NICE National Institute for Health and Care Excellence

NICE guidance

Nivolumab for treating advanced (unresectable or metastatic) melanoma

Technology appraisal guidance
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1 Recommendations

1.1 Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults.

2 The technology

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) is a human monoclonal antibody (immunoglobulin G4) that blocks the programmed cell death-1 receptor (PD-1). This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Nivolumab has a marketing authorisation as monotherapy 'for treating advanced (unresectable or metastatic) melanoma in adults'. It is administered intravenously over 60 minutes at a dose of 3 mg/kg every 2 weeks. The summary of product characteristics recommends that 'treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated'.

2.2 The most common (occurring in 15% or more of people) adverse reactions with nivolumab in clinical trials of advanced melanoma were fatigue, rash, itching, diarrhoea, and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The acquisition cost of nivolumab is £439 per 4 ml (40 mg) vial and £1,097 per 10 ml (100 mg) vial (excluding VAT; company's submission). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The Appraisal Committee 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.

Clinical effectiveness

3.1 The company presented evidence from 3 ongoing phase 3 randomised controlled trials (RCTs; CheckMate-066, CheckMate-067 and CheckMate-037). These trials evaluated the clinical effectiveness of nivolumab monotherapy, administered intravenously (IV) every 2 weeks at a dose of 3 mg per kg of body weight. The company also included a phase 1 dose escalating study (CheckMate-033) as supporting evidence.

3.2 CheckMate-066 was a multicentre, international (no centres in the UK), double-blind RCT that compared nivolumab (n=210) with dacarbazine 1,000mg/m^2 IV every 3 weeks (n=208), in people with untreated advanced melanoma without a BRAF mutation. CheckMate-067 was a multicentre, international (7 UK centres), double-blind RCT that compared nivolumab monotherapy (n=316) or nivolumab combined with ipilimumab (n=314) with ipilimumab monotherapy 3mg/kg IV every 3 weeks (n=315) in people with untreated advanced melanoma with and without the BRAF mutation. The company did not present results for the nivolumab plus ipilimumab arm because it is outside the scope of this appraisal. CheckMate-037 was a multicentre, international (5 UK centres), open-label RCT that compared nivolumab (n=272) with the investigators' choice of chemotherapy (n=133), in people with BRAF mutation-negative advanced melanoma that progressed on or after ipilimumab, and BRAF mutation-positive advanced melanoma that progressed on or after ipilimumab and a BRAF inhibitor (vemurafenib or dabrafenib). The investigators' choice of chemotherapy was dacarbazine or carboplatin plus paclitaxel.

3.3 The company stated that baseline demographics and disease characteristics were generally well balanced across the trials, with the exception of a higher proportion of patients with a history of brain metastases (19.5% compared with

13.5%) and elevated LDH (51.1% compared with 34.6%) in the nivolumab arm of CheckMate-037.

3.4 Overall survival data were only available from CheckMate-066. In CheckMate-067 and 037 the minimum follow-up period was not reached or an insufficient number of events (deaths) had occurred at the time of analysis. Overall survival from CheckMate-066 was based on an interim analysis at a median follow-up of 8.9 months in the nivolumab group and 6.8 months in the dacarbazine group. In the nivolumab group 50 out of 210 (23.8%) of patients had died at the time of the analysis therefore median overall survival could not be estimated. Patients in the dacarbazine group had a median survival of 10.8 months. The corresponding hazard ratio for death in the nivolumab group compared with the dacarbazine group was 0.42 (95% confidence interval [CI]: 0.30 to 0.60).

3.5 All 3 trials reported progression-free survival, defined as the time interval between randomisation and disease progression or death. Nivolumab was associated with statistically significant increases in progression-free survival, compared with dacarbazine and ipilimumab in CheckMate-066 and 067 respectively. However, in CheckMate-037 there was no statistically significant difference in progression-free survival between nivolumab and the comparator (investigators' choice of chemotherapy); see table 2 for results. The company stated that the results from CheckMate-037 were confounded by immaturity of the data, imbalances in the prognostic factors between trial groups, high withdrawal rates in the comparator arm and false-positive progression assessments in the nivolumab arm resulting from the use of Response Evaluation Criteria in Solid Tumours (RECIST criteria).

