

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

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

1 Recommendations

- 1.1 Nivolumab is recommended, within its marketing authorisation, as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease. It is recommended only if the company provides nivolumab according to the commercial arrangement (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease ([NICE technology appraisal guidance 558](#)).

Until recently, standard care for people with completely resected melanoma was routine surveillance. Adjuvant immunotherapies such as dabrafenib with trametinib or pembrolizumab alone are now available for some people.

Clinical evidence shows that adjuvant nivolumab increases how long people live without the cancer coming back compared with adjuvant ipilimumab (an immunotherapy that is not used in the NHS). There are no trials directly comparing nivolumab with standard care in the NHS. But an indirect comparison suggests that people taking nivolumab are likely to live longer before the cancer comes back than with routine surveillance. There are still not enough data from the Cancer Drugs

Fund and the trial to be certain by how much nivolumab increases the length of time people live.

Because of the uncertainty the cost-effectiveness estimates vary. However, the most likely estimates are within what NICE considers a cost-effective use of NHS resources. Therefore, nivolumab is recommended.

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. 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 for 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 the people with known BRAF status who had adjuvant nivolumab 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 (HR 0.71, 95% CI 0.60 to 0.86). Overall survival data were still immature (HR 0.87; 95% CI 0.66 to 1.14). 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. 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 were still immature for nivolumab. The clinical experts explained that 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. Because the trial data are more mature there is a greater degree of certainty with these data than with the data from the Cancer Drug Fund. Clinical experts explained that the subsequent treatments given in the nivolumab arm reflect what is currently used in clinical practice. The committee concluded that subsequent treatment data are still immature but that data from the nivolumab arm of 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 a 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. In response to the appraisal consultation document, the company reiterated that it did not consider that censoring is needed but included analyses both with, and without censoring of ipilimumab. The committee continued to prefer the censored analysis and concluded that, although conservative, for consistency with recurrence-free survival, 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 238. 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

Overall survival is highly uncertain therefore assuming the same hazard of death at 3 to 5 years is appropriate for decision making

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 response to the appraisal consultation document, the company provided new analyses using a partitioned survival model only. It 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). The company did not consider that the ERG's scenarios, (which the committee had preferred and that assumed the same hazard of death for routine surveillance and adjuvant nivolumab after 2 years), were clinically plausible. Patients having routine surveillance were predicted to have lower risk of death than those having ipilimumab after 2 years (contradicting the data in CA184-029). In the company's response to consultation, it presented several analyses suggesting that assuming the same hazard at 2 years is not appropriate (analyses are marked as academic in confidence and therefore cannot be presented here). It considered that the minimum time point should be 4 years (the minimum

follow up in CheckMate 238) and presented a range of scenarios assuming the same hazard of death at 3 to 10 years. The ERG agreed with the company, that based on the new analyses, assuming equal hazard of death at 2 years is too conservative. It considered the company's minimum time point of 3 years, with exploratory analyses up to 5 years (which covers the most recent data cut for CheckMate 238) to be a plausible range. The ERG noted that the timepoint that limits the uncertainty the most is 3 years. The clinical expert considered that the effect of nivolumab on overall survival is likely to last after the 4 years of the minimal follow up in CheckMate 238. The committee concluded that because of the uncertainty around overall survival, the ERG's preferred range of 3 to 5 years is appropriate for decision making. However, it noted that the lower bound of the range may be too conservative.

Subsequent treatments, after equal hazard of death is assumed in the model, are based on treatments in the nivolumab arm in CheckMate 238

3.8 In the ERG's 2 scenarios which assumed the same hazard at 2 years and were considered at the first committee meeting, 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. Subsequent treatments for routine therapy were based on the ipilimumab arm in CheckMate 238 before the same hazard was assumed. The company considered that assuming nivolumab as a subsequent treatment for all people on routine surveillance is incorrect. It based subsequent treatments on CheckMate 238 and after the equal hazard of death is assumed, subsequent treatments for both nivolumab and routine surveillance are based on the nivolumab arm in CheckMate 238, so the same cost and benefits are applied to both arms. After consultation on the appraisal

document, the ERG agreed with the company's choice of subsequent treatment based on committee's preference (see section 3.3). However, it did state that in clinical practice, using immunotherapies for patients whose disease has relapsed during routine surveillance is likely to be higher than for patients whose disease has relapsed on nivolumab. This was explored in 2 illustrative scenarios. The committee concluded that the company's approach after the equal hazard of death is assumed, using the subsequent treatments used in the nivolumab arm from CheckMate 238 for both nivolumab and routine surveillance is appropriate.

Cost-effectiveness results

The cost-effectiveness estimates are uncertain and vary based on the assumptions around the same hazard of death and censoring of the indirect comparison

3.9 The committee considered the revised cost-effectiveness estimates submitted by the company. These included the confidential patient access schemes for nivolumab and ipilimumab but did not include the patient access schemes for subsequent treatments. The company presented a range of incremental cost-effectiveness ratios (ICERs) which explored different assumptions around: equal hazards of death for the nivolumab and routine surveillance arms ranging from 3 years to 10 years (see section 3.7); and uncensored and censored ipilimumab arm indirect comparison (see section 3.5). All the scenarios in the company's model used the subsequent treatments for nivolumab and routine surveillance, after the same hazard of death is assumed, and are based on treatments given in the nivolumab arm in CheckMate 238 (see section 3.8). The company's base case (uncensored indirect comparison and assuming the same hazard of death at 10 years) resulted in an ICER of £14,301 per quality-adjusted life year (QALY) gained. The ICER that was considered the most conservative in the range presented by the company was the censored indirect comparison, assuming the same hazard of death at

3 years, which resulted in an ICER of £29,011 per QALY gained. The ERG's most plausible ICER was the company's highest ICER (£29,011 per QALY gained). The committee agreed that there was uncertainty around the hazard of death (see section 3.7) but concluded that the highest plausible ICER, which could be considered the most conservative, was £29,011 per QALY gained, noting this did not include the discounts for subsequent treatments used in the model.

The most likely estimate is within the range NICE considers a cost-effective use of NHS resources.

3.10 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 3 to 5 years (see section 3.7), then most of the resulting ICERs were less than £30,000 per QALY gained. The committee noted that both the censoring (see [section 3.5](#)) and the lower bound of the same hazard range at 3 years (see section 3.7) are conservative scenarios. Therefore, the committee concluded that the most likely ICER is within the range NICE considers a cost-effective use of NHS resources.

Conclusion

Nivolumab is recommended for routine use

3.11 The committee concluded that the most plausible estimates are within the range NICE considers a cost-effective use of NHS resources. Therefore, nivolumab is recommended for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.

4 Implementation

4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information](#)

[Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has completely resected melanoma with lymph node involvement or metastatic disease and the doctor responsible for their care thinks that nivolumab is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. 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

February 2021

6 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.

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