NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Nivolumab in combination with ipilimumab for treating advanced melanoma

1 Recommendations

1.1 Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.

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) and activates the immune system to attack cancer cells. Nivolumab is administered intravenously. Ipilimumab (Yervoy, Bristol-Myers Squibb) is a fully human antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA‑4), a molecule expressed on T cells that plays a critical role in regulating natural immune responses. Ipilimumab is designed to block the activity of CTLA‑4 resulting in augmentation and prolongation of the T‑cell immune response. Nivolumab in combination with ipilimumab has a UK marketing authorisation 'for the treatment of advanced (unresectable or metastatic) melanoma in adults'. The draft 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 recommended starting dose of the combined regimen is nivolumab 1 mg per kilogram of body weight and ipilimumab 3 mg per kilogram of body weight, administered intravenously over a 90‑minute period every 3 weeks for a total of 4 doses. This is followed by maintenance treatment with nivolumab alone at a dose of 3 mg per kilogram body weight, administered intravenously over a 60-minute period every 2 weeks. The summary of product characteristics states that 'relative to nivolumab monotherapy, an increase in progression-free survival (PFS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression'. It recommends that 'before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy'. It also states that, 'no clear cut-off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS' and recommends that 'treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated'.

2.3 The most common adverse events in people taking nivolumab in combination with ipilimumab in the trials were fatigue, diarrhoea, itching, fever, colitis, nausea, increased transaminases (which can indicate liver damage) and enlargement of the pituitary gland. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Nivolumab is available at a list price of £439 per 4-ml (40-mg) vial (excluding VAT; Monthly Index of Medical Specialities [MIMS] online, accessed April 2016). Ipilimumab is available at a list price of £3,750 per 10-ml (50-mg) vial and £15,000 per 40-ml (200-mg) vial (excluding VAT; British national formulary [BNF], accessed online April 2016). Costs for nivolumab may vary in different settings because of negotiated procurement discounts. The company has agreed a patient access

scheme for ipilimumab with the Department of Health. This scheme provides a simple discount to the list price of ipilimumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

3.1 The appraisal committee (section 7) considered evidence submitted by Bristol–Myers Squibb together with a review of the company submission by the evidence review group (ERG). It also considered evidence received from patient and professional groups. See the committee papers for full details of the evidence.

4 Committee discussion

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

4.1 The committee discussed the current management of advanced melanoma in the NHS, and the potential place of nivolumab plus ipilimumab in the treatment pathway. The committee heard that systemic immunotherapy is the current mainstay of treatment for advanced (unresectable or metastatic) melanoma. Following positive NICE guidance, pembrolizumab and nivolumab monotherapy are now the most commonly used first-line treatment options for advanced (unresectable or metastatic) melanoma regardless of BRAF-V600 mutation status. They have a faster onset of action, higher response rate and better toxicity profile than ipilimumab, which has now been largely superseded for

first-line use. The committee noted that pembrolizumab was included in the final scope of this appraisal but nivolumab monotherapy was not included as a comparator, because it had not been appraised by NICE at the time of scoping. The committee heard from the clinical experts that following the positive NICE recommendation for nivolumab monotherapy, nivolumab and pembrolizumab would be considered for the same group of patients. However, although they are considered to have equivalent efficacy, pembrolizumab has a 3-weekly dosing regimen, compared with 2-weekly for nivolumab, and this was considered to be an advantage of pembrolizumab in clinical practice. The committee was aware that CheckMate-067 was a 3-arm trial that compared nivolumab in combination with ipilimumab against either nivolumab or ipilimumab alone, and it would have been interested in the results of the comparison with nivolumab. However, it was outside the scope of the appraisal and the company chose not to include nivolumab monotherapy in its submission. The committee heard that the BRAF inhibitors (vemurafenib and dabrafenib) are now considered as first-line treatments for only a relatively small proportion (possibly 25%) of patients with BRAF mutation-positive melanoma; in particular, people with rapidly progressive disease, a short life expectancy, or poor prognostic features (high disease burden, raised serum lactate dehydrogenase, poor performance status and multiple, symptomatic brain metastases). For this group of patients, systemic immunotherapy would not normally be used first-line but may be considered for second-line treatment if a BRAF inhibitor was providing an inadequate response.The committee concluded that the most relevant comparator in the scope for this appraisal is pembrolizumab although nivolumab monotherapy, while not in the scope, could have been considered a relevant comparator.

