NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

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

1 Recommendations

1.1 Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating 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;
- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
- the conditions in the managed access agreement are followed.

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.

Why the committee made these recommendations

There are limited treatment options for squamous cell carcinoma of the head and neck that has progressed on platinum-based chemotherapy. The population in the clinical trial for nivolumab had disease that had progressed within 6 months of

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platinum-based chemotherapy (early recurrence). This is a clinically distinct population who have a poor prognosis and whose disease will not be retreated with a platinum drug. In England, these people are usually offered docetaxel.

Clinical trial evidence showed that nivolumab improved overall survival by 2.6 months compared with docetaxel, methotrexate or cetuximab, but longer-term survival benefit, after 2 years, is uncertain. There is also uncertainty about its benefit for tumours expressing less than 1% PD-L1 protein.

Nivolumab meets NICE's criteria to be considered a life-extending end-of-life treatment. However, it cannot be recommended for routine use because the most likely cost-effectiveness estimate would fall between £45,000 and £73,600 per quality-adjusted life year gained.

Nivolumab has the potential to be cost effective, but more evidence is needed to address the clinical uncertainties. It can therefore be recommended for use within the Cancer Drugs Fund while further data are collected as part of a managed access agreement. Collecting further data from people having nivolumab should address the uncertainties about its benefits for longer-term survival and for tumours expressing less than 1% PD-L1 protein.

2 The technology

Nivolumab (Opdivo, Bristol-Myers Squibb)	
Marketing authorisation	Nivolumab has a marketing authorisation in the UK as monotherapy for 'the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy'.
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] online, [accessed December 2016] and company submission). As part of the managed access agreement, the company (Bristol-Myers Squibb) has a commercial access agreement with NHS England. This makes nivolumab available at a reduced cost. The financial terms of the agreement are commercial in confidence.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

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 expert described SCCHN as a debilitating condition with multiple distressing symptoms such as a dry, sore mouth, weight loss and decreased appetite. The clinical experts explained 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 or paclitaxel, cause significant adverse reactions. The committee was aware that the patient experts' submissions stated that the outlook for patients with recurrent or metastatic SCCHN whose disease has relapsed on 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 an unmet need for effective treatment options for people with recurrent or metastatic SCCHN whose disease has progressed on or after platinum-based chemotherapy.

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

3.2 The clinical experts stated that curative treatments, such as surgery and platinum-based therapy, are considered to be first-line treatment for recurrent or metastatic SCCHN. They indicated that about 40% of people who have SCCHN will have recurrence. For early recurrence (disease that has progressed within 6 months of platinum-based therapy), treatment options in clinical practice in England include taxane-based chemotherapies (such as docetaxel or paclitaxel) or methotrexate. However for recurrence after 6 months, the clinical experts stated that the disease will be retreated with a platinum-based therapy. The committee understood that nivolumab would be considered as an option at the point of early recurrence in the treatment pathway, where retreatment with a platinum drug will not be considered and in line with the clinical trial (see section 3.3 and 3.4). 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 on or within 6 months of platinum-based therapy in the NHS. The use of paclitaxel in clinical practice is limited. They also stated that methotrexate is normally reserved for people who have a poor performance status and are not fit enough to have a taxane, or as subsequent therapy for people who have had a 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 on or within 6 months of platinum-based therapy. It also concluded that docetaxel would be the most appropriate comparator for people fit enough to have docetaxel.

Clinical trial evidence

There is uncertainty about the relevance of CheckMate-141 to UK clinical practice

3.3 The clinical effectiveness evidence for nivolumab came from the CheckMate-141 trial comparing 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 trial did not include paclitaxel, which is in NICE's final scope, but it did include cetuximab, which is not in the 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. It therefore concluded that excluding paclitaxel from the trial and including cetuximab, a drug not used in clinical practice (and therefore not included in the NICE scope), introduces some uncertainty about the relevance of CheckMate-141 to UK clinical practice.

