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 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?

Issue date: November 2020

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 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: 25 November 2020

Second appraisal committee meeting: 5 January 2021

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

1 Recommendations

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

1.2 This recommendation is not intended to affect treatment with nivolumab that was started in the Cancer Drugs Fund before final guidance was published. For those people, nivolumab will be funded by the company until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This appraisal reviews the evidence collected in the Cancer Drugs Fund for nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (NICE technology appraisal guidance 558).

During the original appraisal, standard care was routine surveillance. Now, dabrafenib with trametinib is an option and pembrolizumab is available through the Cancer Drugs Fund. These treatments are suitable for some people with this disease.

Clinical evidence shows that nivolumab improves survival without the cancer coming back (recurrence-free survival) compared with ipilimumab. There are currently no trials comparing nivolumab with standard care in the NHS. An indirect comparison suggests that nivolumab is likely to improve recurrence-free survival compared with routine surveillance. The data from the Cancer Drugs Fund and the trial are still quite new so it is uncertain if nivolumab increases the length of time people live, or by how much (overall survival).

Because of this uncertainty the cost-effectiveness estimates vary. The most likely estimates are above what NICE considers a cost-effective use of NHS resources. Therefore, nivolumab is not recommended for routine use. Nivolumab will no longer be available in the Cancer Drugs Fund for this indication after final guidance is published, but people already taking it will be able to continue.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) is indicated 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

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

Price

2.3 The list price is £439 per 40 mg/4 ml concentrate for solution for infusion vial; £1,097 per 100 mg/10 ml concentrate for solution for infusion vial; and £2,633 per 240 mg/24 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed October 2020).

2.4 The company has a commercial arrangement. This makes nivolumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

The appraisal committee was aware that an issue was resolved during the technical engagement stage and agreed that the new flat 4-weekly dose of nivolumab is suitable for decision making.

Clinical pathway

Effective adjuvant treatment options for people with completely resected stage 3 and 4 melanoma are needed

3.1 Melanoma often affects people at a younger age than some other cancers. It has a substantial effect on people and their families and carers. Tumour and associated lymph node resection are standard treatment for most people with stage 3 melanoma, and some people with stage 4 melanoma. Until recently standard care for people with completely resected melanoma was routine surveillance. In 2018, NICE's technology appraisal guidance on dabrafenib with trametinib for the adjuvant treatment of BRAF V600 mutation-positive melanoma recommended it for use. In the previous appraisal of nivolumab, NICE recommended it for use within the Cancer Drugs Fund for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease (stage 3 and stage 4 melanoma; NICE technology appraisal guidance 558). Pembrolizumab is also currently recommended for use in NICE's technology appraisal guidance on pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence. It is recommended the adjuvant treatment of stage 3 melanoma with lymph node involvement in adults who have had complete resection. 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. The clinical expert explained that treatments that can be given very early (in the adjuvant setting) seem to show a clear benefit and hopefully will reduce the number of people returning with metastatic disease. The committee agreed that effective adjuvant treatments for people with completely resected stage 3 and 4 melanoma are needed.

Clinical evidence

Nivolumab improves recurrence-free survival compared with ipilimumab however survival data are still immature

3.2 CheckMate 238 is an ongoing multinational randomised double-blind trial. It compared adjuvant nivolumab with adjuvant ipilimumab in 906 patients (aged 18 years or over) who have had complete resection of stage 3B, 3C, or 4 melanoma. The median age was 56 years for patients who had nivolumab. Approximately half of people with adjuvant nivolumab with reported BRAF status had disease without mutations in the BRAF gene (197/384) and 18% had stage 4 disease (82/453). In the original appraisal for nivolumab, patients in CheckMate 238 had been followed for a minimum of 24 months. A statistically significant improvement in recurrence-free survival was seen with nivolumab compared with ipilimumab (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54 to 0.81). Overall survival data were immature. Since the original appraisal, patients in CheckMate 238 have now been followed for a minimum of 48 months. A statistically significant improvement in recurrence-free survival was seen with nivolumab compared with ipilimumab (results are marked as academic in confidence and therefore cannot be presented here). Overall survival data were still immature. Through the Cancer Drugs Fund, systemic anti-cancer therapy data were collected from people having adjuvant nivolumab for resected stage 3 and 4 melanoma. Between 30 November 2018 and 29 October 2019, 284 people had adjuvant nivolumab. The median age was 63 years old. Most people (78%) had disease without mutations in the BRAF gene and 35% had stage 4 disease. Compared with CheckMate 238, the patients were older, fewer had mutations in the BRAF gene and more had stage 4 disease. At the end of the data collection period, 72% of patients were still having treatment. The estimate of median overall survival was not available. The committee understood that because nivolumab is an adjuvant treatment, collection of survival data could take some time and