Table 1 Clinical-effectiveness outcomes from the CheckMate trials: overall survival

Outcomes	Nivolumab	Comparator	Hazard ratio (95% CI)	p value
Events (death) % CheckMate-066 (nivolumab [n=210] vs dacarbazine [n=208])	23.8	46.2	0.42 (0.30 to 0.60)	<0.001
Median survival (months) CheckMate-066 (nivolumab [n=210] vs dacarbazine [n=208])	Not reached	10.84	Not applicable	Not applicable

Table 2 Clinical-effectiveness outcomes from the CheckMate trials: progression free survival

Outcomes	Nivolumab	Comparator	Hazard ratio (95% CI)	p value
Events (death or progression), % CheckMate-066 (nivolumab [n=210] vs dacarbazine [n=208])	51.4	78.4	0.43 (0.34 to 0.56)	<0.001
Median PFS (months) CheckMate-066 (nivolumab [n=210] vs dacarbazine [n=208])	5.06	2.17	–	<0.05
Events (death or progression) % CheckMate-067 (nivolumab [n=316] vs ipilimumab [n=315])	55.1	74.3	0.57 (0.43 to 0.76)	<0.001
Median PFS (months) CheckMate-067 (nivolumab [n=316] vs ipilimumab [n=315])	6.9	2.9	–	<0.05
Events (death or progression) % CheckMate-037 (nivolumab [n=122] vs investigators' choice of chemotherapy [n=60])	58.2	43.3	0.82 (99.99% CI 0.32 to 2.05)	Not significant
Median PFS (months) CheckMate-037 (nivolumab [n=122] vs investigators' choice of chemotherapy [n=60])	4.67	4.24	–	Not significant

Abbreviations: CI, confidence interval; n, number; PFS, progression free survival; vs, compared with.

3.6 The objective response rate (defined as the proportion of patients with complete or partial response assessed by RECIST criteria) was the primary outcome in CheckMate-037 and a secondary outcome in CheckMate-066 and CheckMate-067. Patients treated with nivolumab had statistically significantly better objective response rate than in the comparator arms in all trials.

3.7 The company included health-related quality of life results only from CheckMate-066. EQ-5D utility index scores and EORTC QLQ-C30 global health status scores were higher at baseline and for the entire period of observation for nivolumab compared with dacarbazine. However, there was no improvement in quality of life from baseline in the nivolumab arm, or a consistent difference in quality of life between nivolumab and dacarbazine.

3.8 The company presented a series of a priori subgroup analyses from the trials, showing improved effectiveness of nivolumab compared with dacarbazine and ipilimumab across most subgroups. Subgroup analyses by BRAF mutation status in CheckMate-067 and Checkmate-037 showed that nivolumab was more effective than the comparator treatments in both subgroups (people with or without BRAF mutation). However, the magnitude of the effect was higher in the subgroup without BRAF mutation. For example, in the nivolumab group of CheckMate-067, median progression-free survival was 7.89 months in people with BRAF mutation-negative melanoma and 5.62 months in people with BRAF mutation-positive melanoma. The median progression-free survival in the ipilimumab group was 2.83 months in people with BRAF mutation-negative melanoma and 4.04 months in people with BRAF mutation-positive melanoma. Subgroup analyses based on the expression of programmed death receptor ligand 1or PD-L1 (defined as PD-L1 positive if 5% or more cells expressed PD-L1, and PD-L1 negative or indeterminate with less than 5% expression) showed nivolumab to be more effective than the comparators regardless of PD-L1 expression. The results were comparatively better in patients who were PD-L1 positive than in the patients who were PD-L1 negative or indeterminate.

3.9 The company also included evidence from a non-randomised, dose-escalation study (CheckMate-003) of nivolumab in patients with solid tumours, including melanoma (n=107), to support the assumption of the maximum treatment duration with nivolumab of 2 years. In patients with advanced melanoma treated with the licensed dose of nivolumab (n=17), median overall survival was 20.3 months and median duration of response to treatment was approximately 2 years.

3.10 The company presented adverse event data from all 3 trials. Fewer people treated with nivolumab had treatment-related adverse events, particularly of grade 3 to 4, than those treated with the comparators in all 3 trials. The company

also highlighted that in CheckMate-067 nivolumab was associated with a favourable safety profile compared to ipilimumab, particularly for common immune system related adverse events.

3.11 The company compared the clinical effectiveness of nivolumab, indirectly, with the comparators listed in the scope using 2 separate networks; for BRAF mutation-negative advanced melanoma (compared with ipilimumab and dacarbazine) and BRAF mutation-positive advanced melanoma (compared with BRAF inhibitors vemurafenib and dabrafenib). The company used patient-level data (for nivolumab, dacarbazine and ipilimumab) or estimated 'pseudo' patient-level data (for vemurafenib and dabrafenib) from the trials. It selected the best-fitting survival function for the outcomes needed for economic modelling after adjusting for covariates for each treatment arm.

Cost effectiveness

3.12 The company submitted a semi-Markov survival model to estimate the cost effectiveness of nivolumab in people with previously untreated advanced (unresectable, metastatic) melanoma. The economic analyses were presented separately for BRAF mutation-negative disease (compared with dacarbazine and ipilimumab) and BRAF mutation-positive disease (compared with dabrafenib, ipilimumab and vemurafenib). The model had 3 health states: pre-progression, progression and death. Utility in the progression-free and progressed states was subdivided into 2 further states: 30 days or more before death; and less than 30 days before death. For modelling resource use, the entire time horizon was divided in to 4 periods: first year after treatment initiation; second year after treatment initiation; third and subsequent years after treatment initiation; and 12 weeks before death. The model adopted a lifetime time horizon of 40 years and a cycle length of 1 week. The model perspective was NHS and personal social services and costs and benefits were discounted at a rate of 3.5% per year.

