

Clinical effectiveness

Both the intention-to-treat population and docetaxel subgroup from CheckMate 141 should inform decision making

3.3 The clinical-effectiveness evidence for nivolumab came from 1 randomised controlled trial (CheckMate 141) that compared nivolumab with the investigator's choice of therapy. Patients randomised to the investigator-choice arm had 1 of 3 possible weekly therapies (docetaxel [47% of patients], methotrexate [41%] and cetuximab [12%]). In the original appraisal, the committee concluded that excluding paclitaxel from

the trial and including cetuximab, a drug not used in clinical practice at that time and therefore not included in the NICE scope, introduced uncertainty about the relevance of CheckMate 141 to UK clinical practice. The committee also concluded, based on the opinion of the clinical experts, that it was valid to assume that docetaxel and paclitaxel were equivalent. But it was not persuaded by the company's assumption that docetaxel is equivalent to methotrexate. For this guidance review, the clinical expert acknowledged that the trial took place in several countries where standard care differs from NHS clinical practice. They suggested that the investigator-choice arm of the trial was an appropriate data source comparison even though cetuximab was not standard care in NHS clinical practice at the time of the original appraisal and methotrexate is only offered to people with poor performance status and may be less effective. The clinical lead for the Cancer Drugs Fund stated that people in the trial (who had an Eastern Cooperative Oncology Group performance status of 0 or 1) would have been fit enough to have docetaxel in NHS clinical practice, and therefore the investigator-choice arm would not be a relevant comparator. The committee noted that the company had presented results for an analysis comparing nivolumab and docetaxel in patients who would have docetaxel (referred to as the 'docetaxel subgroup') in CheckMate 141. The company highlighted that the trial was not powered to detect differences between nivolumab and docetaxel alone and therefore any results had to be treated with caution. The committee acknowledged that this was not a prespecified subgroup analysis and such a comparison was less robust than using the intention-to-treat population, because of the smaller sample size. It acknowledged that use of the intention-to-treat population may underestimate docetaxel's effectiveness because it includes other treatments that are less effective than docetaxel. The committee concluded that the intention-to-treat trial population is the most appropriate data source for this guidance review, as in the original appraisal, but the docetaxel subgroup analysis should also be considered.

The clinical benefit of nivolumab compared with docetaxel alone is not clear

3.4 For this guidance review, the company provided an additional 37 months of follow-up data (up to October 2019) from Checkmate 141. The results for the intention-to-treat population showed that people who had nivolumab lived longer than people who had the investigator-choice treatment (median overall survival for nivolumab was 7.7 months, 95% confidence interval 5.7 to 8.7 months; investigator's choice was 5.1 months, 95% confidence interval 4.0 to 6.2 months; hazard ratio 0.69, 95% confidence interval 0.55 to 0.86). The clinical lead for the Cancer Drugs Fund referred to an amendment update of the clinical protocol for CheckMate 141, which meant that people in the investigator-choice arm could have had nivolumab in the extension phase of the trial. In response to consultation, the company provided the number of people who switched to nivolumab in both the intention-to-treat and docetaxel subgroup population (the exact number of people is confidential so cannot be reported here). The ERG explained that the effect of switching to nivolumab in the comparator arm is unclear, but the percentage of people who switched was low and therefore unlikely to have led to substantial bias. The committee acknowledged that the effect of treatment switching was unknown but agreed that it was unlikely to have had a large effect on the results. The company provided results for the docetaxel subgroup that showed a numerical survival benefit for nivolumab compared with docetaxel, but this was not statistically significant (the exact data are confidential and cannot be reported here). The committee acknowledged that there was uncertainty about the results from the docetaxel subgroup because of the small number of people in the subgroup analysis, and in NHS clinical practice not all patients would have docetaxel. However, it agreed that the subgroup analysis was informative for decision making (see section 3.3). It concluded, based on the evidence that had been presented, that it was uncertain whether nivolumab was clinically effective compared with docetaxel alone.