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 greater 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 nivolumab plus ipilimumab is associated with more frequent and severe adverse effects than nivolumab or pembrolizumab alone, and discussed whether this would affect patients' treatment choices. They heard from the patient expert that, above all, patients want access to the most effective therapies possible. If they were fit enough, patients would be willing to accept the risk of serious treatment-related adverse effects, and a treatment schedule that is more challenging to accommodate, in order to obtain a high response rate. The committee concluded that the availability of an effective new treatment option would be valuable for people with advanced melanoma who are fit enough to tolerate it.

Clinical effectiveness

4.3 The committee discussed the clinical effectiveness of nivolumab plus ipilimumab. The clinical-effectiveness evidence is in the company's submission (pages 38-124) and in the ERG report (pages 29-114). The committee noted that overall survival data from the CheckMate-067 and 069 trials, which compared nivolumab plus ipilimumab with ipilimumab alone (and also nivolumab alone in Checkmate-067), were immature because the number of events (deaths) pre-specified in the statistical analysis plan had not been reached at the time of the company submission. The committee heard from the company that an early exploratory analysis of CheckMate-069 requested by the European Medicines Agency showed an 18-month overall survival rate of 69% in patients taking nivolumab plus ipilimumab, irrespective of BRAF mutation status in the intention-to-treat population. This was nearly double the 18-month overall survival rate of 35% for ipilimumab alone in a pooled analysis of historical trials.The committee noted that the final overall survival data from CheckMate-067 (which compared nivolumab plus ipilimumab with both nivolumab and ipilimumab alone) were not yet available. It was therefore difficult to draw any firm conclusion on relative

overall survival benefit, although the committee noted that the interim overall survival results for the combination regimen compared with ipilimumab alone looked promising.

4.4 The committee considered the Kaplan–Meier curves for progression-free survival from CheckMate-067 in the intention-to-treat population (all people who were randomised), which included people with BRAF mutation-negative melanoma (n=213 in the nivolumab plus ipilimumab arm and n=218 in the ipilimumab arm) and mutation-positive melanoma (n=101 in the nivolumab plus ipilimumab arm and n=97 in the ipilimumab arm). The committee was aware that treatment with nivolumab plus ipilimumab resulted in a significant extension in progression-free survival compared with ipilimumab alone (hazard ratio 0.42, 99.5% confidence interval [CI] 0.31 to 0.57, p<0.001) for the intention-to-treat population. The median progression-free survival was 11.5 months (95% CI 8.9 to 16.7) for nivolumab plus ipilimumab and 2.9 months (95% CI 2.8 to 3.4) for ipilimumab alone.

4.5 The committee noted that in CheckMate-067 treatment with nivolumab plus ipilimumab resulted in an unweighted objective response rate difference of 38% compared with ipilimumab alone (57% in the nivolumab plus ipilimumab arm and 19% in the ipilimumab alone arm, odds ratio 6.11, 95% CI 3.59 to 10.38, p<0.001) for the intention-to-treat population. The committee noted that in CheckMate-069, the investigator-assessed objective response rate was 59% in the nivolumab plus ipilimumab group compared with 11% in the ipilimumab group (odds ratio for response 12.19, 95% CI 4.41 to 33.68, p<0.0001) for the intention-to-treat population, regardless of BRAF mutation status. The committee concluded that nivolumab plus ipilimumab is more effective in the short term than ipilimumab alone, but the long-term benefit of nivolumab plus ipilimumab remains uncertain until further follow-up data are available. The committee had not been presented with any data to establish the relative benefit of nivolumab plus ipilimumab compared with nivolumab alone.

