NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

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

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

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

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

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

After consultation:

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

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

The key dates for this appraisal are:

Closing date for comments: 4 May 2017

Second appraisal committee meeting:

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

1   Recommendations

1.1   Nivolumab is not recommended, within its anticipated marketing authorisation, for treating squamous cell carcinoma of the head and neck in adults whose disease has progressed during or after platinum-based chemotherapy.

1.2   This recommendation is not intended to affect treatment with nivolumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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.

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2 The technology

Description of the technology	Nivolumab (Opdivo, Bristol-Myers Squibb) is a human monoclonal antibody (immunoglobulin G4) that blocks the programmed cell death−1 receptor (PD−1) and activates the immune system to attack cancer cells.
Marketing authorisation	The Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for nivolumab as monotherapy for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.
Adverse reactions	The most common adverse reactions with nivolumab include fatigue, nausea, anaemia, decreased appetite and constipation.
Recommended dose and schedule	3 mg/kg every 2 weeks by intravenous infusion over 60 minutes.
Price	£439 per 40 mg vial and £1,097 per 100 mg vial (excluding VAT; 'British national formulary' [BNF], December 2016 and company's submission).
	The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of nivolumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the evidence review group (ERG). The evidence was considered by the committee before the Committee for Medicinal Products for Human Use (CHMP) recommended granting a marketing authorisation. The committee discussion was therefore based on the trial population of people with recurrent or metastatic squamous cell cancer of the head and neck that has progressed after platinum-based chemotherapy. See the committee papers for full details of the evidence.

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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 recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) that has progressed during or after platinum-based chemotherapy 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.

Clinical management

Clinical need

4.1   The committee noted that recurrent or metastatic SCCHN that has progressed during or after platinum-based chemotherapy has a poor prognosis. The patient expert described SCCHN as a debilitating condition with multiple distressing symptoms such as a dry, sore mouth, weight loss and decreased appetite. The committee heard from clinical experts that people with this condition have limited treatment options and their disease is generally considered incurable at this stage. Existing treatments, normally a taxane-based chemotherapy such as docetaxel and paclitaxel, cause significant adverse reactions. The committee was aware that the patient experts' submissions stated that the current outlook for patients with recurrent or metastatic SCCHN whose disease has relapsed during or after platinum-based chemotherapy is poor. It noted that extending life is of utmost importance to this patient group, as well as improving their quality of life both during and after treatment. The committee concluded that there is a high unmet need for effective treatment options for people with recurrent or metastatic SCCHN whose disease has progressed during or after platinum-based chemotherapy.

Clinical care pathway

4.2   The committee discussed the clinical management of recurrent or metastatic SCCHN and the potential positioning of nivolumab in the clinical care pathway. It understood from the clinical experts that curative

treatments, such as surgery and platinum-based therapy, are considered to be first-line treatment for recurrent or metastatic SCCHN. The clinical experts indicated that about 40% of people who have SCCHN will have a recurrence. For early recurrence, disease that has progressed within 6 months) of platinum-based therapy, current treatment options in clinical practice in England include taxane-based chemotherapies (such as docetaxel and paclitaxel) or methotrexate. The committee understood that nivolumab would be considered as an option at this point in the treatment pathway. The clinical experts agreed that although there is 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 has progressed during or after platinum-based therapy in the NHS (most often prescribed as a 3-weekly treatment regimen) and the use of paclitaxel in clinical practice is limited. They also stated that methotrexate is normally reserved for people whose disease has a poor performance status and 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 that nivolumab is appropriately positioned in the clinical treatment pathway as an option for people with recurrent or metastatic SCCHN whose disease has progressed during or after platinum-based therapy, and that docetaxel would be the most appropriate comparator for people fit enough to have docetaxel.