CheckMate-141 only includes people with disease that progressed within 6 months

3.4 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 noted that the population covered by the marketing authorisation is broader than the trial population. The clinical experts highlighted that the trial population is a specific subset of patients who would usually be excluded from trials because of poor prognosis, and that including them in

CheckMate-141 reflects an important population seen in clinical practice. The European Public Assessment Report from the European Medicines Agency acknowledges that patients with a progression-free interval of more than 6 months since last platinum receive the same treatment as those without prior platinum treatment; that is, platinum-based chemotherapy. It also states that patients whose disease progresses within 6 months of platinum-based therapy, have a poor prognosis and the choice of treatment is not well defined. The committee considered that the information in the European Public Assessment Report further supports its conclusion that nivolumab is appropriately positioned as an option at the point of early recurrence (section 3.2). The committee therefore concluded that, although the marketing authorisation for nivolumab is broad, its recommendations will focus on the population represented in the trial because this underpins the marketing authorisation and is a distinct subset of the population whose disease has progressed after platinum-based chemotherapy.

CheckMate-141 results

Nivolumab improves overall survival, but the benefit after 24 months is uncertain

3.5 The results from the latest database lock on September 2016 showed that nivolumab had a statistically significant overall survival benefit compared with the investigator-choice therapy, with a median overall survival of 7.7 months in the nivolumab arm and 5.1 months in the investigator-choice arm (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.55 to 0.90; p=0.0048). This is a 29% reduction in the risk of death with nivolumab compared with the investigator's choice of therapy. Nivolumab did not similarly improve progression-free survival, which was much the same in both treatment arms (2.0 months for nivolumab and 2.3 months for investigator-choice therapy; HR 0.87; 95% CI 0.69 to 1.11; p=0.2597). 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. The committee concluded that there was significant improvement in overall survival in the nivolumab group, with survival rates almost tripling (21.5%) compared with the investigator-choice group (8.3%) at 18-month follow-up, but the incremental overall survival benefit beyond 24 months is uncertain.

Docetaxel is equivalent to paclitaxel in clinical effectiveness, but not to methotrexate

3.6 The clinical experts explained 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 on and after platinum-based therapy, it is often reserved for people who have a poorer performance status and who are less able to tolerate the toxicity of taxane-based chemotherapy. Therefore, the clinical experts' opinion was that the population of patients for whom methotrexate is suitable is likely to be different to the population who will be offered docetaxel. The committee noted that subgroup results from CheckMate-141 showed that nivolumab is more effective in improving overall survival compared with methotrexate than when compared with docetaxel (HR 0.64; 95% CI 0.43 to 0.96 and 0.82; 95% CI 0.53 to 1.28 respectively), suggesting that docetaxel appears to be more effective than methotrexate. The committee concluded that it is valid to assume that docetaxel and paclitaxel are equivalent, but it was not persuaded by the company's assumption that docetaxel is equivalent to methotrexate.

There is evidence of nivolumab's benefit for tumours expressing 1% or more PD-L1 protein, but at lower expression levels the benefit is not clear

3.7 The committee discussed the company's pre-planned subgroup analyses according to expression of the PD-L1 protein (1% or more, or less than 1%). It understood that in general patients whose tumours express PD-L1 (1% or more), especially those with higher levels of expression, have a better response to checkpoint inhibitors, such as nivolumab. This is plausible because it is the main proposed mechanism of action of the drug. The committee specifically considered the Kaplan–Meier overall survival curves from the September 2016 database lock for the pre-specified subgroups of PD-L1 expression. 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 5 months of therapy. Although the curves for the less than 1% group separated after 5 months, the committee noted that this was based on small patient numbers; therefore, it was difficult to establish the overall survival benefit in this group. The committee concluded that there is evidence of nivolumab's benefit compared with investigator-choice therapy in the 1% or more group, shown by a median overall survival gain of 3.4 months with nivolumab and a corresponding hazard ratio of 0.53 (95% CI 0.37 to 0.77), but that the benefit for the less than 1% group is much less convincing, with the median overall survival gain of 0.6 months (HR 0.83; 95% CI 0.54 to 1.29).