4.6 The committee discussed whether the clinical effectiveness of nivolumab plus ipilimumab would vary depending on the expression of programmed death receptor ligand 1 (PD-L1) as referred to in the summary of product characteristics (see section 2.2). The committee noted that the Committee for Medicinal Products for Human Use (CHMP) stated that 'relative to nivolumab monotherapy, an increase in progression-free survival for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression'. The committee heard from a clinical expert that this was an exploratory analysis requested by the European Medicines Agency and that PD-L1 expression is not routinely assessed in clinical practice. Furthermore, there is no universally agreed threshold for PD-L1 expression. The committee concluded that PD-L1 expression may be one of the factors that influence clinical decision making, but it would not be appropriate for NICE to base recommendations on PD-L1 expression at present.

4.7 The committee discussed the adverse events associated with nivolumab plus ipilimumab. It noted that, in the trials, nivolumab plus ipilimumab was associated with a higher rate of high-grade or serious adverse events than ipilimumab alone. The committee heard from clinicians that the presence of elevated transaminases (commonly alanine transaminase and aspartate transaminase) indicating liver damage is one of the most common serious adverse effects related to treatment with nivolumab plus ipilimumab, and that clinicians routinely monitor transaminases and can deal with this complication if it occurs. Other serious adverse events included diarrhoea and colitis requiring hospitalisation, which are recognised complications of ipilimumab, and there were a few treatment-related deaths in the nivolumab plus ipilimumab groups in the trials (none in CheckMate-067 and 3 in CheckMate-069). The committee concluded that although the adverse events related to nivolumab plus ipilimumab were significant and could be severe, the additional effectiveness of this treatment is likely to outweigh the potential risk of serious adverse events

in patients who are fit enough and willing to tolerate this combination immunotherapy regimen.

4.8 The committee considered the likely duration of treatment with nivolumab plus ipilimumab in clinical practice. It noted that after the initial course of combined therapy, the summary of product characteristics recommends continuing treatment with nivolumab 'as long as clinical benefit is observed or until treatment is no longer tolerated by the patient'. The company stated in its submission that nivolumab would not be expected to be given beyond 2 years. The committee heard from the clinical experts that there is no evidence that treatment with nivolumab should stop at 2 years. It heard from a patient expert that patients who are currently having nivolumab expressed concern that their treatment might be stopped after 2 years regardless of whether they were still benefiting from it. The committee concluded that the 2-year treatment duration cap proposed by the company was arbitrary and not based on clinical evidence, and that there was considerable uncertainty about the optimum duration of treatment. However, based on the discontinuation rate in clinical trials, the committee considered that only a small number of patients would still be having treatment after 2 years. The committee appreciated that there is considerable uncertainty about the optimum duration of treatment with nivolumab. 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 discussed the cost-effectiveness evidence presented by the company and its critique by the evidence review group (ERG). The cost-effectiveness evidence is in the company's submission (pages 125-216), in the appendices to the company's submission and in the ERG report (pages 115-232). The company's model compared

nivolumab plus ipilimumab with ipilimumab alone 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 company's economic evaluation to be complex and reliant on too many assumptions. The committee noted that the ERG's main concern related to the company's assumptions about post-progression survival in the model (see the ERG report, pages 185-186 and 195-197). However, the committee was aware that the ERG was able to change the parameters in the model to compensate for that assumption (see the ERG report, pages 236-237). Therefore, the committee accepted that the structure of the company's model for the BRAF mutation-negative population comparing nivolumab plus ipilimumab with ipilimumab monotherapy could be used for the purposes of decision-making in this appraisal.

4.10 The committee went on to look specifically at the assumptions made by the company in its modelling of the BRAF mutation-positive population comparing nivolumab plus ipilimumab, with ipilimumab alone, dabrafenib and vemurafenib. The committee considered that the modelling used for the BRAF mutation-positive population was very complex, and also made it very difficult to compare the effectiveness versus ipilimumab alone and the BRAF inhibitors (see the ERG report, page 198). The committee recalled their earlier view that BRAF inhibitors were not relevant comparators for the patient population for whom the combination of nivolumab with ipilimumab might be used and that immunotherapy was used regardless of BRAF mutation status in most patients. The committee therefore concluded that the most clinically relevant comparison was the cost effectiveness of nivolumab plus ipilimumab in the mixed population (BRAF mutation-positive and mutation-negative) for whom immunotherapy was considered appropriate. The committee further concluded that the ERG's exploratory modelling comparing nivolumab plus ipilimumab against ipilimumab in the mixed population (BRAF

mutation-positive and mutation-negative) could be used for the purposes of decision-making in this appraisal.