Clinical effectiveness

Overview of the CheckMate-141 trial

4.3   The committee noted that the clinical-effectiveness evidence for nivolumab came from 1 study (CheckMate-141) that compared nivolumab with the investigator's choice of therapy. Patients randomised to the investigator-choice arm had 1 of 3 possible therapies (docetaxel [47% of patients], methotrexate [41%] and cetuximab [12%]). The study did not include paclitaxel, which is in the NICE final scope, but it did include cetuximab which is not in the NICE scope and is not considered by clinical experts to be established practice in England for this group of people. The

committee was aware that because of lack of clinical evidence, a meaningful comparison with paclitaxel was not possible. The committee noted that the trial included adults with recurrent or metastatic SCCHN that progressed within 6 months of platinum-based therapy, in either the early or locally advanced disease stage. However it heard from the company that the population in the anticipated marketing authorisation is expected to be broader than the trial population. The clinical experts highlighted that the trial population is a subset of patients who would usually be excluded from trials because of poor prognosis, and that including them in CheckMate-141 reflects clinical practice. The committee concluded that, although the expected marketing authorisation for nivolumab will be broad, its recommendations will focus on the population represented in the trial because this underpins the marketing authorisation. In addition, the exclusion of paclitaxel from the trial and the inclusion of cetuximab, a drug not included in the NICE scope, introduces some uncertainty about the relevance of CheckMate-141 to UK clinical practice.

4.4   The committee heard from the clinical experts that docetaxel and paclitaxel can be assumed to have the same clinical effectiveness, but that this assumption cannot be extended to methotrexate. Although methotrexate is used in clinical practice to treat recurrent or metastatic SCCHN in patients whose disease has progressed during and after platinum-based therapy, it is often reserved for people whose condition has a poorer performance status and who are less able to tolerate the toxicity related to taxane-based chemotherapy. Therefore, the clinical experts' opinion was that the population of patients considered suitable for treatment with methotrexate is likely to be different to the population that will be offered docetaxel. The committee concluded that the assumption of equivalency between docetaxel and paclitaxel appears valid, but it was not persuaded by the company's assumption that docetaxel is equivalent to methotrexate.

CheckMate-141 trial results

Overall population

4.5   The committee noted that analysis of data from the trial start to the
         database lock on December 2015 showed that nivolumab had a
         statistically significant overall-survival benefit compared with the
         investigator-choice arm, with a median overall survival of 7.5 months in
         the nivolumab arm and 5.1 months in the investigator-choice arm (hazard
         ratio [HR] 0.70; 97.73% confidence interval [CI] 0.51 to 0.96; p=0.0101).
         This is a 30% reduction in the risk of death with nivolumab compared with
         the investigator's choice of therapy. But, nivolumab did not give a similar
         improvement in progression-free survival, with median progression-free
         survival being much the same in both treatment arms (2.0 months for
         nivolumab and 2.3 months for investigator-choice therapy; HR 0.89; 95%
         CI 0.70 to 1.1; p=0.3236). The clinical experts stated that progression-free
         survival is not an appropriate outcome because it does not accurately
         reflect the delayed response associated with immunotherapies. The
         experts also noted that progression measured using Response Evaluation
         Criteria in Solid Tumours (RECIST) may not accurately capture a person's
         health-related quality of life. Results from the latest data-cut from
         CheckMate-141 (September 2016) were similar to the December 2015
         results. The committee concluded that CheckMate-141 showed significant
         improvement in overall survival in the group having nivolumab, with
         survival rates doubling in the nivolumab arm (36%) compared with the
         investigator-choice arm (16.6%) at 12-month follow-up, but the
         incremental overall-survival benefit beyond 24 months is uncertain.

Subgroup results

4.6   The committee discussed the company's pre-planned subgroup analyses
         according to the expression of programmed death receptor ligand 1
         (PD-L1; 1% or more, or less than 1%). It understood that, in general,
         patients whose tumours express PD-L1, especially those with higher
         levels of expression, have a better response to checkpoint inhibitors, such

as nivolumab, which is plausible because this is the main proposed mechanism of action of the drug. The committee specifically considered the Kaplan–Meier overall-survival curves for the pre-specified subgroups of PD-L1 expression (1% or more, and less than 1%) up to the database lock on December 2015. It noted that there was early and consistent separation of the curves for the '1% or more' group but almost complete overlap of the curves for the 'less than 1%' group, during the first 9 months of therapy. The committee concluded that there is evidence of benefit for nivolumab compared with investigator-choice therapy in the PD-L1 '1% or more' group, shown by a median overall-survival difference of 4.1 months with nivolumab and a corresponding hazard ratio of 0.55 (CI 0.36 to 0.83). But, the benefit in the group with a PD-L1 of less than 1% is uncertain, with median overall survival of 5.7 months for nivolumab and 5.8 months for investigator-choice therapy (HR 0.89; 95% CI 0.54 to 1.45).