3.13 The company based the patient characteristics in the model on CheckMate-066 for BRAF mutation-negative disease and from the vemurafenib arm of BRIM-3 for BRAF mutation-positive disease. The model allowed subsequent treatment with ipilimumab for people having nivolumab and other comparator treatments except ipilimumab. In the base case, 29.7% and 22.0% people with

BRAF mutation-negative and BRAF mutation-positive melanoma respectively, had subsequent ipilimumab treatments.

3.14 In the model, the clinical-effectiveness estimates for nivolumab and dacarbazine were based on patient-level data from CheckMate-066. For ipilimumab, patient-level data from the MDX010-20 trial were used. MDX010-20 was a phase 3 trial that evaluated the efficacy of ipilimumab in people with previously treated advanced melanoma. For BRAF inhibitors, the company identified 2 trials; BRIM-3 and BREAK-3. Both were phase 3 trials that evaluated vemurafenib and dabrafenib respectively, in people with BRAF mutation-positive advanced melanoma. The company generated pseudo patient-level data from published Kaplan–Meier curves for BRAF inhibitors based on the vemurafenib BRIM-3 (base case) or dabrafenib BREAK-3 (scenario analysis) and assumed that both are equally effective. The company considered the log-normal and generalised gamma distributions to be the best fit for overall survival and progression-free survival respectively, for BRAF inhibitors. The company used the same methods for deriving transition probabilities in BRAF mutation-positive disease as it did in BRAF mutation-negative disease, except that the baseline patient characteristics for the BRAF mutation-positive disease were taken from the BRIM-3 trial.

3.15 Time to progression was modelled using Kaplan–Meier data from CheckMate-066 (for nivolumab and dacarbazine) and from MDX010-20 (for ipilimumab) for the first 100 days, followed by fitted parametric curves using the Gompertz distribution in the base case. For pre-progression survival, the company used Kaplan–Meier data adjusted by covariates for the length of follow-up because none of the fitted curves provided an acceptable visual fit to the observed data.

3.16 The company applied survival data from the trials in the model for the first 3 years for nivolumab and ipilimumab, and for the first 2 years for dacarbazine and BRAF inhibitors. Long-term overall survival was modelled using the registry data from the American Joint Committee on Cancer for BRAF inhibitors and dacarbazine. For modelling long-term survival in patients treated with nivolumab and ipilimumab, the company used pooled data on survival from 12 ipilimumab studies as reported by Schadendorf et al (2015) and applied these from year 3 onwards for nivolumab and ipilimumab. The company also applied mortality data for England as background mortality in the model.

3.17 For 'time on treatment' with nivolumab, a log-logistic parametric curve was fitted to the CheckMate-066 trial data to calculate the proportion of patients continuing to have nivolumab in each cycle. The base case assumed maximum duration of treatment with nivolumab of 2 years. The model estimated that at 2 years, 23% of patients with BRAF mutation-negative melanoma and 20% of patients with BRAF mutation-positive melanoma would still be having nivolumab. The treatment effect of nivolumab was assumed to be maintained on discontinuation of therapy in the base case, based on observational data from CheckMate-003 and UK clinical expert opinion. This assumption was tested in scenario analyses. For dabrafenib, vemurafenib and dacarbazine the model assumed that treatment would continue until disease progression, in accordance with the marketing authorisations. The company stated that although ipilimumab is usually given for a maximum of 4 doses, patients could have ipilimumab for up to 16 doses (4 doses for the induction and up to 12 further doses if needed, based on the design of MDX010-20).

3.18 The model included adverse events for endocrine disorder (any grade), diarrhoea (grade 2+) and other adverse events (grade 3+), based on data from CheckMate-066 for nivolumab and dacarbazine, and CheckMate-067, BREAK-3 and BRIM-3 trials for ipilimumab, dabrafenib and vemurafenib respectively.

3.19 The company used EQ-5D values from CheckMate-066, using regression analysis to estimate utility values for health states in the model. The values used for each stage (pre-progression and post progression) depended upon time to death (30 days or more and less than 30 days):

- pre-progression stage and 30 days or more from death, 0.8018
- pre-progression stage and less than 30 days from death, 0.7795
- post-progression stage and 30 days or more from death, 0.7277
- post-progression stage and less than 30 days from death, 0.7054.

3.20 The modelled utility decrements for adverse events were based on Beusterien et al., 2009. These were applied at the start of the model and then periodically to patients who were still on treatment after every 35 weeks.

