NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease 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 document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using nivolumab for adjuvant treatment of resected stage III and IV melanoma 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: 28 September 2018

Second appraisal committee meeting: 16 October 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Nivolumab is not recommended, within its marketing authorisation, as monotherapy for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.

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 no trials directly comparing adjuvant nivolumab with routine surveillance, which is usual current management for completely resected stage III and IV melanoma. This means there is uncertainty about the clinical effectiveness of nivolumab compared with routine surveillance. Evidence from an ongoing trial shows improved recurrence-free survival with nivolumab compared with ipilimumab. However, the effect on overall survival with nivolumab in this trial is uncertain because it is still ongoing.

The cost-effectiveness estimates for nivolumab are uncertain because of the uncertainty in the clinical evidence. Therefore, nivolumab cannot be recommended for routine use in the NHS for the adjuvant treatment of completely resected melanoma with involvement of lymph nodes or metastatic disease.

The committee could not recommend nivolumab for use within the Cancer Drugs Fund because, based on the current analyses, it is not possible to assess whether nivolumab has plausible potential to be cost effective.

2 Information about nivolumab

Marketing authorisation indication	Nivolumab (Opdivo; Bristol-Myers Squibb) has a marketing authorisation as 'monotherapy for the adjuvant treatment of adult patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection'.
Dosage in the marketing authorisation	3 mg/kg nivolumab administered intravenously over 60 minutes every 2 weeks for up to 12 months.
Price	£439 per 4 ml vial; £1,097 per 10 ml vial (excluding VAT; British national formulary [BNF] online [accessed August 2018]). The company has a commercial arrangement (commercial access agreement; simple discount), which would apply if the technology had been recommended. This makes nivolumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

Clinical need and current management

People with completely resected stage III and IV melanoma have a high unmet clinical need

3.1 Melanoma is becoming more common and often affects people at a younger age than other cancers. It has a substantial effect on patients, their carers and the wider society. Five-year survival estimates are about 50−55% for stage III disease and 8−24% for stage IV disease. People with fully resected melanoma are still at high risk of disease recurrence; 5-year relapse-free survival is 28%−44% for stage III melanoma and less for stage IV melanoma. The clinical and patient experts noted that significant developments in the treatment of melanoma in recent years,

particularly the introduction of immunotherapies in the metastatic setting, have had a positive effect on the life expectancy and quality of life of people living with advanced disease. The patient expert emphasised the importance of access to additional treatment options, particularly in the adjuvant setting, for people living with melanoma. The committee concluded that people with fully resected stage III and IV melanoma have a high unmet clinical need and would value new treatment options.

The aim of adjuvant treatment is to cure the disease and it is an important development in managing stage III and IV melanoma

3.2 The clinical experts noted that resection of the tumour and associated lymph nodes in people with evidence of regional node metastases is the standard first-line treatment for most people with stage III and some people with stage IV resectable melanoma. However, they explained that surgical practice is changing for patients with stage IIIa disease because of publication of the MSLT2 trial; this showed that there is no overall survival benefit in these patients after full resection, including the sentinel lymph nodes. All patients in the key trial for adjuvant nivolumab (CheckMate 238) had had full resection. However, the clinical experts also explained that using nivolumab in the adjuvant setting was unlikely to influence surgical practice. Currently, the standard of care for people with completely resected stage III and IV melanoma is routine surveillance. This includes regular clinical review and imaging. Adjuvant radiotherapy and immunotherapy after tumour removal are not widely used in UK practice. The clinical experts explained that the aim of adjuvant treatment is to remove any residual microscopic disease after resection to reduce the risk of relapse and progression to metastatic disease, which is currently considered incurable. If the curative aims of adjuvant treatment are met then this would represent a substantial benefit to patients. However, the clinical experts also acknowledged that some patients do not relapse after routine surveillance and that if nivolumab is used in the

adjuvant setting it might affect subsequent treatment for people who develop disseminated disease.