4.7   The committee also discussed the results for the subgroups based on human papillomavirus type 16 (HPV-p16) status (positive or negative), noting the non-statistically significant survival benefit with nivolumab compared with investigator-choice therapy in the HPV-p16 negative group. The clinical experts stated that around 50% of people with SCCHN in the UK are HPV-p16 positive, according to a recent trial. They stated that SCCHN does respond to treatments whatever the person's HPV-p16 status, but it responds better and has more favourable outcomes in people who are HPV-p16 positive than in those who are HPV-p16 negative. The clinical experts considered this to be a generic response to treatment and not specific to checkpoint inhibitors and highlighted the uncertainty about linking response in patients who are positive for HPV-p16 to PD-L1 inhibitors. Having heard the views of the clinical experts, the committee concluded that although there seems to be a differential benefit according to HPV-p16 status, it was not an important determinant of the efficacy of nivolumab treatment and therefore would not be considered further.

Generalisability of results to the UK

4.8   The committee discussed the generalisability of the results from CheckMate-141 to the UK population, and noted the higher male population in the trial (83%, compared with 70% of the SCCHN population in the UK). The clinical experts stated that this is likely to be because more men than women tend to participate in trials and most large studies report a higher male ratio in the trial population. The committee noted that different overall-survival results for nivolumab were reported for males (HR 0.65; 95% CI 0.48 to 0.88) and females (HR 0.93; 95% CI 0.47 to 1.85). The committee also discussed the differences in the overall-survival hazard ratios between trial participants from North America (HR 0.55; 95% CI 0.36 to 0.85) and the European Union (HR 0.91; 95% CI 0.62 to 1.33) and how this could affect the applicability to the UK setting. The clinical experts noted that the results for the female and European Union subgroups are not statistically significant because of the small sample sizes in these subgroups. They also highlighted that docetaxel is the most frequently used treatment in the European Union whereas methotrexate is the preferred treatment of choice in North America. Given that docetaxel may be a more effective therapy than methotrexate, this may explain the difference in outcomes for the 2 continents. The company also highlighted during the clarification stage that the difference could be because of a lower proportion of people who are HPV-p16 positive or who have never smoked in Europe than in North America.The committee concluded that although there are some differences between the trial population and the UK population, the data from CheckMate-141 could be used for its decision-making.

Adverse reactions

4.9   The committee noted that nivolumab is better tolerated than docetaxel and that most patients report a higher quality of life with nivolumab. The number of patients stopping treatment because of adverse events in CheckMate-141 was similar for both groups (21.6% for nivolumab compared with 24.3% for investigator-choice therapy). No new safety

concerns for nivolumab were identified in CheckMate-141. The clinical experts highlighted the improvement in quality of life with immunotherapy agents, such as nivolumab. The committee concluded that nivolumab is associated with less severe adverse reactions compared with chemotherapy agents, such as docetaxel.

Cost effectiveness

4.10   The committee discussed the company's cost-effectiveness evidence and its critique by the evidence review group (ERG). The committee noted that the company presented a 3-state partitioned survival model that compared nivolumab with the investigator's choice of either docetaxel, methotrexate or paclitaxel. Estimated overall survival, progression-free survival and time-to-treatment discontinuation based on data from the investigator-choice arm were assumed to apply to docetaxel, methotrexate and paclitaxel (assuming equivalence between these treatments). The committee concluded that the model structure is appropriate for its decision-making.

Extrapolation methods

4.11   The committee noted that the company used parametric models to estimate overall survival, progression-free survival and time-to-treatment discontinuation across the time horizon of the model. For each outcome, the company fitted the same parametric distribution independently to each treatment arm. The committee noted that the company chose the log-normal, generalised gamma and log-logistic distributions for overall survival, progression-free survival and time-to-treatment discontinuation (respectively) based on statistical fit, visual inspection and clinical plausibility. It also noted that the ERG agreed with the company's choice of parametric distribution. The committee was concerned that the company's approach assumed that the probability of death in the investigator-choice and the nivolumab arms reduced over time. The committee and the clinical experts did not consider this assumption to be clinically plausible. The committee also did not consider it plausible that