Results from CheckMate-141 are relevant to the UK population

3.8 The committee noted that there were more men in the trial population (83%) than in the SCCHN population in the UK (70%). The clinical experts stated that this is likely to be because more men than women take part in trials. The committee noted that different overall survival results for nivolumab were reported for men (HR 0.65; 95% CI 0.48 to 0.88) and women (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 Europe (HR 0.91; 95% CI 0.62 to 1.33) and how this could affect the

applicability of the results to the UK. The clinical experts noted that the results for women and for the European subgroup are not statistically significant because of the small number of people in these subgroups. They also highlighted that docetaxel is the most frequently used treatment in Europe whereas methotrexate is the preferred treatment in North America. Given that docetaxel may be a more effective therapy than methotrexate (see section 3.6), this may explain the difference in outcomes for the 2 continents. The committee concluded that although there are some differences between the trial population and the UK population, the CheckMate-141 results are relevant to the UK population.

Adverse reactions

Drug-related serious adverse reactions are fewer with nivolumab than with conventional chemotherapy

3.9 The clinical experts explained that immunotherapy such as 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). The committee heard that immunotherapies cause rare but significant immune-related adverse reactions such as pneumonitis, which could result in prolonged stays in hospital. The company submission reported 5 occurrences of pneumonitis in the nivolumab arm, although only 2 of them (less than 1% of patients in the nivolumab arm) were classified as grade 3 or 4. No new safety concerns for nivolumab were identified in CheckMate-141. The committee concluded that nivolumab causes fewer adverse reactions known to be associated with conventional chemotherapy such as docetaxel, but can also cause rare, and potentially serious, immune-related adverse reactions.

Economic model

The company's model structure is appropriate for decision-making

3.10 The committee noted that the company presented a 3-state partitioned survival model comparing 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, although it noted that assuming clinical equivalence between some of the comparators is uncertain (see section 3.6).

Extrapolation methods

The piecewise model is preferred for extrapolating survival

3.11 The company used parametric models to estimate overall survival, progression-free survival and time-to-treatment discontinuation across the time horizon of the model, based on the latest data cut from CheckMate-141. 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 distribution for overall survival and the generalised gamma distribution for progression-free survival and time-to-treatment discontinuation 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 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 early trial data and that most of the 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 immunotherapy 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 and that the advice was published before immunotherapy was 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.

The log normal distribution is more appropriate than the exponential distribution for the piecewise analysis

3.12 The committee previously concluded that the piecewise exponential model explored in the ERG's scenario analyses was more plausible for extrapolating survival. However, in response to the appraisal consultation document, the company expressed concerns with the piecewise exponential model:

- It is associated with logical inconsistencies; the overall survival curve falls below the progression-free survival and time-to-treatment discontinuation curves, suggesting that people who have died are modelled to still progress and remain on treatment.
- It predicts substantially lower 2-year survival for nivolumab than seen in CheckMate-141, regardless of cut-off point used.
- It contradicts the long-term survival evidence from trials of advanced squamous non-small-cell lung cancer (CheckMate-003 and -017), which show decreasing hazard of death with nivolumab from around 3 years onwards.

The ERG confirmed that there were inconsistencies with the overall survival curves crossing the other curves in the piecewise exponential model. The committee noted a clinical expert's consultation comment that the exponential curve is not plausible because there is a plateau in the survival curve seen in a small minority of people having nivolumab for other indications. The committee agreed with the ERG that it is difficult to make inferences from other disease areas because the populations may have different survival prospects. However, it was persuaded that the crossing survival curves made the exponential distribution inappropriate. The company and the ERG stated that the curves did not cross with the company's log normal distribution (using the fully parametric or the piecewise approach). The committee maintained its concerns about the fully parametric approach (see section 3.11) and did not consider it further. The committee also expressed concerns about the long tails associated with the log normal distribution. However, because no other distributions were explored by the company, the committee accepted the company's piecewise log normal model.