3.21 The resource use categories in the model were treatment costs, health-state

resource-use costs and cost for treating adverse events. The same sources were used for estimating these costs in a recent NICE technology appraisal of ipilimumab for previously untreated advanced melanoma. Resource use for health states was estimated based on the MELODY observational study that collected data on resource use in patients with advanced melanoma. Other costs were sourced from MIMS, NHS reference costs 2013 to 2014, and Personal Social Services Research Unit (PSSRU) 2014.

3.22 The company presented base-case results using the list prices for all drugs (see tables 3 and 4). In the company's base-case analyses, nivolumab provided a total of 4.31 and 4.27 quality-adjusted life years (QALYs) in the BRAF mutation-negative melanoma and BRAF mutation-positive melanoma groups respectively. When compared with ipilimumab the absolute increment in QALY gained with nivolumab was 1.67 and 1.82 for BRAF mutation-negative melanoma and BRAF mutation-positive melanoma respectively. The fully incremental comparisons with all comparators demonstrated that for BRAF mutation-negative melanoma, ipilimumab was extendedly dominated (that is, it had an incremental cost effective ratio [ICER] relative to dacarbazine, higher than that of the next most effective strategy, nivolumab). Nivolumab had an ICER of £23,583 per QALY gained compared with dacarbazine (see table 3). Similarly, in BRAF mutation-positive melanoma nivolumab dominated (that is, provided more QALYs at lower cost than) both dabrafenib and vemurafenib. Nivolumab was more costly and more effective than ipilimumab, with an ICER of £7,346 per QALY gained (see table 4). Because ipilimumab, vemurafenib and dabrafenib are recommended by NICE only with patient access schemes, these results were not used for decision-making and are included here for illustration only. The ERG re-ran these analyses incorporating the confidential discounted prices agreed in the patient access schemes for all 3 comparators; these results are commercial in confidence and cannot be reported here.

3.23 The company's deterministic sensitivity analyses showed that results were most sensitive to changes in the parameters defining the fitted parametric curves, time on treatment, utility parameters and administration cost.

ERG comments

3.24 The ERG considered that the CheckMate trials were well designed and well conducted and provide appropriate evidence for the clinical effectiveness of nivolumab. The ERG noted that the results (notably for overall survival) presented by the company were interim and therefore uncertain.

3.25 The ERG agreed with the company that differences between the trials would not allow a meaningful meta-analysis, particularly because there was not a common comparison group. The ERG expressed concern about 2 of the clinical assumptions underlying the indirect treatment comparison; that previous melanoma treatment experience does not have an independent impact on treatment effect in advanced melanoma, and that there is no difference between treatment effects by BRAF mutation status.

3.26 The ERG commented that the structure of the model was consistent with the disease pathway and that the methods applied in the economic analyses were appropriate and followed the methodological guidance stipulated in the NICE reference case. The ERG noted that the company presented economic analyses only for previously untreated melanoma although the marketing authorisation includes people who have had previous treatment.

3.27 The ERG did not agree with all of the company's modelling assumptions and noted that there is considerable uncertainty in the cost-effectiveness results because of the assumptions made, particularly for long-term overall survival and time on treatment for nivolumab.

3.28 The ERG did not agree with the company's assumption that patients having nivolumab would have similar long-term survival as those having ipilimumab. It commented that extrapolation of survival data from CheckMate-66 would have been the most appropriate method for estimating long-term survival. In exploratory analyses the ERG extrapolated long-term survival for nivolumab using a Gompertz distribution in its preferred scenario (see tables 3 and 4).

3.29 The ERG did not agree with the company's choice of survival curve used in the model for time to progression for nivolumab. The ERG suggested that other survival curves (instead of Gompertz) may be plausible for nivolumab, and it used

a Weibull distribution (best visual fit) in its preferred scenario (see tables 3 and 4).

3.30 For BRAF mutation-positive melanoma, the ERG noted that the total cost for the BRAF inhibitors in the model depended on the type of survival curve chosen to model their effect on progression-free survival. The company used a generalised gamma curve; the ERG explored other survival curves for the BRAF inhibitors and considered a log-normal distribution to be the best fit for its preferred scenario (see table 4).

3.31 The ERG conducted exploratory analyses that included using alternative survival functions for time to progression for nivolumab, and for progression-free survival for BRAF inhibitors (vemurafenib and dabrafenib). The ERG also explored using extrapolated survival data from CheckMate-066 to model long-term survival for nivolumab.

3.32 The ERG's preferred scenario included a combination of some of the scenarios mentioned in sections 3.28, 3.29 and 3.30:

- a Weibull distribution for time to progression for the nivolumab arm
- a lognormal distribution for progression-free survival for BRAF inhibitors (vemurafenib and dabrafenib)
- a Gompertz distribution for extrapolated trial data, for long-term overall survival for the nivolumab arm.

3.33 The ERG explored the effect of 2 alternative assumptions for maximum treatment duration with nivolumab on its preferred scenario: 3 years, or no maximum treatment duration.