4.11 The committee considered the ERG's preferred base-case scenario comparing nivolumab plus ipilimumab with ipilimumab alone. This included both BRAF mutation-negative and mutation-positive disease in the same ratio as that in CheckMate-067, with a number of changes. The committee noted that, using the list prices, this increased the company's base case incremental cost-effectiveness ratio (ICER) for nivolumab plus ipilimumab compared with ipilimumab alone from £10,400 per quality-adjusted life year (QALY) gained (in the BRAF mutation-negative population) to £19,300 per QALY gained (for the mixed population). The committee further considered the cost effectiveness when the patient access scheme discounts were applied and noted that the ICER remained below £30,000 per QALY gained.

4.12 The committee considered the cost effectiveness of nivolumab plus ipilimumab compared with pembrolizumab alone, which they considered to be the most clinically relevant comparator in the scope based on the testimony of clinical experts. The committee was disappointed that the company did not include this comparison in its original submission and only provided it during the clarification response stage of the appraisal process. In its clarification response, the company produced a meta-analysis of the hazard ratios for overall survival and progression-free survival based on data from CheckMate-067 and 2 pembrolizumab trials (Keynote-006 and Keynote-002) to compare nivolumab plus ipilimumab with ipilimumab alone and with pembrolizumab alone. In the BRAF mutation-negative population, ipilimumab alone was dominated by pembrolizumab. In the BRAF mutation-positive population, dabrafenib, vemurafenib and ipilimumab were dominated by pembrolizumab and nivolumab plus ipilimumab and therefore excluded from the analysis. The committee noted that, compared with pembrolizumab, nivolumab plus ipilimumab resulted in an increase of 1.63 and 1.64 QALYs and an ICER of £29,900 and £27,900 per QALY gained for the BRAF mutation-negative

and mutation-positive populations respectively when list prices were used. The committee was aware that the ERG considered this comparison to be unreliable due to the assumptions made by the company (see section 5.6.2.3 of the ERG report, pages 225-226). The committee noted that the company had access to data from CheckMate-067 which included a comparison of nivolumab plus ipilimumab with nivolumab alone. If the company had presented that comparison (even though nivolumab monotherapy was not included in the scope) it would have been very helpful to reduce the uncertainty about the cost effectiveness of nivolumab plus ipilimumab compared with the PD-1 inhibitors, which are thought to be clinically equivalent. The committee considered that the most appropriate cost-effectiveness analysis within the scope would have been the comparison of nivolumab plus ipilimumab with pembrolizumab alone in the mixed population (that is, BRAF mutation-positive and mutation-negative) using the ERG's preferred model assumptions. The committee concluded, that within the scope, the comparison with pembrolizumab was the most relevant to current UK clinical practice, and there remained some uncertainty about the robustness of this comparison.

4.13 The committee considered the ICERs from the ERG's preferred base case and the company's comparison of nivolumab plus ipilimumab against pembrolizumab, recalculated to include the discounted prices in the patient access schemes for 2 comparators (pembrolizumab and ipilimumab), which are commercial in confidence. The committee took into account uncertainties in the clinical and cost-effectiveness evidence. The committee recalled that the using the ERG's preferred base case, the ICER for nivolumab plus ipilimumab compared with ipilimumab was less than £30,000 per QALY gained in the mixed population of BRAF mutation-positive and mutation-negative advanced melanoma when the patient access scheme prices were used. Although it noted that the ERG's preferred base case had not been applied to the comparison of nivolumab plus ipilimumab against pembrolizumab, it concluded that, on balance, the

ICER for nivolumab plus ipilimumab compared to pembrolizumab is likely to be less than £30,000 per QALY gained in the mixed population of BRAF mutation-positive and mutation-negative advanced melanoma when the patient access scheme prices were used in the model. It therefore considered that nivolumab plus ipilimumab could be considered a cost-effective use of NHS resources.