There is evidence of nivolumab's benefit for tumours with a PD-L1 score of 1% or higher, but at a lower PD-L1 score the benefit is not clear

3.5 In the original appraisal, the committee concluded that there was evidence of nivolumab's benefit for tumours expressing 1% or more PD-L1 protein, but at lower expression levels the benefit was not clear. For this guidance review, the company provided subgroup analyses based on the latest available data (up to 15 October 2019) for PD-L1 of 1% and above and PD-L1 of less than 1% subgroups in the intention-to-treat population of CheckMate 141. For the subgroup with a PD-L1 score of 1% and above, the median overall-survival gain was 3.6 months with nivolumab compared with investigator-choice treatment (hazard ratio 0.54, 95% confidence interval 0.39 to 0.76). For the less than 1% PD-L1 group, the median overall-survival gain was 1 month (hazard ratio 0.74, 95% confidence interval 0.50 to 1.10). The clinical expert explained that in clinical practice the availability of PD-L1 testing varies across the NHS in England, and that PD-L1 scores might not be available for all people at the time when treatment is started. The clinical lead for the Cancer Drugs Fund advised that testing for PD-L1 status should now be routine for people with recurrent or metastatic SCCHN. Some people do not get testing because of issues with accessing tissue, or they do not get a score because of assays not working. The clinical expert suggested that the PD-L1 score may not be as good a predictor of treatment outcome as previously thought. The committee noted that PD-L1 testing in SCCHN would become routine in the NHS now that pembrolizumab is recommended for treating SCCHN in adults whose tumours express 1% or more PD-L1. It acknowledged that there was uncertainty about the results from the subgroup analyses based on PD-L1 expression because of the small number of people in the subgroup analysis. However, it considered it was important to explore them because of NICE's recommendation for using pembrolizumab to treat tumours with a PD-L1 score of 1 or higher, meaning that nivolumab is likely to be used more often to treat SCCHN with a low or indeterminate PD-L1 score than in the

CheckMate 141 population (see section 3.2). The committee concluded that there was evidence that nivolumab is clinically beneficial for tumours with a PD-L1 score of 1% and above but the benefit for those with a low PD-L1 score was less certain.

Clinical experience with nivolumab in the Cancer Drugs Fund reflects the trial results

3.6 As well as new data from CheckMate 141, data from the Systemic Anti-Cancer Therapy (SACT) dataset was available for this review. Data was collected from 506 people who had nivolumab through the Cancer Drugs Fund between October 2017 and October 2019. The clinical expert explained that clinical experience with nivolumab is positive and outcomes reflect what was seen in the clinical trials. The 1-year overall survival was similar between the nivolumab arm of the intention-to-treat population in CheckMate 141 and the SACT data (CheckMate 141 data 33.4%, 95% confidence interval 27.5 to 39.5; SACT data 34%, 95% confidence interval 29% to 38%). The median overall survival in CheckMate 141 was longer (7.7 months, 95% confidence interval 5.7 to 8.7 months) than in the SACT data (6.5 months, 95% confidence interval 5.6 to 7.6 months). However, the 95% confidence intervals overlapped. The time to treatment discontinuation in the SACT data was 3.0 months (95% confidence interval 2.7 to 3.3 months), which is longer than in CheckMate 141 (results are confidential and cannot be reported). The committee noted that the SACT data had a median follow-up of 6.2 months compared with a minimum follow up of 48.2 months in the trial.

Modelling overall survival and time to treatment discontinuation

The company's piecewise model is appropriate to extrapolate overall survival, but fully parametric models may also be plausible

3.7 In the original appraisal, the committee accepted that a piecewise model was appropriate for estimating overall survival in the intention-to-treat population. The model used Kaplan–Meier data followed by a lognormal

distribution, but the time point from which to extrapolate was uncertain. For this guidance review, the company used data from the intention-to-treat population of the trial. It extrapolated from 96 weeks in line with the median follow up of the trial. This resulted in a 5-year survival of 5.7% and a 10-year survival of 2.6%. The clinical expert estimated that it was plausible that between 1% and 5% of people having nivolumab will be alive at 5 years, and that few people survive up to 10 years. In its response to technical engagement, the company used the same extrapolation method for the docetaxel subgroup. In response to consultation, it presented evidence of the goodness of fit for this method to the docetaxel subgroup data, and also explored fully parametric methods. The ERG agreed that the company's piecewise method was appropriate to extrapolate overall survival using both the intention-to-treat and docetaxel subgroup data. The committee noted that the company's fully parametric models, in particular the lognormal, could also be plausible and may be useful for decision making. It concluded the company's piecewise model was appropriate to extrapolate overall survival using both the intention-to-treat and docetaxel subgroup data.