Clinical evidence

Nivolumab has not been directly compared with routine surveillance in a clinical trial

3.3 There are no head-to-head trials comparing nivolumab with routine surveillance in the adjuvant setting. The key trial in the company submission was CheckMate 238, an ongoing multinational randomised double-blind study. It compared adjuvant nivolumab with adjuvant ipilimumab in 906 patients (aged 18 years or over) who have had complete resection of stage IIIB, IIIC, or IV melanoma. After patients had been followed for a minimum of 24 months, a statistically significant improvement in recurrence-free survival (RFS) was seen with nivolumab compared with ipilimumab (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54 to 0.81; p<0.0001). Investigator-assessed disease recurrence or death was reported in 171 (37.7%) and 221 (48.8%) patients who had nivolumab and ipilimumab respectively. The committee acknowledged that although median RFS had been reached (at 30.8 months in the nivolumab arm compared with 24.1 months in the ipilimumab arm), the data were still immature, with heavy censoring in the Kaplan−Meier curve. It also noted that although median follow-up had not been reached for the secondary outcome of distant metastasis-free survival at the most recent data cut (minimum of 24-months follow-up), a statistically significant benefit for nivolumab compared with ipilimumab had been shown (HR 0.76, 95% CI 0.59 to 0.98). The committee also accepted that nivolumab appeared to be less toxic than ipilimumab. It concluded that nivolumab was a more effective treatment than ipilimumab in terms of RFS. However, it emphasised that CheckMate 238 had not provided any evidence on the relative efficacy of adjuvant nivolumab compared with routine surveillance.

Differences between the trials in the company's indirect treatment comparison mean the results are uncertain

3.4 Given the lack of direct comparisons with routine surveillance, the company conducted an indirect treatment comparison (ITC) for RFS using data from CheckMate 238 and another multinational randomised double-blind trial (CA184-029). CA184-029 compared ipilimumab with placebo in 951 patients (aged 18 years or over) with high-risk stage III cutaneous melanoma who had had complete regional lymph node dissection. Because the company had access to the individual patient data for both trials, it chose to do an individual patient data meta-regression analysis. It used this approach to generate parametric survival curves for adjuvant nivolumab and routine surveillance to determine the treatment effect for RFS between 12 weeks and 10 years. The treatment effect up to 12 weeks and after 10 years was estimated from other data sources. Log-logistic curves were selected based on goodness of fit to the observed data from CheckMate 238 (assessed on visual inspection and by statistical measures) and clinical plausibility according to expert opinion. The committee recognised concerns raised by the ERG about differences between the trials that had informed the individual patient data meta-regression ITC. In particular, it noted that patients in the ipilimumab group of CA184-029 had treatment for up to 3 years, whereas patients in CheckMate 238 were restricted to ipilimumab for 1 year. It concluded that the outcomes of ipilimumab treatment may not be comparable, making the estimate of relative effect for nivolumab compared with placebo potentially unreliable. The committee agreed with the ERG that the company's ITC may have produced estimates that were 'overly optimistic', but that an analysis in which patients who had ipilimumab after a year were censored probably represented a 'worst case' scenario. Although there were limitations with both approaches, the committee concluded that because the trial is still ongoing more conservative RFS estimates were preferred. It also noted that the inclusion criteria for CheckMate 238 differed from

those for CA184-029. Checkmate 238 only included patients with stage IIIB, IIIC and IV disease, whereas CA184-029 also included patients with stage IIIA disease but not patients with stage IV disease. Although attempts were made to adjust for these imbalances, the committee concluded that the reliability and generalisability of the results of the company's ITC for RFS were uncertain.