3.34 The results of the ERG exploratory analyses are summarised in tables 3 and 4. Please note that all analyses presented here used the list price for comparators and were not used in the decision making process.

Table 3 Results of the company's base-case analysis and the ERG's exploratory analyses for BRAF mutation-negative melanoma (using the list price for all comparators)

Technology	Incremental costs £	Incremental QALYs	ICER (£/QALY)
Company's base-case analysis: Dacarbazine	–	–	–
Company's base-case analysis: Ipilimumab	£48,429	1.41	Extendedly dominated by dacarbazine and nivolumab
Company's base-case analysis: Nivolumab	£72,578	3.08	£23,583
Nivolumab (Weibull for TTP) **ERG exploratory analyses**	£72,237	2.73	£18,117
Nivolumab (extrapolated long-term OS from trial) **ERG exploratory analyses**	£70,761	2.02	£36,072
ERG preferred scenario (see section 3.32) **ERG exploratory analyses**	£69,725	1.32	Dominated by ipilimumab
ERG preferred scenario + nivolumab for 3 years **ERG exploratory analyses**	£84,257	1.31	Dominated by ipilimumab
ERG preferred scenario + no maximum treatment duration for nivolumab **ERG exploratory analyses**	£155,177	1.28	Dominated by ipilimumab

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life years; TTP, time to progression.

Dominated: provides fewer QALYs at greater cost than the comparator. Extendedly dominated: a combination of 2 of its comparators provides equal health at a reduced cost.

Table 4 Results of the company's base-case analysis and the ERG's exploratory analyses for BRAF mutation-positive melanoma (using the list price for all comparators)

Technology	Incremental costs £	Incremental QALYs	ICER (£/QALY)
Ipilimumab **Company's base-case analysis**	–	–	–
Nivolumab **Company's base-case analysis**	£13,374	1.82	£7,346
Dabrafenib **Company's base-case analysis**	£6,228	−2.57	Dominated by nivolumab
Vemurafenib **Company's base-case analysis**	£24,659	−2.56	Dominated by nivolumab
Nivolumab (Weibull for TTP) **ERG exploratory analyses**	£13,060	1.48	£8,836
Dabrafenib (lognormal for PFS) **ERG exploratory analyses**	£4,860	−0.75	Dominated by nivolumab
Vemurafenib (lognormal for PFS) **ERG exploratory analyses**	£19,605	−0.74	Dominated by nivolumab
Nivolumab (extrapolated long-term OS from trial) **ERG exploratory analyses**	£10,978	0.40	£27,171
ERG preferred scenario (see section 3.32) **ERG exploratory analyses**	£4,860	−0.76	Dominated by ipilimumab
ERG preferred scenario + nivolumab for 3 years **ERG exploratory analyses**	£22,574	−0.18	Dominated by ipilimumab
ERG preferred scenario + no maximum treatment duration for nivolumab **ERG exploratory analyses**	£83,858	−0.21	Dominated by ipilimumab

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality-adjusted life years; TTP, time to progression.

Dominated: provides fewer QALYs at greater cost than the comparator. Extendedly dominated: a combination of 2 of its comparators provides equal health at a reduced cost.

3.35 Full details of all the evidence are in the Committee papers.

4 Committee discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of nivolumab having considered evidence on the nature of advanced (unresectable or metastatic) melanoma and the value placed on the benefits of nivolumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee discussed the current management of advanced melanoma in the NHS, and the potential place of nivolumab in the treatment pathway. The Committee understood that for advanced (unresectable or metastatic) melanoma that does not have a BRAF-V600 mutation (BRAF mutation-negative or 'wild type' disease) ipilimumab is the most common treatment option. For melanoma with BRAF-V600 mutations (BRAF mutation-positive disease), the Committee heard that there is a choice between the BRAF inhibitor agents (vemurafenib and dabrafenib), or the immunotherapy agent ipilimumab. The choice would usually be based on whether the disease is progressing rapidly (when a BRAF inhibitor would be used) or more slowly, when ipilimumab would be used. The long survival benefit shown in a proportion of patients treated with ipilimumab (based on 5-year overall survival data) has led to an increasing interest in immunotherapy agents. The Committee noted that programmed cell death-1 (PD-1) receptor inhibitors such as nivolumab and pembrolizumab appear to have a faster onset of action and higher response rate than ipilimumab, and may also be more suitable for treating high-volume disease. Nivolumab and pembrolizumab have similar mechanisms of action (consisting of an antibody, which blocks the PD-1 receptor), and both are recommended for use in the same place in the treatment pathway. The clinical experts considered that although some people with rapidly progressing BRAF mutation-positive melanoma will continue to have BRAF inhibitors as first-line treatment, it was expected that nivolumab and pembrolizumab would be suitable for more people than ipilimumab. The Committee noted that pembrolizumab was not included in the scope of this appraisal. However, following the recent positive NICE recommendations for pembrolizumab (pembrolizumab for treating advanced melanoma after disease

progression with ipilimumab or pembrolizumab for advanced melanoma not previously treated with ipilimumab) the Committee heard from the clinical experts that nivolumab and pembrolizumab would be considered for the same group of patients. However, pembrolizumab is not yet in routine clinical use and therefore could not be considered as a comparator for the purpose of this appraisal. The Committee was aware that dacarbazine is now used only after the other available treatments, because it has not been shown to improve overall survival. The Committee concluded that the most relevant comparators for this appraisal were ipilimumab, vemurafenib and dabrafenib.