the risk of death would become almost similar to that of the general population towards the end of the model's 20-year time horizon, which the company's approach suggested. It heard from the company that people whose condition is in remission could have a similar mortality risk to that of the general population. The committee noted that the log-normal curve was not a good fit to the earlier parts of the trial data and that most of differences in mortality between the 2 treatment arms were in this phase of the model. The committee also expressed concerns about the applicability of standard parametric curves for estimating survival with immune-oncology drugs compared with chemotherapy drugs. It heard from the company that the modelling approach was strictly in accordance with the NICE Decision Support Unit's technical support document 14. But, the committee considered that the technical support document does not adequately reflect the mechanism of action of immunotherapy treatments and that the advice was published before immunotherapy drugs were available. The committee agreed that it would be better to use the observed Kaplan–Meier data for the first phase of the model and then fit an appropriate distribution at a reasonable time point, that is, a piecewise model.

4.12   In response to the committee's request for additional analyses, the company kept its original base-case approach for overall survival and progression-free survival (see section 4.11), but using the generalised gamma model for time-to-treatment discontinuation and the latest data-cut from CheckMate-141 for all outcomes. The company presented 5-year survival data from CheckMate-003 (a study of advanced squamous non-small-cell lung cancer after progression while having platinum or taxane therapy) to support the long-term survival predicted by the log-normal curve. In a scenario analysis, the company explored a piecewise approach with an exponential distribution. It stated that the exponential model did not allow for a possible plateau in the survival curve for nivolumab as seen in other indications and it did not reflect the ongoing survival benefits that nivolumab could offer. Therefore, it did not present

incremental cost-effectiveness ratios (ICERs) for this scenario. But it did present ICERs based on the observed Kaplan–Meier data from 20-, 36- and 48-weeks with extrapolation from each time point using the log-normal distribution. Although the ERG considered the company's base-case approach to be appropriate, it also presented ICERs from an exploratory analysis using the exponential curve in the piecewise model at the same time-points used by the company. The committee did not accept the company's rationale for using the log-normal distribution for the entire modelled time horizon or in the piecewise analysis because of the uncertainty about predicted survival as previously discussed (see section 4.11). Therefore, the committee concluded that the ERG's piecewise approach using the exponential curve was more plausible for extrapolating overall survival.

Long-term treatment effect

4.13   The committee was concerned that the treatment effect of nivolumab was assumed to persist for the entire time horizon of 20 years in the model. The company presented a separate scenario analysis assuming that the survival benefit for nivolumab compared with the comparators continued for 5 years or 10 years only. The committee questioned whether the survival benefit would stay constant up to 5 years irrespective of treatment duration, and noted the comments from the clinical experts that there is evidence from other indications that the treatment benefit with nivolumab could last up to 5 years. The committee noted that although the survival benefit was stopped at 5 years in the company's scenario analysis, the quality-of-life benefit was assumed to last across the time horizon of the model, which was questionable. It therefore concluded that the company's scenario of a continued treatment benefit lasting up to 5 years was plausible, but the assumption that the benefit would stay constant after treatment is stopped is uncertain.

Stopping rule

4.14   The committee noted that the company's updated base case included a 2-year clinical stopping rule in which only 25% of patients who were still

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having treatment with nivolumab after 2 years carried on having treatment, and all other parameters were the same. The company also explored the effect of altering the proportion assumed to stay on treatment after 2 years to 50% and 75%, as well as having no stopping rule. The committee noted that the company's base-case extrapolation of time-to-treatment discontinuation predicted that about 3% of patients would still be having nivolumab at 2 years whereas the latest CheckMate-141 data, taken from the September 2016 data-lock, reported 8.2% of patients to be progression free at the same time point. The committee further noted that the stopping rule had only been applied to costs of treatment and not treatment benefit. It noted the comment from the company and the clinical experts that people can stop nivolumab treatment for reasons other than progression, while still having the benefits from the treatment. The committee was not aware of any indication of a 2-year stopping rule in the trial protocol, as seen with previous appraisals in which this stopping rule was accepted. The committee noted that the company's submission stated that treatment with nivolumab in the trial was allowed to continue after progression if patents were still having benefits and tolerating the drug, but the proportion of patients who were still having treatment and the average treatment duration in the trial was unclear to the committee. Given the uncertainty about the stopping rule, the committee concluded that it would only consider analyses without the stopping rule to inform its recommendations.