Nivolumab may improve RFS compared with routine surveillance but the magnitude of the benefit is unclear

3.5 The results of the ITC only informed part of the company's analysis for RFS for nivolumab compared with routine surveillance. On the basis that the Kaplan−Meier plot from CheckMate 238 showed there was a statistically significant change in the risk of recurrence at 12 weeks, the company decided to use alternative data sources to determine the treatment effect up to this point. Between 0 weeks and 12 weeks the treatment effect for the nivolumab arm was based on the Kaplan−Meier data from CheckMate 238. Because no equivalent data were available for routine surveillance, the company determined the effect of this intervention up to 12 weeks by applying a hazard ratio to the Kaplan−Meier data from the placebo group in CA184-029. The hazard ratio was derived by fitting a Cox proportional hazards model to the ipilimumab groups of CheckMate 238 and CA184-029, with censoring applied at 12 weeks. The company then fitted the survival curves that had been generated from the individual patient data meta-regression analysis from 12 weeks and these were used to determine the relative treatment effect up to 10 years. However, after this point, the company estimated RFS in each arm by applying a hazard ratio to the American Joint Committee on Cancer version 8 registry data for overall survival (OS). The hazard ratio was based on data from an interferon trial (Arguala et al. 2017). The committee noted that it was unclear whether the registry data reflected current OS expectations because of the recent advances in melanoma treatment. It also noted that interferon is not currently used in

routine practice and has a different mechanism of action to nivolumab. Overall, the committee considered that the methodologies used to estimate RFS for the comparison of interest were extremely complex. It also thought that the use of multiple data sources, some of which were potentially inappropriate, added to the uncertainty that had already been noted in the outputs of the ITC. It concluded that although it was very likely that nivolumab prolonged RFS compared with routine surveillance, the RFS curves presented did not provide a reliable indication of the size of this benefit.

Adverse events

Although nivolumab is well tolerated, toxicity risks are very important for a preventative treatment

3.6 CheckMate 238 showed that nivolumab was generally well tolerated. The clinical and patient experts explained that this was also the case in clinical practice, particularly compared with ipilimumab and chemotherapy. The committee noted that the common side effects which occur during treatment are generally manageable. However, immunotherapy (such as nivolumab) works by altering the immune system, and the clinical experts explained that about 10−20% of people develop irreversible endocrine disorders, in particular thyroiditis, with nivolumab. The committee was aware some who have fully resected stage III disease do not relapse (see section 3.1). It heard from the clinical experts that, for people considered to be at lower risk of relapse, careful assessment and discussion about the risks and potential benefits of nivolumab would be needed. The committee concluded that although the risk of adjuvant nivolumab inducing serious adverse events is likely to be small, it could result in some people who would not have relapsed on routine surveillance having long-term irreversible adverse effects and agreed with the experts that careful assessment of the likely benefits of treatment would be important.

The company's economic model

The company's surrogacy analysis for OS is flawed

3.7 Data on OS from CheckMate 238 are incomplete as the trial is still ongoing. The company chose a surrogacy analysis to predict OS for nivolumab and routine surveillance for use in their economic analysis. The ERG explained that there were several limitations to this analysis, including that it was an exploratory and unvalidated method, and relied on data from studies of interferon (not currently used in the NHS for melanoma). The ERG highlighted a key methodological inconsistency: the derived hazard ratio from the surrogacy relationship was applied to a baseline generalised gamma survival model that does not support the use of proportional hazards. The ERG also noted that it was unclear whether the proportional hazards assumption held for OS with nivolumab compared with routine surveillance and therefore whether the analysis was appropriate. Another substantive issue was that the final OS estimates for both nivolumab and routine surveillance generated through the surrogacy analysis were underpinned by data from the placebo arm of CA184-029, which probably underestimated OS because more effective follow-on treatments are now available. The committee also considered that the inclusion criteria for the surrogacy analysis were poorly justified, and that the total number of data points contributing to the analysis was small. Furthermore, it noted that the results of the surrogacy analysis were not substantiated by clinical evidence and were based on an estimate of RFS based on an indirect comparison. In summary, the committee concluded that the OS results based on the surrogacy analysis were not robust.