4.2 The Committee discussed the clinical needs of people with advanced melanoma. It heard from the patient expert that melanoma has a major effect on people's health and quality of life. Having a choice of treatments would be particularly valuable to people with this condition, allowing them and their doctors to choose treatments that take into account their individual needs and preferences and giving them a feeling of more control over their condition. The Committee noted that a course of nivolumab treatment requires more frequent intravenous administration for a longer duration (every 2 weeks for as long as continued clinical benefit is observed, potentially up to 2 years or more) than ipilimumab (every 3 weeks, up to a total of 4 doses) and discussed whether this would affect patients' treatment choices. They heard from the patient expert that, above all, patients want effective therapies and would wish to have access to those which were most effective, even if the treatment schedule was more challenging to accommodate. The Committee was also aware that treatment with ipilimumab can be associated with severe side effects, and heard that patients would be willing to take an alternative with an improved toxicity profile even if it requires more frequent administration. The Committee concluded that the availability of an effective new treatment option with acceptable tolerability would be valuable for people with advanced melanoma.

4.3 The Committee discussed the clinical effectiveness of nivolumab. It noted that overall survival data are currently only available from the CheckMate-066 trial that compared nivolumab with dacarbazine. These data were based on short-term follow-up (median duration 8.9 months in the nivolumab group). Early analysis of the data showed a significant overall survival benefit for nivolumab, resulting in the trial being stopped early and being unblinded. The Committee heard from the company that updated 2-year overall survival data, published in

abstract form, showed that the overall survival benefit was maintained at 2 years (57.7% of patients in the nivolumab arm were alive compared with 26.7% of patients in the dacarbazine arm [hazard ratio of 0.43, 95% confidence interval: 0.33 to 0.57]). The Committee recognised that dacarbazine is now infrequently used except in the context of palliative care, and that the effectiveness of nivolumab compared with ipilimumab is more relevant to clinical practice. The Committee noted that overall survival data from CheckMate-067 (which compared nivolumab with ipilimumab) are not yet available, and it was therefore difficult to draw any firm conclusion on relative overall survival benefit.

4.4 The Committee considered the Kaplan–Meier curves for progression-free survival from CheckMate-067, noting that they showed better progression-free survival with nivolumab than ipilimumab for the entire duration of observation (approximately 20 months). The Committee discussed whether, in some patients, the benefit of nivolumab was likely to be maintained long term, as had been shown in the ipilimumab trials. It recognised that this depended on the biological plausibility of nivolumab and ipilimumab, both immunotherapy agents, having a similar effect on disease suppression. The Committee recognised that there is currently no evidence to suggest that nivolumab will differ from ipilimumab in this respect. However, it emphasised that there was no trial evidence to directly support this conclusion. The Committee concluded that nivolumab is more effective in the short term than ipilimumab, but the long-term benefit of nivolumab remains highly uncertain until further follow-up data are available.

4.5 The Committee considered whether there were likely to be differences in the clinical effectiveness of nivolumab for people with and without BRAF mutation. The Committee noted that CheckMate-066 only included people with BRAF mutation-negative melanoma, but subgroup analyses from CheckMate-067 and CheckMate-037 suggest that nivolumab is somewhat less effective in BRAF mutation-positive disease compared with BRAF mutation-negative disease. The Committee heard from the company that these differences were not substantial. The Committee also heard from the clinical experts that there is no biologically plausible reason why treatment effect would be dependent on BRAF mutation status, and that in clinical practice the effectiveness of immunotherapy agents is considered to be independent of BRAF status. The Committee concluded that nivolumab is effective for both BRAF mutation-negative and BRAF mutation-positive melanoma.

4.6 The Committee discussed whether there were likely to be differences in the clinical effectiveness of nivolumab depending on the expression of programmed death receptor ligand 1 (PD-L1). The Committee heard from the clinical experts that PD-L1 expression is not routinely assessed in clinical practice. It also heard that although in the clinical trials an arbitrary threshold of 5% was used to define subgroups (PD-L1 positive ≥5%, or indeterminate <5%), there is no universally agreed threshold. The Committee noted that subgroup analyses showed that nivolumab appeared effective regardless of PD-L1 expression. The Committee agreed that because of its mechanism of action, nivolumab was expected to be effective in patients with PD-L1 expression. However, it concluded that the clinical effectiveness of nivolumab had also been demonstrated in the PD-L1 indeterminate group.