Utility values

4.15   The committee noted that the company applied treatment-dependent utilities derived from EQ-5D-3L data from CheckMate-141 to the progression-free and progressed-disease health states in the model. The committee noted that to address the ERG's and committee's concerns about missing health-state utility data, the company used a mixed model regression analysis to estimate utility scores in its revised base case.The ERG agreed that the mixed model approach had the benefit of accounting for autocorrelation and missing data, but they could not verify that this had

been appropriately dealt with because of insufficient details about methods and model diagnostics from the company. The clinical experts highlighted that missing data could lead to the benefit of nivolumab being underestimated if they were for seriously ill patients in the investigator-choice arm, who could not fill in the patient-reported outcome forms. The clinical experts also highlighted possible bias from self-selection of patients at later time points, who may be different from trial participants at baseline. The committee noted that there were very few patients in the investigator-choice arm at later time points of the trial, further increasing uncertainty.

4.16   The committee noted that the company's re-analysis of utility values produced almost identical scores for the 2 treatment groups in the progression-free health states as well as similar scores in the nivolumab arm in the progression-free and progressed-disease states. There was a different percentage of patients with progressed disease in the nivolumab arm compared with the comparator arm and the committee questioned the high utility value assigned to nivolumab treatment in the post-progression state after treatment stopped and disease progressed. The company stated that the definition of progression using the old RECIST criteria does not accurately capture progression while on immunotherapies and that the lasting benefits shown in the utility scores reflect the toxic nature of comparator therapies. In a scenario analysis, the ERG used treatment-independent utilities to account for this uncertainty and for the missing data. This increased the company's ICER range for the scenario without a stopping rule from between £44,000 and £47,000 per quality-adjusted life year (QALY) gained to between £62,000 and £67,000 per QALY gained. However, the committee heard from the ERG that using treatment-independent utilities disregards the possible quality-of-life benefit associated with nivolumab identified by the clinical experts. The committee concluded that the utility values calculated by the company's mixed model approach were associated with significant uncertainty. Although the committee preferred the ERG's conservative approach of

using treatment-independent utilities, it acknowledged that this scenario was pessimistic and some potential quality-of-life benefits with nivolumab had not been captured. It therefore agreed that the most appropriate utility estimates would likely lie between the company's estimates and the ERG's estimates.

4.17   The committee had concerns about the company's assumption that the quality-of-life benefit of nivolumab continued indefinitely for the duration of the modelled time horizon. The committee acknowledged that nivolumab is associated with quality-of-life benefits as a result of reduced side effects, and with improved clinical outcomes because of longer treatment duration. It also noted that evidence from clinical studies suggests that the treatment effect associated with immunotherapies continues for a small number of patients even after treatment is stopped, which was also supported by the clinical experts. But, the committee considered that the benefit would decrease gradually over time and cannot be assumed to extend over a person's lifetime. In response to the request by the committee to explore decreasing quality-of-life benefits, the company submitted an analysis in which quality of life was modelled to decline in the 30 days before death. The ERG was unclear how this analysis met the committee's request and would have preferred a different approach. The committee noted that this adjustment of quality of life should be included in the economic modelling, although a decline from an earlier time point would have been more appropriate. It also supported the ERG's questioning of the plausibility of extrapolating the high post-progression utility over the modelled time horizon and whether this utility increase compared with investigator-choice therapy could be assumed to continue after treatment stopped, especially considering the pathology of progressed disease for head and neck cancer. The ERG highlighted further uncertainty in the utility scores by calculating confidence intervals around the point estimates, which were shown to be wider in the nivolumab arm than in the investigator-choice arm. The committee concluded that it was implausible that the quality-of-life benefit would stay

at a continuous level for the lifetime of the patient after treatment was stopped.

Other considerations

4.18 The committee noted that the request for further subgroup analyses according to the expression of PD-L1 (both 1% or more, and less than 1%) after the first committee meeting was declined by the company, who considered that focusing on these subgroups was inappropriate for decision-making. But, the committee disagreed with this assessment and reiterated its interest in seeing data exploring the possible clinical effectiveness of nivolumab in this subpopulation.