The company's base-case partitioned survival model uses unvalidated methodology

3.8 The company presented 3 models comparing nivolumab with routine surveillance: a partitioned survival model with 3 health states (recurrence

free, post recurrence and death), which was its base case and generated an incremental cost-effectiveness ratio (ICER) of £8,882 per quality-adjusted life year (QALY) gained compared with routine surveillance; and 2 further alternative Markov models (Markov I and Markov II). The company ICERs included a commercial access agreement for nivolumab (in the adjuvant and metastatic setting) and a patient access scheme for ipilimumab in the metastatic setting but did not take account of commercial arrangements for other agents used in the metastatic setting because the discounts agreed with the NHS are commercial in confidence. The committee recognised that, by providing alternative model options, the company showed that it had attempted to investigate some of the uncertainties in its base case. All 3 models had a cycle length of 28 days and a time horizon of 60 years. The committee noted that these aspects of the model designs were not contentious and that the population was in line with the NICE scope. It also noted that the results of Markov I model (ICER: £8,567 per QALY gained) were very similar to the company's base case. However, the Markov II results differed substantially in terms of both the incremental costs and the incremental life year gains. Consequently, the final ICER estimate also differed (£18,685 per QALY gained). The committee considered that the surrogacy method was unvalidated and had several potential flaws. Therefore, the committee's preferred model was Markov II, which was the only one that did not rely on the OS predictions derived from the surrogacy analysis. It considered this model further.

The ERG's base-case ICER in the Markov II model was higher than company's estimates because of different assumptions about subsequent treatments

3.9 The ERG's preferred ICER was based on the Markov II model structure. The company's partitioned survival base-case model assumed that subsequent treatments could be based on CheckMate 238. Specifically, everyone having nivolumab would have the same subsequent treatments as those in the nivolumab arm of CheckMate 238 and everyone having

routine surveillance would have the same subsequent treatments as those in the ipilimumab arm of CheckMate 238. The ERG considered that this may not be the case, and noted that the Markov II design enabled the uncertainty of this assumption to be explored. The ERG considered this particularly important because, in contrast to the partitioned survival model, in which the results of the surrogacy model informed the OS predictions, the OS results of Markov II were heavily influenced by which follow-on treatments were used. In its Markov model II, the company predicted that the proportion of people having immunotherapy for metastatic disease would be lower in the nivolumab arm compared with the routine surveillance arm. It assumed 14% of patients in the nivolumab arm would receive subsequent pembrolizumab or nivolumab, compared with 51% receiving these drugs as subsequent treatments after routine surveillance. The ERG's alternative suggestion was that those who progressed on routine surveillance would have nivolumab, and those who had had adjuvant nivolumab would have ipilimumab. In addition, they incorporated alternative estimates for RFS that were based on censoring for ipilimumab use beyond 1 year in the indirect comparison. Together these adjustments produced an ICER above the level that could be considered a cost-effective use of NHS resources (£32,758 per QALY gained). When commercial access arrangements for all agents used in the metastatic setting the ICER was higher. The committee considered the ERG's adjustments to the company Markov II model and noted that the use of the alternative estimates for RFS only increased the ICER slightly and the main driver of the change in the cost-effectiveness estimate was the different assumptions about subsequent treatments. From this the committee concluded that the robustness of the assumptions about subsequent treatments was a key factor in determining whether the Markov II model was appropriate for decision making.