4.7 The Committee discussed the adverse events associated with nivolumab. It noted that, in the trials, nivolumab was associated with a lower incidence of high-grade or serious adverse events than ipilimumab or chemotherapy. The Committee concluded that the adverse events related to nivolumab were manageable, and also favourable when compared with chemotherapy and ipilimumab.

4.8 The Committee considered the likely duration of nivolumab treatment in clinical practice. It noted that the summary of product characteristics recommends treatment 'as long as clinical benefit is observed or until treatment is no longer tolerated by the patient'. Clinical advisers to the company had assumed that nivolumab will be given up to a maximum of 2 years. The Committee heard from the clinical experts that there is no evidence to indicate an optimum duration of treatment with nivolumab. It heard from the company that nivolumab reactivates the immune system and that it was plausible that a course of treatment shorter than 2 years might be equally effective. The Committee also heard that regimens shorter than 2 years are currently being investigated in clinical trials. Nevertheless, the clinical experts acknowledged that it may be difficult to stop nivolumab treatment at 2 years if patients are still experiencing benefit. The Committee appreciated that there is considerable uncertainty about the optimum duration of treatment with nivolumab, which will not be clarified until further trials are published. The Committee also expressed the view that a review of this guidance after 2 years (to coincide with the review of pembrolizumab guidance) should be recommended, at which time overall survival data will be more mature,

and the optimum duration of treatment may have been clarified.

Cost effectiveness

4.9 The Committee considered the company's model, which compared nivolumab with ipilimumab and dacarbazine in BRAF mutation-negative disease, and with ipilimumab, vemurafenib and dabrafenib in BRAF mutation-positive disease, for people with previously untreated advanced (unresectable or metastatic) melanoma. The Committee noted that the ERG considered the structure of the model to be reasonable and consistent with the disease pathway. The Committee noted that the company used covariate-adjusted parametric curves fitted to patient-level data from different trials to capture the clinical effectiveness of nivolumab and the comparators, rather than relative effectiveness from the clinical trials or an indirect treatment comparison. The Committee noted that in the company's deterministic sensitivity analyses, the results were most sensitive to the choice of the fitted parametric curves. The Committee noted the particular concerns expressed by the ERG about the company's approach to modelling overall survival. The Committee accepted the structure of the company's model, but gave further consideration to the assumptions used in the modelling of survival.

4.10 The Committee noted that in the company's base-case analysis, nivolumab was more effective than ipilimumab, with an incremental quality-adjusted life year (QALY) gained of 1.67 and 1.82 for BRAF mutation negative-melanoma and BRAF mutation-positive melanoma, respectively. However, in the ERG's preferred scenario, nivolumab appeared less effective than ipilimumab. The Committee expressed concerns about the substantial difference between these results and discussed possible reasons for the difference. It understood that the main reason for this discrepancy was the different approaches taken by the company and the ERG for modelling time to progression and long-term survival for patients having nivolumab.

4.11 The Committee then discussed the differences in the approaches taken by the company and the ERG. It noted that the ERG preferred a Weibull curve to the Gompertz curve, which had been used by the company to model time to progression for nivolumab. The Committee appreciated that this would slightly

decrease the total QALY gain with nivolumab, but agreed that on its own switching to a Weibull curve would have a minimal effect on the overall cost-effectiveness. More significant was the company's assumption that patients having nivolumab would have a comparable long-term survival benefit to that seen in the ipilimumab trials. The Committee recalled its conclusion that the evidence on long-term survival with nivolumab is highly uncertain, and noted that the ERG considered that overall survival for nivolumab would be better modelled by extrapolation of the CheckMate-066 data. This approach, when combined with implementing the ERG's preferred curve for time to progression, substantially reduced the QALYs gained with nivolumab (to approximately half of those gained in the company base case), and resulted in it generating fewer QALYs (that is, being less effective) than ipilimumab. The Committee noted that this was at odds with the substantial short-term progression-free survival benefit for nivolumab compared with ipilimumab shown in CheckMate-067, which it thought would not be unreasonable to expect to translate into a survival benefit. The Committee also heard from the company representative that their model predicted that 50% of patients would be alive at 2 years; this was in line with the updated survival analysis of CheckMate-066 in which 57% of patients were alive at 2-year follow up. The Committee, while accepting the uncertainty, considered that nivolumab was likely, on the basis of current evidence, to produce a greater QALY gain than ipilimumab. It therefore accepted that the company's analysis represented a reasonable approach to estimate the cost effectiveness of nivolumab.