The company's and the ERG's extrapolation methods for time to treatment discontinuation for the docetaxel subgroup are both plausible

3.8 In the original appraisal, using the intention-to-treat population, the committee concluded that none of the parametric distributions fitted the time to treatment discontinuation data well. It preferred the generalised gamma distribution for both arms in the model for this population. In this guidance review, the company presented an alternative approach using different distributions for the 2 treatment arms. It used the 2-spline normal distribution for the nivolumab arm, because it had a better statistical and visual fit to the data than the generalised gamma distribution. The method used for the investigator-choice arm is confidential and cannot be reported here. In its response to technical engagement, the company used the same extrapolation method for the docetaxel subgroup. The ERG preferred using the generalised gamma distribution for both arms, as in

the original appraisal and in line with the NICE Decision Support Unit's technical support document 14. The ERG advised that when the stopping rule was removed (see section 3.9), using the company's preferred extrapolation for time to treatment discontinuation resulted in overall survival falling below time to treatment discontinuation, which is implausible. Therefore, the ERG advised that the generalised gamma distribution should be used to extrapolate time to treatment discontinuation for both arms in all scenarios in which the stopping rule was removed. The committee noted that real-world treatment discontinuation data was available from the SACT cohort, in which the time to treatment discontinuation was generally longer than in CheckMate 141. The committee considered this would result in a higher incremental cost-effectiveness ratio (ICER). In response to consultation, the ERG explained that using different distributions in the 2 arms might introduce bias. Therefore, it preferred to use the generalised gamma distribution to estimate time to treatment discontinuation for both treatment arms in the docetaxel subgroup. The committee concluded that both the company's and the ERG's extrapolations for time to treatment discontinuation for the docetaxel subgroup were plausible, and it would consider both. It also concluded that the time to treatment discontinuation in the SACT cohort was informative.

Stopping rule and continued treatment effect

Analyses without a stopping rule are more appropriate for decision making

3.9 In the original appraisal, the committee concluded that analyses without a nivolumab stopping rule are more appropriate for decision making than analyses that included a stopping rule. The 2-year stopping rule was only accepted in the context of the Cancer Drugs Fund. In this guidance review, the patient experts and the clinical expert agreed that people might be disappointed if treatment was beneficial but was stopped at 2 years. The clinical expert confirmed that people who can tolerate and

benefit from treatment should be able to have it until their disease progresses, or they have intolerable side effects or choose to stop. People who stopped nivolumab after 2 years but whose disease has not progressed would be offered platinum-based chemotherapy. The clinical expert explained that people who are alive 5 years after treatment started are considered 'cured' from the disease. In response to consultation, the company provided an updated base case that included a 5-year stopping rule. It explained that the 5-year stopping rule was based on clinical expert opinion that people are considered 'cured' at 5 years. It explained that extrapolated data from the trial resulted in 1% of people remaining on treatment at 5 years. The committee considered there to be no clinical evidence that nivolumab can be curative and questioned whether the low numbers on treatment at 5 years reflects real life. The ERG explained that having low numbers of people on treatment at 5 years is not a plausible reason to include a stopping rule. The committee noted that there was no stopping rule included in the trial, and that some people were still taking nivolumab after 2 years. It acknowledged that a stopping rule had been accepted in previous appraisals for nivolumab and other similar drugs, whether or not it was included in the trial. However, in this instance, the committee concluded that a stopping rule was not appropriate as stated in the original appraisal that recommended nivolumab for use only in the Cancer Drugs Fund.

Continued treatment benefit up to 5 years is plausible

3.10 In the original appraisal, the committee concluded that it was plausible that the treatment benefit of nivolumab continued for 5 years after treatment started. For this guidance review, the company provided a smoothed hazard-rates plot for overall survival for the intention-to-treat population for nivolumab and investigator-choice treatment. The plot suggested that the hazard rates seemed to meet at around 5 years. This indicates that there was no difference in the treatment effect of the 2 arms at 5 years. In response to consultation, the company provided an updated plot, suggesting the hazard rates did not converge at 5 years. However,

the ERG concluded that the rates do converge at 5 years and included treatment waning at 5 years after the start of treatment in its base-case analysis. In CheckMate 141, people in the investigator-choice arm could have had nivolumab during the extension phase of the trial (see section 3.4). The committee acknowledged that this crossover could decrease the apparent relative effectiveness of nivolumab compared with investigator's choice. But the percentage of people who switched to nivolumab was low, so any bias is not likely to be substantial (see section 3.4). It concluded that it was plausible that nivolumab's treatment effect matches that of standard care at 5 years after treatment started.