The company's assumptions about subsequent treatments are not realistic

3.10 The committee asked the experts to consider about how adjuvant nivolumab might affect the likely treatment options for people who went on to develop distant recurrence. The clinical experts agreed with comments submitted by the clinical lead for the Cancer Drugs Fund that this would depend on the timing of relapse. People relapsing early are likely to have ipilimumab alone, whereas rechallenging with PD-1 based therapies would be more likely for people relapsing after 2 years. The clinical experts also noted that assuming people only have one type of treatment for metastatic disease was also potentially misleading as many will have multiple lines of treatment. In particular, it was noted that people with BRAF mutations are likely to have both PD-1-based and BRAF-inhibitor-based treatments. The committee reflected on the company's assumptions about how many people would have nivolumab or pembrolizumab monotherapy after adjuvant treatment (see section 3.9). It noted that the clinical experts considered that the estimates used by the company for further immunotherapy after adjuvant nivolumab were lower than would be expected. The committee concluded that this made the company's estimate of cost effectiveness unreliable. It also recognised the ERG's concern that another major limitation of the Markov II results was that multiple disparate data sources were used to inform post-relapse survival, and that this added to the uncertainty in cost-effectiveness estimates derived from this model.

The committee considered all ICERs presented to be unreliable

3.11 The committee acknowledged that, at present, it was not known what treatments people would have if they developed metastatic disease after nivolumab. Some of the uncertainties in the company's Markov II model applied equally to the ERG's exploratory analysis of the Markov II model; both were based on RFS estimates that were uncertain (see section 3.4) and both relied on transition probability estimates between the recurrence-free and post-recurrence health states which were informed by data

sources that were potentially unreliable. However, the committee considered the assumptions about subsequent treatments to be crucial to decision making (see section 3.10) noting that the estimated use of immunotherapy in the company's Markov II model is too low, resulting in the ICER also being an underestimate. While accepting that the post-progression treatments might not be identical post-nivolumab and post-surveillance, the committee considered that it would be helpful to see a Markov II model that assumed equivalent post-progression treatments in the two arms. This would show how much of the benefit of adjuvant nivolumab is because of a reduction in the number of people progressing to incurable disseminated disease (the main aim of treatment) and how much of the modelled benefit is attributable to different therapies (with different efficacies) being given on progression. It also expressed concern that the company model did not appear to account sufficiently for administration costs, as highlighted by NHS England.

Conclusion

Nivolumab cannot be recommended for the adjuvant treatment of completely resected stage III and IV melanoma

3.12 The committee noted that the clinical effectiveness of nivolumab in terms of OS was very uncertain because the trial is ongoing. Therefore the benefit of changing the strategy for managing completely resected stage III and IV melanoma from routine surveillance to adjuvant nivolumab is as yet unknown. This uncertainty meant that the cost-effectiveness estimates were uncertain. The committee concluded that nivolumab for the adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease cannot be recommended for routine commissioning in the NHS.

Cancer drugs fund

Nivolumab cannot be recommended for use in the CDF

3.13 Having concluded that nivolumab could not be recommended for routine use, the committee considered whether it could be recommended within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. It noted the uncertainties in the clinical-effectiveness data for nivolumab, which related to the treatment benefit compared with routine surveillance. It considered that treatment probably leads to improvements in RFS, but that the size of the effect was uncertain and that no reliable estimate of the OS benefit had been presented by the company. Because of the uncertainty in the underlying clinical evidence, all the cost-effectiveness estimates were considered uncertain, so the committee was unable to conclude that the technology had plausible potential to be cost effective. In particular, the committee considered that, without further scrutiny of the Markov II approach and exploration of other post-progression treatment strategies, the cost effectiveness was highly uncertain. It recognised that it might be possible to resolve some of the clinical uncertainties within the Cancer Drugs Fund, for example, when more mature RFS and OS data from CheckMate 238 becomes available in 2019. Data about the proportion of patients having various subsequent therapies could also be collected within the Cancer Drugs Fund. It also recognised that nivolumab represented a potentially important change in the treatment pathway for melanoma. However, it concluded that a more detailed consideration of the modelling and inputs was needed and a plausible potential for cost effectiveness would need to be demonstrated before it could recommend nivolumab for use in the CDF.

4 Proposed date for review of guidance

4.1 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.

Dr Jane Adam
Chair, Appraisal Committee
August, 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Juliet Kenny

Technical Lead

Eleanor Donegan

Technical Adviser

Thomas Feist

Project Manager

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