The most appropriate time point to extrapolate the trial data is uncertain

3.13 For the piecewise log normal model, the company explored 3 different time points from which to extrapolate the Kaplan–Meier data, that is, 20, 36 and 48 weeks. The committee had concerns with each of the options presented and considered that the choice of an appropriate time point would be arbitrary. Also, it noted that varying the time points had an inconsistent effect on the model result. As the time point moved from 20 to 36 weeks, the incremental cost-effectiveness ratio (ICER) decreased, but it increased when the time point moved from 36 to 48 weeks. The committee recognised that the most appropriate time point from which to extrapolate the trial data was uncertain and concluded that it would consider all 3 options.

The modelled progression-free survival and time-to-treatment discontinuation is uncertain

3.14 The committee recalled its concerns at the first meeting that none of the parametric distributions fitted the progression-free survival and time-to-treatment discontinuation data well. It noted that the progression-free survival curve substantially underestimated the observed 2-year progression-free survival data from CheckMate-141. The committee concluded that this introduced further uncertainty in the model.

Long-term treatment effect

Continued treatment benefit up to 5 years is plausible, but assuming constant benefit after treatment stops is uncertain

3.15 The committee was concerned that nivolumab's treatment effect was assumed to persist for the entire time horizon of 20 years in the model. The company presented separate scenario analyses assuming that nivolumab's survival benefit 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. It noted the comments from the clinical experts that there is evidence from other indications that nivolumab's treatment benefit could last up to 5 years. The committee noted that although 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 (section 3.17). It therefore concluded that the company's scenario of a continued survival benefit lasting up to 5 years was plausible, but assuming that the benefit would stay constant after treatment stops is uncertain.

Stopping rule

Analyses without a stopping rule are more appropriate for decision-making

3.16 The committee noted that the company's updated base case included a 2-year stopping rule in which only 25% of patients who were still having treatment with nivolumab after 2 years carried on having treatment, and all other model parameters were the same. The company also explored

the effect of altering the proportion of patients 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 database 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 treatment costs 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 treatment benefit. The committee was not aware of a 2-year stopping rule in the trial protocol, as seen in previous appraisals. It noted that the company's submission stated that nivolumab treatment in the trial was allowed to continue after progression if patients were still having benefit and tolerating the drug, but the proportion of patients who were still having treatment and the average treatment duration in the trial was unclear. Given the uncertainty about the stopping rule, the committee concluded that it would only consider analyses with the stopping rule in the context of potential inclusion in the cancer drugs fund, as an approach to managing risk.

Utility values

Quality-of-life benefit cannot be assumed to remain constant

3.17 To address the ERG's and the committee's initial concerns about missing health-state utility data, the company used a mixed model regression analysis to estimate utility scores based on EQ-5D-3L data from CheckMate-141. The ERG agreed that the mixed model approach had the benefit of accounting for autocorrelation and missing data. The committee noted that the company's 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 committee and the ERG also questioned 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. The company stated that the definition of progression using the old RECIST criteria does not accurately capture progression while on immunotherapy and that the lasting benefits shown in the utility scores reflect the toxic nature of comparator therapies. 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 clinical trial evidence suggests that the treatment effect associated with immunotherapy 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 quality-of-life benefit would decrease gradually over time and cannot be assumed to extend over a person's lifetime. 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 the same level for the lifetime of the patient after treatment was stopped.

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

3.18 The committee was concerned 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 of nivolumab had not been captured. In response to consultation, the company presented treatment-independent utility analysis estimated from the mixed model, which was different from the ERG's approach of using a simple average. The committee noted that the company presented several approaches for estimating utilities, all of which had limitations. However it accepted the company's preferred approaches for estimating treatment-dependent utilities (model 6) and treatment-independent utilities (model 7) and agreed that the most appropriate utility estimates would likely lie between these 2 estimates.