Most plausible ICER

4.19 The committee noted that the company's updated base-case ICER, with a 25% stopping rule applied at 2 years, ranged from £41,000 to £45,000 per QALY gained for nivolumab compared with docetaxel, paclitaxel and methotrexate. This range further increased to between £44,000 and £47,000 per QALY gained when a stopping rule was not applied. The company's own scenario analyses, using the piecewise approach with lognormal extrapolation for overall survival (see section 4.12) and without a stopping rule, produced a wide range of ICERs, from £38,000 to £53,000 per QALY gained, depending on the time point for extrapolation. The ERG's exploratory base-case, which excluded a stopping rule, had little effect on the ICERs. However, the committee's preferred assumption using the ERG's piecewise approach with the exponential distribution (see section 4.12) produced ICERs ranging from £66,000 to £75,000 per QALY gained for nivolumab compared with docetaxel, paclitaxel and methotrexate. Incorporating the committee's preferred assumption of using treatment-independent utilities (see section 4.16), also increased the ICERs significantly so that they ranged from £62,000 to £67,000 per QALY gained for nivolumab compared with docetaxel, paclitaxel and methotrexate. The committee considered that the ICER would be higher if both assumptions were included together in the same analysis. Therefore,

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the committee concluded that the ICERs for nivolumab compared with the comparators (particularly docetaxel) using its preferred assumptions and incorporating the confidential patient access scheme for nivolumab were substantially above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). It agreed that the ICER would remain substantially above this range even when the utility estimates are assumed to lie between the company's and the ERG's estimates (see section 4.16).

4.20   The committee had previously concluded that there is evidence of differential clinical benefits with nivolumab according to levels of PD-L1 expression (see section 4.6). Therefore it considered that nivolumab could be more cost effective for the subgroup with higher levels of PD-L1 expression than the overall population covered by the marketing authorisation. However, because the company did not present cost-effectiveness analyses according to levels of PD-L1 expression, the committee could not consider whether a positive recommendation could be made for the subgroup with a PD-L1 expression of 1% or more.

Innovation

4.21   The committee noted the company's view that nivolumab has the potential to help address the considerable unmet clinical need of people with recurrent or metastatic SCCHN whose disease has progressed during or after platinum-based therapy, and who currently have limited treatment options available to them at an end-of-life stage. The committee heard from the clinical and patient experts that nivolumab is innovative in its potential to make a significant and substantial effect on health-related benefits. It understood that nivolumab is generally well-tolerated compared with taxane-based chemotherapy agents, such as docetaxel and paclitaxel, and shows an improvement in overall-survival benefit compared with currently available agents. The committee agreed that nivolumab addresses an unmet need in a debilitating condition for which few treatment options are available. It acknowledged that there may be

potential quality-of-life benefits with nivolumab which have not been captured in the committee's preferred analysis using treatment-independent utilities, but it had accounted for this in its decision-making (see section 4.16 and section 4.19).

End-of-life considerations

4.22 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. It noted the evidence presented by the company, which showed that people with recurrent or metastatic SCCHN whose disease has progressed during or after platinum-based therapy have a life expectancy of less than 24 months. The life expectancy of these patients is estimated to be 5.1 months, based on median overall survival in the investigator-choice arm of the CheckMate-141 trial. Using the ERG's piecewise scenario analysis, the overall survival gain with nivolumab ranged from 3.56 to 3.83 months when the 20-, 28-, 36- and 48-week cut-off points were considered. It accepted that there is enough evidence to show that nivolumab offers an extension to life of at least an additional 3 months, compared with current NHS treatment. The committee concluded that nivolumab met all the criteria to be considered a life-extending end-of-life treatment. Given the committee considered that the most plausible ICER was likely to be above £50,000 per QALY gained (see section 4.19), it concluded that the amount of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for nivolumab to be considered a cost-effective use of NHS resources. Therefore, the committee concluded that nivolumab could not be recommended for SCCHN that has progressed during or after platinum-based chemotherapy.