considered it was positive that overall survival data was still immature for nivolumab. The clinical experts explained that usually if a treatment has a clinically meaningful difference in recurrence-free survival then it was likely that this would be reflected in overall survival. In practice, many patients who had started treatment with nivolumab had done so 18 months ago. A few patients' disease had relapsed early, within a year, but most were still disease free. The committee concluded that nivolumab improves recurrence-free survival compared with ipilimumab. However, it is not known if nivolumab increases the length of time people live, or by how much, because the survival data are still immature.

Although the data on subsequent treatments are still immature, the data from Checkmate 238 reflect clinical practice

3.3 The committee noted that a number of therapies are currently available if the cancer comes back after adjuvant nivolumab (see NICE's Pathway on melanoma). These include immunotherapy (nivolumab with ipilimumab, nivolumab monotherapy, pembrolizumab monotherapy and ipilimumab monotherapy), and targeted therapy for people with disease with mutations in BRAF gene (encorafenib with binimetinib, trametinib with dabrafenib, dabrafenib monotherapy, and vemurafenib monotherapy). Further data on subsequent treatments collected from Checkmate 238 were marked academic in confidence by the company so cannot be included here. The evidence from the Cancer Drugs Fund after use of adjuvant nivolumab is limited, and to date only 14% of people have had subsequent treatments. Most people had nivolumab with ipilimumab (34%), ipilimumab (29%), trametinib with dabrafenib (22%) and encorafenib with binimetinib (15%). However, because the data are immature, they are based on disease that relapsed early, so may not be representative of all completely resected stage 3 and 4 melanoma. The clinical experts stated that the fact that the data are immature is positive, because it suggests that the number of people whose disease comes back after adjuvant nivolumab is low. The clinical experts explained that the choice of subsequent treatment will depend on many factors. They

agreed that most people who can tolerate a combination therapy would be offered nivolumab with ipilimumab after both routine surveillance and adjuvant nivolumab. People who cannot tolerate a combination therapy may be offered monotherapy (the choice of immunotherapy is likely to depend on whether adjuvant nivolumab was given, and, if it was, on the time since the last dose). People with disease with mutations in the BRAF gene may choose targeted therapies because they are less toxic and can be taken orally (immunotherapy is delivered by intravenous infusion). Clinicians agreed that the subsequent treatments in CheckMate 238 are consistent with what would be expected to be used in the clinical practice. The committee concluded that subsequent treatment data are still immature but that data from CheckMate 238 reflect clinical practice.

Indirect comparison of nivolumab with routine surveillance

Despite changes to the classification of the disease, the patients in the trials are similar to patients in the NHS

3.4 No trial directly compared nivolumab with routine surveillance in the adjuvant setting. The company did an indirect comparison using individual patient data for recurrence-free survival and overall survival from the CheckMate 238 and CA184-029 trials. CA184-029 is an multinational randomised double-blind trial. It compared ipilimumab with placebo in 951 patients (aged 18 years or over) with high-risk stage 3 cutaneous melanoma who had had complete regional lymph node dissection. CA184-029 trial did not include any patients with stage 4 disease, while CheckMate 238 does not include patients with stage 3A disease. However, the new American Joint Committee on Cancer (AJCC) 8th edition criteria mean that some patients with stage 3B disease in CheckMate 238 could now be classed as having stage 3A disease. The clinical experts noted that CA184-029, CheckMate 238 and KEYNOTE 054 (an ongoing trial of adjuvant pembrolizumab compared with placebo in patients with resected high-risk stage 3 melanoma) show similar results across all disease stages. They stated that in practice,

people with all these stages of disease would be treated the same way. The committee concluded that the difference in the staging of disease in the trials was not too much of a concern because the patients in the trials were similar to those seen in the NHS.