Most plausible ICER

The most plausible ICER is between £45,000 and £73,600 per QALY gained, but closer to the upper end of the range

3.19 The committee considered its preferred assumptions based on the evidence:

- docetaxel as the most relevant comparator (see section 3.2)
- the piecewise model using the log normal distribution to model overall survival (see section 3.12)
- treatment benefit with nivolumab lasting up to 5 years (see section 3.15)
- no stopping rule for nivolumab treatment (see section 3.16)
- using both treatment-dependent and treatment-independent utility values (see section 3.18) and
- using the ERG's amendments to the company's model (adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatments).

The resulting ICER including the patient access scheme for nivolumab compared with docetaxel was between £45,000 and £58,500 per quality-

adjusted life year (QALY) gained (depending on the time point for extrapolation) for the analysis using the treatment-dependent utility values. Corresponding analysis using treatment-independent utility values resulted in ICERs between £57,200 and £73,600 per QALY gained (depending on the time point for extrapolation). Taking into account its conclusion about the most appropriate utility values (see section 3.18), the committee concluded that the most plausible ICER would fall between £45,000 and £73,600 per QALY gained. The committee agreed that the most plausible value would possibly lie closer to the upper end of the range, given the uncertainties with:

- the long tail of the log normal model (see section 3.12)
- the modelling of progression-free survival and time-to-treatment discontinuation (see section 3.14)
- assuming a constant treatment benefit for up to 5 years after treatment stops (see section 3.15) and
- using investigator-choice data to model all comparators, thereby underestimating the effectiveness of docetaxel (see sections 3.6 and 3.10).

Accounting for cost savings from other indications is not appropriate

3.20 The committee discussed the company's proposed scenario of incorporating cost savings for nivolumab from other indications as a result of the revised patient access scheme for SCCHN. It acknowledged that there would be a wider benefit to the NHS because the simple discount proposed in the patient access scheme would apply across all indications, but it noted that taking this into account was outside its approved methods. The committee concluded that it was not appropriate to incorporate these benefits into the cost-effectiveness analyses, taking into account the most plausible ICER and the uncertainty identified.

Innovation

All potential quality-of-life benefits are accounted for in the committee's decision

3.21 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 on or after platinum-based therapy, and who have limited treatment options available to them at end of life. The committee heard from the clinical and patient experts that nivolumab is innovative in its potential to have a significant and substantial effect on health-related benefits. It understood that nivolumab is generally well-tolerated compared with taxanes, such as docetaxel and paclitaxel, and shows an improvement in overall survival benefit compared with currently available drugs. The committee agreed that nivolumab addresses an unmet need for a debilitating condition with few treatment options. It acknowledged that there may be potential quality-of-life benefits of nivolumab that 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 sections 3.18 and 3.19).

End of life

Nivolumab meets the end-of-life criteria but the ICERs are too high for it to be recommended for routine commissioning

3.22 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 on or within 6 months of 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 CheckMate-141, or between 8.16 and 9.84 months based on the

piecewise log normal model (depending on the time point for extrapolation of the trial data). Using the piecewise log normal model, the overall survival gain with nivolumab ranged from 4.68 to 6.24 months when the 20-, 36- and 48-week time points were considered. The committee accepted that there is enough evidence to show that nivolumab extends life by 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 3.19), it concluded that the 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 on or after platinum-based chemotherapy.

Cancer Drugs Fund

Nivolumab has potential to be cost effective for the full trial population with the commercial access agreement

3.23 Having concluded that nivolumab could not be recommended for routine use, the committee then considered if it could be recommended for treating SCCHN within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee noted that the ICER with the patient access scheme discount was outside the range normally considered a cost-effective use of NHS resources for the full trial population irrespective of PD-L1 expression. So nivolumab did not have plausible potential for satisfying the criteria for routine use for the full trial population. The committee questioned whether nivolumab has plausible potential for satisfying the criteria for routine use for people with tumour PD-L1 expression of 1% or more. It previously concluded that there is

evidence of differential clinical benefit with nivolumab according to level of PD-L1 expression (see section 3.7). Therefore it considered that nivolumab could be more cost effective for people with higher levels of tumour PD-L1 expression than for the overall population covered by the marketing authorisation, with ICERs possibly below £50,000 per QALY gained. However, because the company initially did not present cost-effectiveness analyses according to levels of PD-L1 expression, the committee could not judge with certainty whether this would be the case.