Cancer Drugs Fund

4.23 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to

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the NICE process and methods guides. The committee heard from the company that nivolumab should not be considered for funding through the Cancer Drugs Fund because it would prefer that it be available through routine commissioning. But, the committee discussed whether nivolumab would meet the criteria for the Cancer Drugs Fund. The committee noted that the ICER with the patient access scheme discount applied was outside the range normally considered a cost-effective use of NHS resources for the whole population of people with SCCHN whose disease progressed during or after platinum based chemotherapy, and so nivolumab did not have the plausible potential for satisfying the criteria for routine use. It also noted that although there were uncertainties in the evidence for this appraisal, the clinical-effectiveness evidence from CheckMate-141 was relatively mature and there were no clinical uncertainties that could be addressed by collecting outcome data from people in the NHS to inform a further update of the guidance. The committee concluded that nivolumab did not meet the criteria to be considered for use in the Cancer Drugs Fund.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy	Section
Key conclusion		
Nivolumab is not recommended, within its marketing authorisation, for treating squamous cell carcinoma of the head and neck (SCCHN) in adults whose disease has progressed during or after platinum-based chemotherapy. The committee concluded that CheckMate-141 showed significant improvement in overall survival in the group having nivolumab compared with the investigator-choice arm, but the incremental long-term overall-survival benefit is uncertain. It also concluded that there is evidence of benefit in both the PD-L1 (1% or	1.1, 4.5 to 4.7

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more) and HPV-p16 positive groups, however, the benefit in the PD-L1 (less than 1%) and HPV-p16 negative groups is uncertain.		
The committee concluded that the incremental cost-effectiveness ratios (ICERs) for nivolumab compared with the comparators (particularly docetaxel) using its preferred assumptions (including a piecewise extrapolation approach with the exponential distribution and treatment-independent utilities) and incorporating the confidential patient access scheme for nivolumab were substantially above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per quality-adjusted life year [QALY] gained).		4.19
The committee concluded that nivolumab met all the criteria to be considered a life-extending end-of-life treatment. Given the committee considered that the most plausible ICER was likely to be above £50,000 per QALY gained, it concluded that the amount of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for nivolumab to be considered a cost-effective use of NHS resources.		4.22
The committee concluded that nivolumab did not meet the criteria to be considered for use in the Cancer Drugs Fund.		4.23
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard that people with SCCHN have limited treatment options and their disease is generally considered incurable at this stage.	4.1
The technology		

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Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee concluded that there is a high unmet need for effective treatment options for people with SCCHN whose disease has progressed during or after platinum based chemotherapy, and that nivolumab is associated with quality-of-life benefits as a result of reduced side effects, and with improved clinical outcomes because of longer treatment duration. The committee acknowledged that there may be potential quality-of-life benefits with nivolumab which have not been captured in the committee's preferred analysis using treatment-independent utilities, but it had accounted for this in its decision-making	4.1, 4.17, 4.21
What is the position of the treatment in the pathway of care for the condition?	Nivolumab is positioned in the clinical treatment pathway as an option for people with SCCHN whose disease has progressed during or after platinum-based therapy and a taxane, usually docetaxel, is an appropriate comparator.	4.2
Adverse reactions	The committee concluded that nivolumab is associated with less severe adverse reactions compared with chemotherapy agents, such as docetaxel.	4.9
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	Clinical-effectiveness evidence for nivolumab came from 1 study (CheckMate-141) that compared nivolumab with the investigator's choice of therapy. The study did not include paclitaxel, which was specified as a comparator in the NICE final scope, and included cetuximab which was not in the NICE scope and not considered established practice in England for this group of people. The committee was aware that because of lack of clinical evidence, a meaningful comparison with paclitaxel was not possible.	4.3
Relevance to general clinical practice in the NHS	The committee concluded that although there are some differences between the trial population and the UK population, the data from CheckMate-141 could be used for its decision-making.	4.8

Uncertainties generated by the evidence	The committee concluded that the exclusion of paclitaxel from the trial and the inclusion of cetuximab, a drug not included in the NICE scope, introduces some uncertainty about the relevance of CheckMate-141 to UK clinical practice.	4.3
	It also noted considerable uncertainty in the pre-planned subgroup analyses in the PD-L1 (1% or more) because of the early and consistent separation of the curves during the first 9 months of therapy. The committee also agreed that there was a differential benefit according to HPV p16 status, but that it was not an important determinant of the efficacy of nivolumab treatment and therefore would not be considered further.	4.6, 4.7
	The committee also noted a higher male population in the trial and differences in the overall-survival results for participants in the European Union and North America as potential areas of uncertainty.	4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that there is evidence of benefit in both the PD-L1 (1% or more) and HPV-p16 positive groups. However, the benefit in the PD-L1 (less than 1%) and HPV-p16 negative groups is uncertain.	4.6, 4.7