4.14 The committee noted that the company had stated that nivolumab plus ipilimumab 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 England. Although the committee accepted that the combination of nivolumab and ipilimumab was associated with a higher response rate than ipilimumab alone, it noted that the increased toxicity made it a promising new advance only for people who are fit enough to tolerate the considerable related adverse effects. The committee did not identify any specific health-related benefits which had not been captured in the QALY calculation.

4.15 The committee did not formally consider whether the end-of-life criteria applied because the technology was considered to be a cost-effective use of NHS resources without this. However, the committee was aware that as pembrolizumab was considered to be the most clinically relevant comparator and it had not been presented with extension to life evidence for nivolumab and ipilimumab compared with pembrolizumab, it would have been unable to decide whether this criterion had been met.

4.16 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion '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. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Nivolumab in combination with ipilimumab for advanced melanoma**	**Section**
Key conclusion		
Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults only when the company provides ipilimumab with the discount agreed in the patient access scheme. The committee concluded that the incremental cost-effectiveness ratio (ICER) for nivolumab plus ipilimumab compared with pembrolizumab (the most clinically relevant comparator) was likely to be less than £30,000 per quality adjusted life year (QALY) gained. Review of this guidance after 2 years should be recommended, when matured overall survival data and the results of studies investigating optimum treatment duration will be available.		1.1, 4.13, 6.1
Current practice		

Clinical need of patients, including the availability of alternative treatments	The committee heard from the clinical experts that nivolumab and pembrolizumab are considered to have equivalent efficacy in treating advanced melanoma. The committee concluded that the most relevant comparator included in the scope was pembrolizumab although nivolumab monotherapy, while not in the scope, could have also been considered a relevant comparator. The committee concluded that the availability of an effective new treatment option such as nivolumab in combination with ipilimumab would be valuable for people with advanced melanoma who are fit enough to tolerate it.	4.1, 4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The company had stated that nivolumab plus ipilimumab 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 England.	4.14

What is the position of the treatment in the pathway of care for the condition?	The committee accepted that the combination of nivolumab plus ipilimumab is a promising new advance in the treatment of melanoma regardless of BRAF mutation status, but only for people who are fit enough to tolerate the considerable related adverse effects.	4.14
Adverse reactions	The committee noted that, in trials, nivolumab plus ipilimumab was associated with a higher rate of high-grade or serious adverse events than ipilimumab alone. The presence of elevated transaminases (commonly alanine transaminase and aspartate transaminase) indicating liver damage is one of the most common serious adverse effects related to treatment with nivolumab plus ipilimumab, and is routinely monitored by clinicians. There were some treatment-related deaths in the nivolumab plus ipilimumab groups in the trials (none in CheckMate-067 and 3 in CheckMate-069). Diarrhoea and colitis requiring hospitalisation are also recognised complications of ipilimumab The committee concluded that although the adverse events related to nivolumab plus ipilimumab were significant and could be severe, the additional effectiveness of this treatment is likely to outweigh the potential risk of serious adverse events in patients who are fit enough and willing to tolerate this combination immunotherapy regimen.	4.7
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The committee noted that progression-free survival and immature overall survival data were available from the CheckMate-067 and 069 trials. The committee was aware that treatment with nivolumab plus ipilimumab resulted in a significant extension in progression-free survival compared with ipilimumab alone (hazard ratio 0.42, 99.5% confidence interval [CI] 0.31 to 0.57, p<0.001) for the intention-to-treat population. The median progression-free survival was 11.5 months (95% CI 8.9 to 16.7) for nivolumab plus ipilimumab and 2.9 months (95% CI 2.8 to 3.4) for ipilimumab alone. Due to the immaturity of the overall survival data, it was difficult for the committee to draw any firm conclusion on relative overall survival benefit, although the committee noted that the interim overall survival results for the combination regimen compared with ipilimumab alone looked promising. An indirect treatment comparison of nivolumab plus ipilimumab against pembrolizumab was presented which reported statistically significant benefits in progression-free and overall survival.	4.3, 4.4, 4.5