3.24 The company subsequently proposed a commercial access agreement to include nivolumab in the Cancer Drugs Fund for all patients irrespective of PD-L1 expression. The company also presented cost-effectiveness results for subgroups according to PD-L1 expression, highlighting that these analyses were subject to uncertainty because of the small patient numbers and because CheckMate-141 was not powered to show a difference between the PD-L1 subgroups. The committee agreed that the results for the subgroups are unreliable and subject to significant uncertainty because of the small patient numbers in the trial and possibly the company's use of the distribution appropriate to extrapolate survival for the full trial population rather than identifying appropriate ones for the subgroups; therefore they are not suitable for decision-making.

3.25 The committee noted that the company's proposal included a 2-year stopping rule for nivolumab treatment. Although it had previously concluded that it would not consider a stopping rule for routine commissioning, the committee accepted that it would be reasonable to manage access while in the CDF, and understood from the CDF clinical lead that a 2-year stopping rule could be implemented as has been done for other indications and similar immunotherapy treatments. The committee noted that the ICERs for the full trial population using the commercial access agreement was between £30,377 and £49,408 per QALY gained depending on the time point used for extrapolation. It therefore concluded that nivolumab showed plausible potential for being

cost effective for the full trial population, incorporating a 2-year stopping rule and with the commercial access agreement.

Uncertainties about long-term overall survival benefit and PD-L1 expression can be addressed by collecting further data

3.26 The committee considered that the uncertainties about the overall survival benefit beyond 2 years could be addressed by collecting longer follow-up survival data from CheckMate-141, specifically according to levels of PD-L1 expression. It understood that the company's proposal for nivolumab in the Cancer Drugs Fund would include collecting longer-term survival data for the full trial population and for the PD-L1 subgroups. The committee stressed the importance of collecting prevalence and outcome data by PD-L1 expression, stating that any recommendation for the full trial population would depend on a clear commitment from the company to collect these data. It was concerned that PD-L1 testing was not done routinely for SCCHN in the NHS and questioned the feasibility of the company's proposal to collect data by PD-L1 expression. It considered that collecting data from the Systemic Anti-Cancer Therapy dataset may be used to supplement follow-up data from CheckMate-141. The committee was reassured that the company would help set up the testing for PD-L1 expression if the drug is recommended for use within the Cancer Drugs Fund. It was also reassured that NHS England will work with the company to enable PD-L1 data to be collected through the Cancer Drugs Fund. Therefore the committee was satisfied that the necessary data to address its concerns could be collected through the Cancer Drugs Fund.

Recommendation

3.27 The committee were reassured about the data collection arrangements and considered that nivolumab showed plausible potential to be cost effective for the full trial population with a 2-year stopping rule and the commercial access agreement. Therefore it recommended nivolumab for

use within the Cancer Drugs Fund for SCCHN that has progressed on or within 6 months of platinum-based chemotherapy only if the conditions of the managed access agreement are followed.

Equalities

3.28 No equality issues were identified.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has squamous cell carcinoma of the head and neck 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 and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

4.3 Nivolumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Bristol-Myers Squibb have a commercial access agreement that makes nivolumab available to the NHS at a reduced cost. The financial terms of

the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to [NICE to add details at time of publication]

5 Review of guidance

5.1 The data collection period is expected to end in September 2019, when 4-year follow-up data from the CheckMate-141 clinical trial is available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

5.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies

Professor Gary McVeigh
Chair, appraisal committee
September 2017

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.

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