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that CheckMate-141 showed significant improvement in overall survival in the group having nivolumab, with survival rates doubling in the nivolumab arm (36%) compared with the investigator-choice arm (16.6%) at 12-month follow-up, but the incremental overall-survival benefit beyond 24 months is uncertain.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that the company presented a 3-state partitioned survival model that compared nivolumab with the investigator's choice of either docetaxel, methotrexate or paclitaxel. The committee concluded that the model structure is appropriate for its decision-making.	4.10

| Uncertainties around and plausibility of assumptions and inputs in the economic model | The committee expressed concerns about the applicability of standard parametric curves for estimating survival with immune-oncology drugs compared with chemotherapy drugs. It agreed that it would be better to use the observed Kaplan–Meier data for the first phase of the model and then fit an appropriate distribution at a reasonable time point. It noted that none of the distributions fitted to the overall survival, progression-free survival and time-to-treatment discontinuation curves were a good fit to the data and considered the ERG's piecewise approach using the exponential distribution to be more plausible approach. | 4.11, 4.12 |
| | The company's assumption that the quality-of-life benefit of nivolumab continues indefinitely for the duration of the modelled time horizon, use of a high utility value assigned to nivolumab treatment in the post-progression state after treatment is stopped and disease progression, missing data, long-term treatment effect and the incorporation of a stopping rule were also noted as further areas of uncertainty. | 4.13, 4.14, 4.15, 4.16, 4.17 |

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

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? | The committee noted that the company applied treatment-dependent utilities derived from EQ-5D-3L data from CheckMate-141 to their model and that these utility values, calculated by the mixed model approach, were associated with significant uncertainty.

The committee noted that there may be potential quality-of-life benefits with nivolumab which have not been captured in the committee's preferred analysis using treatment-independent utilities, but it had accounted for this in its decision-making. | 4.15

4.16, 4.21 |
|---|---|---|
| Are there specific groups of people for whom the technology is particularly cost effective? | The committee concluded that there is evidence of benefit for nivolumab compared with investigator-choice therapy in the PD-L1 '1% or more' group, but the benefit in the group with a PD-L1 of less than 1% is uncertain. The company declined the request to provide cost-effectiveness analysis according to PD-L1 expression. | 4.6, 4.20 |
| What are the key drivers of cost effectiveness? | The ERG's piecewise approach with the exponential distribution and treatment-independent utilities increased the ICERs significantly relative to the company's preferred method of using the log-normal curve for the full time horizon of the model and treatment-dependent utilities. | 4.12, 4.16, 4.19 |

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Most likely cost-effectiveness estimate (given as an ICER)	The committee's preferred assumption using the ERG's piecewise approach with the exponential distribution produced ICERs ranging from £66,000 to £75,000 per QALY gained for nivolumab compared with docetaxel, paclitaxel and methotrexate. Incorporating the committee's preferred assumption of using treatment-independent utilities also increased the ICERs significantly so that they ranged from £62,000 to £67,000 per QALY gained for nivolumab compared with docetaxel, paclitaxel and methotrexate. The committee considered that the ICER would be higher if both assumptions were included together in the same analysis.	4.19
Additional factors taken into account		
End-of-life considerations	The committee concluded that nivolumab met all the criteria to be considered a life-extending end-of-life treatment. Given the committee considered that the most plausible ICER was likely to be above £50,000 per QALY gained, it concluded that the amount of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for nivolumab to be considered a cost-effective use of NHS resources.	4.22

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| Cancer Drugs Fund | The committee noted that all the ICER's for nivolumab with the patient access scheme discount applied were outside the range normally considered a cost-effective use of NHS resources, and so nivolumab did not have the plausible potential for satisfying the criteria for routine use. It considered that there were no clinical uncertainties that could be addressed by collecting outcome data from people in the NHS to inform a further update of the guidance. The committee concluded that nivolumab did not meet the criteria to be considered for use in the Cancer Drugs Fund. | 4.23 |
| Equalities considerations and social value judgements | No equalities issues were identified by the committee and experts. | |

5 Proposed date for review of guidance

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

Professor Gary McVeigh

Chair, appraisal committee

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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.

Sana Khan
Technical Lead

Nwamaka Umeweni
Technical Adviser

Kate Moore
Project Manager

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