Relevance to general clinical practice in the NHS	The committee considered that nivolumab plus ipilimumab is a promising treatment for people with BRAF mutation-positive and mutation-negative advanced melanoma for whom immunotherapy is considered appropriate.	4.14
Uncertainties generated by the evidence	The committee noted that the final overall survival data from CheckMate-067 (which compared nivolumab plus ipilimumab with both nivolumab and ipilimumab alone) were not yet available.	4.3
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that nivolumab plus ipilimumab is more effective in the short term than ipilimumab alone, but the long-term benefit of nivolumab plus ipilimumab remains uncertain until further follow-up data are available. The committee had not been presented with any data to establish the relative benefit of nivolumab plus ipilimumab compared with nivolumab alone.	4.5
Evidence for cost effectiveness		

Availability and nature of evidence	The company's model compared nivolumab plus ipilimumab with ipilimumab alone 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 immunotherapy was used in the majority of patients, regardless of BRAF mutation status. The most clinically relevant comparison presented by the company was the cost effectiveness of nivolumab plus ipilimumab in the mixed population (BRAF mutation-positive and mutation-negative) for whom immunotherapy was considered appropriate. The committee further concluded that the ERG's exploratory modelling comparing nivolumab plus ipilimumab against ipilimumab in the mixed population (BRAF mutation-positive and mutation-negative) could be used for the purposes of decision-making in this appraisal.	4.9, 4.10

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee was aware that the evidence review group (ERG) considered the comparison between nivolumab plus ipilimumab against pembrolizumab to be uncertain due to assumptions made by the company. The comparison with pembrolizumab was the most relevant to current UK clinical practice, and there remained some uncertainty about the robustness of this comparison.	4.9, 4.12
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted that the company had stated that nivolumab plus ipilimumab 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 England. The committee did not identify any specific health-related benefits which had not been captured in the QALY calculation.	4.14

Are there specific groups of people for whom the technology is particularly cost effective?	No.	
What are the key drivers of cost effectiveness?	The modelling of post-progression survival was the biggest driver of cost effectiveness.	4.10
Most likely cost-effectiveness estimate (given as an ICER)	The committee considered the ICERs from the ERG's preferred base case and the company's comparison of nivolumab plus ipilimumab against pembrolizumab, recalculated to include the discounted prices in the patient access schemes for 2 comparators (pembrolizumab and ipilimumab), which are commercial-in-confidence. The committee recalled that using the ERG's preferred base case, the ICER for nivolumab plus ipilimumab compared with ipilimumab alone was less than £30,000 per QALY gained in the mixed population of BRAF mutation-positive and mutation-negative advanced melanoma when the patient access scheme prices were used. Although it noted that the ERG's preferred base case had not been applied to the comparison of nivolumab plus ipilimumab against pembrolizumab, it concluded that, on balance, the ICER for nivolumab plus ipilimumab compared to pembrolizumab is	4.13

	likely to be less than £30,000 per QALY gained in the mixed population of BRAF mutation-positive and mutation-negative advanced melanoma when the patient access scheme prices are used. It therefore considered that nivolumab plus ipilimumab could be considered a cost-effective use of NHS resources.	
Additional factors taken into account		
Patient access schemes (PPRS)	The committee took into account the patient access schemes available for ipilimumab and pembrolizumab in the comparison of nivolumab plus ipilimumab compared with pembrolizumab. The patient access discounts are commercial in confidence.	4.13
End-of-life considerations	The committee did not formally consider whether the end-of-life criteria applied because the technology was considered to be a cost-effective use of NHS resources without this. The committee noted that pembrolizumab was considered to be the most clinically relevant comparator but it was not presented with extension to life evidence for nivolumab and ipilimumab compared with pembrolizumab. Therefore, if the end-of-life criteria had needed to be considered, the committee would have been unable to decide whether this criterion had been met.	4.15

Equalities considerations and social value judgements	None.	

5 Implementation

5.1 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.

5.2 The Welsh Assembly Minister for Health and Social Services has 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 3 months of the guidance being published.

5.3 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 doctor responsible for their care thinks that nivolumab in combination with ipilimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Bristol–Myers Squibb have agreed that ipilimumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations.

Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

6 Review of guidance

6.1 The guidance on this technology will be considered for review 2 years after publication along with guidance on other immunotherapies for advanced melanoma (such as technology appraisal guidance 268, 319, 357 and 366). The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
May 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

Richard Diaz

Technical Lead

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