Utility values in the economic model

The most appropriate utility values lie between the treatment-dependent and the treatment-independent estimates

3.11 In the original appraisal, the committee agreed that the most appropriate utility estimates would lie between the treatment-dependent utilities and the treatment-independent utilities. The clinical expert explained that the effect on quality of life was similar for the different treatment options available for recurrent and metastatic SCCHN. The patient experts and the clinical expert confirmed that people's quality of life diminishes during the last months of life. In response to consultation, the company updated its base case to use a different set of utility estimates. These utility values varied depending on whether somebody was on or off treatment, and whether they were having nivolumab or investigator-choice treatment. The committee noted the company's utility values were derived from surveys done during the trial. However, about one-third of people in the intervention arm and half of people in the investigator-choice arm did not complete the survey, so there is a large amount of missing data. The clinical lead for the Cancer Drugs Fund noted that some of the utilities applied in the company's updated approach were implausible. For example, people in the investigator-choice arm who were progression-free and on treatment had a higher utility value compared with those who were

progression-free and off treatment. The exact utility values are confidential and cannot be reported here. The committee agreed that the company's updated utility model generated implausible values, and it therefore preferred the models used in the original appraisal. The ERG advised that using the company's treatment-dependent utility model meant that utility benefits associated with nivolumab continue for the rest of a person's life. The company attempted to resolve this life-long benefit by including time-to-death disutilities, but the ERG stated this is not a reasonable approach. The ERG preferred to use treatment-independent utility values in its base case. The committee noted that, in the trial, people could continue having nivolumab after they progressed if the investigator thought they were still benefiting. If people were perceived not to be benefiting, they would stop taking nivolumab. Therefore, the committee considered it is not reasonable to assume an ongoing utility benefit after people had stopped treatment. The treatment-independent utilities are based solely on progression state, whereas the treatment-dependent utilities assume nivolumab has a benefit that continues for the rest of a person's life. Therefore, the committee considered that treatment-dependent utilities were likely to lead to better outcomes and lower ICERs. It concluded that the most appropriate utility values are between the treatment-dependent and the treatment-independent estimates and are likely to be closer to the treatment-independent values.

End of life

Life expectancy for people with recurrent or metastatic SCCHN is less than 24 months

3.12 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. In the original appraisal, the data showed that life expectancy for people with SCCHN that has progressed within 6 months of having platinum-based chemotherapy was less than 24 months. The committee did not hear any evidence to change this conclusion.

Therefore, it concluded that nivolumab met the short life-expectancy criterion.

Nivolumab meets the life-extending element of the end of life criteria

3.13 In the latest data available for CheckMate 141, the median overall survival for the intention-to-treat population for nivolumab was 7.7 months (95% confidence interval 5.7 to 8.7 months) compared with 5.1 months (95% confidence interval 4.0 to 6.2 months) for investigator's choice. The model predicted a mean survival benefit for nivolumab of between 6.8 and 9.2 months in this population. The median overall-survival results for the docetaxel subgroup are confidential and cannot be reported here. When the docetaxel subgroup data was used in the company's base-case model, the mean overall-survival benefit for nivolumab was estimated to be 6.7 months. Although the clinical effectiveness of nivolumab was uncertain in the docetaxel subgroup (see section 3.4), the committee concluded that nivolumab offered a survival benefit of more than 3 months compared with docetaxel. This is regardless of whether the investigator-choice or docetaxel subgroup data was used in the model. In CheckMate 141, nivolumab also increased the median overall survival by more than 3 months in people whose tumours had a PD-L1 score of 1% or above (see section 3.5). In people whose tumours had a PD-L1 score of less than 1% the increase in median survival was only 1 month, and this was not statistically significant (see section 3.5). In response to consultation, the company provided updated overall-survival modelling using a variety of extrapolation methods for PD-L1 with a combined positive score of less than 1%. The model estimated a mean overall-survival benefit of greater than 6 months for the subgroup with PD-L1 less than 1%. The committee concluded although there is uncertainty about the PD-L1 less than 1% subgroup, the life-extending element was met in that subgroup. Therefore, nivolumab meets the life-extending element of the end of life criteria.

Cost effectiveness

The company's base case does not reflect the committee's preferred assumptions

3.14 The committee agreed it would have preferred the company's base case to:

- include treatment-dependent and treatment-independent utility values, with committee preference towards treatment-independent utilities (see section 3.11)
- assume no treatment benefit for nivolumab 5 years after start of treatment, and
- exclude the stopping rule.