Censoring of overall survival is preferred in the indirect treatment comparison

3.5 Patients in CheckMate 238 had ipilimumab up to 1 year, while patients had ipilimumab up to 3 years in CA184-029. Therefore patients from CA184-029 who had treatment with ipilimumab beyond 1 year were excluded (censored) in the analysis of recurrence-free survival in the original appraisal of nivolumab. This is because the longer duration of ipilimumab treatment in CA184-029 could result in a more optimistic indirect comparison for nivolumab. In this appraisal, the company's fitted parametric curves with censoring suggested that nivolumab is likely to improve recurrence-free survival compared with routine surveillance. The results of the indirect comparisons were marked academic in confidence by the company so cannot be included here. The company used the censored analysis for recurrence-free survival, but not for overall survival. It explained that censoring excluded patients with the best prognosis introduced large informative censoring (excluding patients because of reasons related to the trial results in biased estimates). Therefore, the company did not consider that censoring was suitable for overall survival. The company also considered that the number of censored patients was too large. The ERG agreed that censoring was likely to bias the indirect comparison against nivolumab. However, it noted that 25% of patients in CA184-029 had ipilimumab for more than 1 year (and 13% of patients had ipilimumab for 3 years). The ERG preferred the censored analysis (reflecting the ipilimumab regimen in CheckMate 238) of overall survival. The committee considered the difference in ipilimumab treatment duration of the 2 trials to be a limitation of the indirect comparison. It agreed that the censored analysis is likely to be biased towards routine surveillance and viewed it as a conservative scenario. However, for consistency with

recurrence-free survival, the committee concluded that the censored overall survival analysis is preferred.

The company's economic models

The partitioned survival model is preferred

3.6 Because of immature survival data, 2 models, a partitioned survival model and a state transition model, were considered in the original appraisal of nivolumab. During this appraisal, an indirect comparison was done for both recurrence-free survival and overall survival. However, only the partitioned survival model used the overall survival data. The state transition model based post-recurrence survival on weighted subsequent treatment-specific survival data obtained from published sources. This meant that it included a number of assumptions to estimate post-recurrence survival. The ERG noted that the estimates of life years for recurrence-free survival from the state transition model were different to the partitioned survival model. This was despite both using the same CheckMate 238 data, which suggested that the state transition model lacked face validity. The ERG therefore considered only the partitioned survival model for its preferred base case. The company agreed that there are limitations to estimating post-recurrence survival from the literature. However, they explained that the state transition model offers an alternative approach that is not based on the immature overall survival data from CheckMate s238. They stated that both models should be explored because they were both considered in the original appraisal of nivolumab. The committee noted that both models had their strengths and limitations. Because the main uncertainty was the modelling of overall survival (see sections 3.2, 3.5 and 3.7), and only the partitioned survival model allowed exploration of assumptions around the CheckMate 238 overall survival data extrapolation, the committee concluded that the partitioned survival model was preferred.

Survival modelling in the partitioned survival model

Because overall survival is highly uncertain, the committee preferred the more conservative approach taken by the ERG

3.7 In the original appraisal of nivolumab, overall survival in the placebo group in CA184-029 was not considered to reflect that of routine surveillance because of advances in subsequent treatments since the trial started. In this appraisal, the company extrapolated the overall survival data from the indirect comparison for 10 years and used the American Joint Committee on Cancer data for long-term survival (the same as the extrapolation of recurrence-free survival). Subsequent treatments were based on treatments in the ipilimumab and nivolumab arm in CheckMate 238. The committee noted that data from CheckMate 238 reflect clinical practice (see section 3.3). Because of the uncertainties around the overall survival estimates, the ERG explored assumptions about improvements in overall survival for routine surveillance in line with advancements in treatments for disease recurrence. Their 2 approaches both assumed the hazard of death for routine surveillance and adjuvant nivolumab was set to be the same after 2 years (for example, that survival for routine surveillance is the same as survival for nivolumab after 2 years). However, one approach assumed the same treatments for routine surveillance and adjuvant nivolumab, based on the subsequent treatments in the nivolumab arm in CheckMate 238. The other approach assumed that nivolumab (for simplification to represent immunotherapy treatment) would be the subsequent treatment for all people having routine surveillance. In both approaches, nivolumab subsequent treatments were based on treatments in the nivolumab arm in CheckMate 238. The company considered that assuming nivolumab as a subsequent treatment for all people on routine surveillance is incorrect. After technical engagement, the company explored an alternative hazard of death assumption in a scenario based on median recurrence-free survival for nivolumab (assuming the same hazard of death at a later time point than the ERG's scenario; median