4.12 The Committee noted that time spent on treatment was a key factor influencing the cost-effectiveness results. The Committee was aware that currently the maximum duration of treatment is unclear. It noted that the ERG had explored the impact of increasing treatment duration from 2 years to 3 years, and also a scenario with no maximum treatment duration. The Committee noted that increasing treatment duration increased the total cost associated with nivolumab, but did not increase the QALY gained; this decreased slightly. It understood that this was because more time spent on nivolumab treatment resulted in more adverse events. The Committee concluded that lack of evidence on the optimal duration of treatment made the cost-effectiveness results uncertain. The Committee agreed that there would be more clarity when the results from studies comparing different durations of treatment become available.

4.13 The Committee noted that the company stated that nivolumab was innovative

and a step change in the management of advanced melanoma because it treats a life-threatening and seriously debilitating condition, meets a high unmet need and provides a significant advantage over other treatments used in the UK. Although the Committee did not consider the mechanism of action of nivolumab to be unique, it agreed that the low toxicity and the favourable adverse effect profile of nivolumab compared with other treatments represent a promising new advance in immunotherapy for the treatment of metastatic melanoma. However, it could not identify any specific health-related benefit that had not already been captured in the QALY calculation.

4.14 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.15 The Committee agreed that the life expectancy of people with advanced (unresectable or metastatic) melanoma is short, generally less than 24 months. The Committee noted the company's comment that the difference in restricted mean survival in CheckMate-066 between nivolumab and dacarbazine was 3.6 months. The Committee noted that the median overall survival was not reached in the nivolumab arm of any of the trials, so the magnitude of the survival gain was uncertain, but was reassured that the updated survival data from

CheckMate-066 demonstrated that survival benefit in nivolumab-treated patients was maintained, and that the median survival in the nivolumab group had still not been reached in the updated analysis. The Committee was aware that in addition to advanced melanoma, nivolumab is also licensed for treating advanced or metastatic squamous non-small-cell lung cancer after prior chemotherapy; the company estimated the total population for whom nivolumab is indicated to be about 2200 people. The Committee concluded that this represented a small patient population, and that nivolumab meets all the criteria to be considered a life-extending, end-of-life treatment.

4.16 The Committee considered the ICERs from the company's base cases, recalculated to include the discounted prices in the patient access schemes for 3 comparators (ipilimumab, vemurafenib and dabrafenib), which are commercial in confidence. The Committee took into account uncertainties in the clinical and cost-effectiveness evidence, and the supplementary advice for appraising life-extending, end-of-life treatments. It concluded that, on balance, the ICER for nivolumab is likely to be less than £30,000 per QALY gained in both BRAF mutation-positive and BRAF mutation-negative advanced melanoma. It therefore considered nivolumab to be a cost effective use of NHS resources.

4.17 The Committee was aware of NICE's position statement about the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism. It acknowledged 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal of nivolumab. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the cost effectiveness of nivolumab for treating advanced (unresectable or metastatic) melanoma.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because nivolumab was made available in the NHS through the early access to medicines scheme, NHS England has indicated that this guidance will be implemented 30 days after final publication.

5.2 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.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance 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 draft guidance.

5.4 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 advanced (unresectable or metastatic) melanoma and the healthcare professional responsible for their care thinks that nivolumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Dr Justin Daniels
Consultant Paediatrician, North Middlesex University Hospital

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Mr Adrian Griffin
Vice President, Health Technology Assessment and International Policy, Johnson & Johnson

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

Ms Sarah Parry
Clinical Nurse Specialist – Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Mr Stephen Sharp
Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

Mr David Thomson
Lay member

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.

Dr Anwar Jilani
Technical Lead

Eleanor Donegan
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre (SHTAC):

- Cooper K, Kalita N, Streit E, et al. Nivolumab for treating advanced (unresectable or metastatic) melanoma: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), October 2015.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Companies were also invited to make written submissions. Professional or expert and patient or carer groups gave their expert views on nivolumab by making a submission to the Committee. Companies, professional or expert and patient or carer groups, and other consultees, have the opportunity to appeal against the final appraisal determination.

Company

- Bristol-Myers Squibb (nivolumab)

Professional or expert and patient or carer groups:

- British Association of Dermatologists
- British Association of Skin Cancer Specialist Nurses (BASCSN)
- Cancer Research UK
- Melanoma Focus
- Melanoma UK
- Royal College of Nursing
- Royal College of Physicians
- UK Clinical Pharmacy Association

- UK Oncology Nursing Society

Other consultees:

- Department of Health
- NHS England
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Roche Products (vemurafenib)

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on nivolumab by providing oral evidence to the Committee.

- Dr Christine Parkinson, Consultant in Medical Oncology, nominated by organisation representing Melanoma Focus – clinical expert
- Dr Louise Fearfield, Consultant Dermatologist, nominated by organisation representing British Association of Dermatologists (BAD) – clinical expert
- Mrs Gillian Nuttall, nominated by organisation representing Melanoma UK – patient expert

Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bristol-Myers Squibb

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