In response to consultation, the company did not provide a scenario that included all the committee's preferred assumptions. The committee concluded the intention-to-treat population is the most appropriate data source, but agreed that the company's analyses using the docetaxel subgroup data and by PD-L1 status were of interest and would be considered in its decision making. Because of the uncertainty, an acceptable ICER for nivolumab compared with docetaxel using the intention-to-treat population is toward the lower end of the range normally considered a cost-effective use of NHS resources.

Nivolumab's cost effectiveness is highly uncertain

3.15 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER and whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high

level of uncertainty in the docetaxel subgroup and PD-L1 subgroups, specifically about the clinical effectiveness (see sections 3.4 and 3.5). There is also uncertainty around the most appropriate utility values (see section 3.11).

The maximum acceptable ICER is substantially below £50,000 per QALY gained

3.16 Because the conditions of a life-extending treatment at the end of life had been met, the committee considered the maximum acceptable ICER in the context of applying a QALY weight of 1.7 to the range of ICERs normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Because of the uncertainties about docetaxel efficacy being underestimated in the intention-to-treat population (see section 3.3), clinical effectiveness in PD-L1 subgroups (see section 3.5), different overall-survival extrapolations increasing the ICER (see section 3.7), and time to treatment discontinuation based on SACT data increasing the ICER (see section 3.8), the committee decided that the maximum acceptable ICER would be substantially below £50,000 per QALY gained.

Nivolumab is likely to be a cost-effective use of NHS resources

3.17 The company's base-case assumptions differed from the committee's preferred assumptions. The company's base case included a lifetime treatment benefit of nivolumab, treatment-dependent utilities and a 2-year stopping rule. Also, the time to treatment discontinuation was extrapolated using different distributions in the 2 arms. The committee agreed that the most likely ICER for nivolumab compared with docetaxel, based on its preferred assumptions and using treatment-dependent and treatment-independent utilities, would be substantially below £50,000 per QALY gained. Taking into account the updated commercial arrangement, the ICER was within the range that could be considered a cost-effective use of NHS resources when the stopping rule was removed, a 5-year treatment waning effect was applied, and time to treatment

discontinuation was extrapolated using the generalised gamma distribution in the 2 arms (see section 3.8). When the treatment-independent utility values were applied instead of the treatment-dependent utilities in the same scenario the ICER increased but it still remained within the range that could be considered cost effective. It concluded that incorporating the company's updated commercial arrangement meant that its preferred ICERs were in the range that could be considered cost effective, even though some uncertainties remained. So, nivolumab is recommended for routine use in the NHS.

Equality issues

The recommendations apply equally to all people with SCCHN

3.18 A patient expert questioned whether age is an equality issue in this appraisal. The clinical expert confirmed that there is no age limit for treatment with nivolumab. The committee heard from the Cancer Drugs Fund clinical lead that data collected by Public Health England from NHS patients in England showed that many older patients had taken nivolumab while it was available in the Cancer Drugs Fund. The committee concluded that there was no relevant equality issue.

Other factors

3.19 The company did not highlight any additional benefits that had not been captured in the QALY calculations.

Conclusion

Nivolumab is recommended for routine commissioning

3.20 The committee recommended nivolumab, within its marketing authorisation, for recurrent or metastatic SCCHN after platinum-based chemotherapy in adults. In the original appraisal, the committee concluded that docetaxel was the most relevant comparator, and that assuming clinical equivalence between some of the comparators was

uncertain. This meant that using investigator-choice data from the intention-to-treat population to model all comparators would likely underestimate the effectiveness of docetaxel. In this guidance review, the committee acknowledged the uncertainty surrounding the intention-to-treat population with regards to the docetaxel comparator. Based on the ICERs for nivolumab compared with docetaxel, the committee concluded that the cost-effectiveness estimates were unlikely to exceed its acceptable maximum even though some uncertainties remained. Therefore, nivolumab is recommended.

4 Implementation

4.1 Section 7 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.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) - A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 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.

4.4 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 recurrent or metastatic SCCHN after platinum-based chemotherapy 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.

5 Review of guidance

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

Lindsay Smith
Chair, appraisal committee
September 2021

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 D.

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.

Verena Wolfram, Nigel Gumbleton
Technical leads

Nicola Hay, Hannah Nicholas
Technical advisers

Kate Moore
Project manager

ISBN: [to be added at publication]