recurrence-free survival is marked as academic in confidence and therefore cannot be presented here) and based subsequent treatments on the nivolumab arm in CheckMate 238. The company also stated that the state transition model may be more appropriate to explore post-recurrence survival. It presented a state transition model scenario based on pooled CheckMate 238 post-recurrence survival data and noted that this scenario does not use data from CA184-029. The committee considered the approaches presented by the ERG and company. It focused on the analyses using the partitioned survival model (see section 3.6). The committee agreed that the assumptions in the company's base case were likely to be too optimistic. This was because of uncertainties in the overall survival extrapolation due to advances in subsequent treatments in routine surveillance. The committee recognised the ERG's approaches, assuming the same hazard of death at 2 years, were likely to be conservative, and potentially biased against nivolumab. However, the committee concluded that because of the uncertainty around overall survival, it preferred the ERG's more conservative approach.

Cost-effectiveness results

The cost-effectiveness estimates are uncertain, but they are higher than what NICE considers cost effective

3.8 The committee considered the cost-effectiveness estimates, which included the confidential patient access schemes for nivolumab and ipilimumab. It noted the company's base case resulted in incremental cost-effectiveness ratios (ICERs) from £14,301 per quality-adjusted life year (QALY) gained to £16,171 per QALY gained for the partitioned survival model and state transition model respectively. The committee noted that the ERG's scenarios using the partitioned survival model resulted in a range of ICERs:

- Scenario 1: applying censoring for overall survival indirect comparison resulted in an ICER of £17,404 per QALY gained.

- Scenario 2: assuming that the hazard of death for routine surveillance and adjuvant nivolumab is the same after 2 years, and subsequent treatments for nivolumab and routine surveillance are based on treatments given in the nivolumab arm in CheckMate 238, resulted in an ICER of £28,809 per QALY gained.
- Scenario 3: assuming that the hazard of death for routine surveillance and adjuvant nivolumab is the same after 2 years; that subsequent treatments for nivolumab are based on treatments given in the nivolumab arm in CheckMate 238; and subsequent treatment for routine surveillance is nivolumab (representing immunotherapy), resulted in an ICER of £40,009 per QALY gained.
- Scenario 4: applying censoring for overall survival indirect comparison, and the same hazard of death for routine surveillance and adjuvant nivolumab after 2 years with subsequent treatments for nivolumab and routine surveillance based on the nivolumab arm in CheckMate 238 (Scenario 1 and 2) resulted in an ICER of £37,371 per QALY gained.
- Scenario 5: applying censoring for overall survival indirect comparison and the same hazard of death for routine surveillance and adjuvant nivolumab after 2 years, subsequent treatments for nivolumab are based on treatments given in the nivolumab arm in CheckMate 238, and subsequent treatment for routine surveillance is nivolumab (Scenario 1 and 3) resulted in an ICER of £52,012 per QALY gained.

The committee noted there was considerable uncertainty around the assumptions of overall survival and subsequent treatments in the model and therefore in the resulting ICERs. NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

When the committee took into account all the confidential patient access schemes for subsequent treatments and the committee's preferences of the censoring of overall survival (see section 3.5) and the same hazard of death for routine surveillance and adjuvant nivolumab after 2 years (see section 3.7), then the resulting ICERs were all over £30,000 per QALY gained. The committee concluded that all the ICERs are higher than what NICE considers a cost-effective use of NHS resources.

Cancer Drugs Fund

Nivolumab cannot remain in the Cancer Drugs Fund

3.9 The aim of a Cancer Drugs Fund guidance review is to decide whether or not the drug can be recommended for routine use. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease may not remain in the Cancer Drugs Fund once the guidance review has been completed (see section 6.19 of the guide to the processes of technology appraisal).

Conclusion

Nivolumab is not recommended for routine use

3.10 The committee concluded that the most plausible estimates are higher than what NICE considers a cost-effective use of NHS resources. Therefore nivolumab is not recommended for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.

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.

Brian Shine
Chair, appraisal committee
November 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

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.

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.

Marcela Haasova
Technical lead

Joanna Richardson
Technical adviser

Thomas Feist
Project manager

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