nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)

SMC No. (1187/16)

Bristol-Myers Squibb Pharmaceuticals Ltd

07 October 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission assessed under the end of life and orphan equivalent process

*nivolumab (Opdivo®)* is accepted for restricted use within NHS Scotland.

**Indication under review**: in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults.

**SMC restriction**: for the first-line treatment of advanced melanoma

In a randomised, double-blind, phase III study of adults with previously untreated advanced melanoma nivolumab in combination with ipilimumab was associated with a clinically important and statistically significant improvement in progression-free survival when compared with a single-agent immunotherapy. Overall survival data are immature.

The base-case economic analysis submitted by the company assumed that responding patients were treated for a maximum of 18 months.

SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of nivolumab and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,**  
**Scottish Medicines Consortium**

Published 07 November 2016
**Indication**
Nivolumab in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

**Dosing Information**
The recommended dose is 1mg/kg nivolumab administered as an intravenous (IV) infusion over 60 minutes every three weeks for the first four doses in combination with 3mg/kg ipilimumab administered IV over 90 minutes.

This is then followed by a second phase in which 3mg/kg nivolumab is administered as an IV infusion over 60 minutes every two weeks.

Treatment with nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Refer to the summary of product characteristics for further detail.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

**Product availability date**
11 May 2016.
Nivolumab for this indication meets SMC end-of-life and orphan-equivalent criteria.

**Summary of evidence on comparative efficacy**
Nivolumab is a monoclonal antibody which binds to the programmed death-1 (PD-1) receptor found in T-cells. The PD-1 receptor is a negative regulator of T-cell activity which is involved in the control of T-cell immune responses. PD-L1 and PD-L2 are proteins produced by cancer cells that interact with the PD-1 receptor and switch off the activity of T-cells. Nivolumab blocks PD-L1 and PD-L2 from binding to the PD-1 receptor and prevents T-cell deactivation.1 Ipilimumab is also a T-cell potentiator that specifically blocks the inhibitory signal of cytotoxic T-lymphocyte antigen-4 (CTLA-4), resulting in T-cell activation, proliferation and lymphocyte infiltration into tumours, leading to cell death.² Both medicines stimulate the body’s immune system to target and destroy the tumour.

This submission is for an extension to the licensed indication for nivolumab allowing it to be used with ipilimumab (combination regimen). Nivolumab and ipilimumab as monotherapy have previously been reviewed by SMC for advanced melanoma in adults: ipilimumab was accepted for use, and nivolumab was accepted for restricted use for patients previously untreated with ipilimumab. Vemurafenib and dabrafenib, licensed as monotherapy for the treatment of adult patients with BRAF V600 mutant-positive advanced melanoma, have been accepted by SMC for restricted use as first-line therapy. Pembrolizumab, which has the same mechanism of action
as nivolumab, has been accepted by SMC for use in patients previously untreated with ipilimumab.

The submitting company has requested that SMC considers nivolumab plus ipilimumab when positioned for use for the first-line treatment of advanced melanoma.

The pivotal evidence for the combination of nivolumab plus ipilimumab is the phase III multi-centre, randomised, double-blind, controlled study CHECKMATE 067. The phase II study CHECKMATE 069 provides supportive data.

CHECKMATE 067 recruited adults with histologically confirmed advanced melanoma (stage III unresectable or stage IV disease) who had no previous systemic treatment for their advanced disease. Patients were required to have good performance status (Eastern Co-operative Oncology Group [ECOG] performance status 0 or 1). The melanoma was required to be measurable as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and with known BRAF V600 mutation status.

Patients were randomised in a 1:1:1 ratio to nivolumab plus ipilimumab (combination group), nivolumab monotherapy, or ipilimumab monotherapy. The combination group received nivolumab 1mg/kg plus ipilimumab 3mg/kg on weeks one and four of a six-week cycle for two cycles; then, from cycle three onwards, nivolumab 3mg/kg every two weeks. Patients in the ipilimumab monotherapy group received ipilimumab 3mg/kg every three weeks for four doses only. Patients in the nivolumab monotherapy group received nivolumab 3mg/kg every two weeks ongoing. All study treatments were administered by intravenous (IV) infusion. Randomisation was stratified by: metastasis stage (American Joint Committee on Cancer [AJCC] stage M0, M1a, or M1b versus M1c), BRAF V600 mutation status (positive versus negative), and PD-L1 status (positive versus negative or indeterminate). Study treatment was continued until unacceptable toxicity, withdrawal of consent or disease progression as per RECIST v1.1, although patients could continue beyond disease progression if still deriving clinical benefit and tolerating treatment.

There were two co-primary outcomes: overall survival and progression-free survival (PFS) analysed in the intention-to-treat population, which was all randomised subjects. Overall survival was defined as the time from the date of randomisation to the date of death due to any cause. PFS was defined as the time from randomisation to the first occurrence of either investigator-assessed disease progression (according to RECIST version 1.1) or death. The study was designed to compare the nivolumab-containing groups with ipilimumab monotherapy; efficacy results for the nivolumab plus ipilimumab and ipilimumab monotherapy groups are presented in this document only.

Data cut-off for the analysis of PFS was in February 2015, at a median follow-up ranging between 12.2 and 12.5 months across all treatment groups.

Subgroup analysis of the stratification factors for randomisation (BRAF mutation status, AJCC stage, and PD-L1 status) were conducted for PFS. Hazard ratios in these subgroups all favoured nivolumab plus ipilimumab over ipilimumab monotherapy. There were no interaction tests reported to identify any potential treatment-effect modifiers. However, the subgroup analysis suggests that while PD-L1 status may influence the treatment effect of nivolumab monotherapy, this does not appear to be the case for the combination regimen.
Table: Primary outcomes for CHECKMATE 067 for relevant treatment groups

<table>
<thead>
<tr>
<th>Outcome (data cut-off)</th>
<th>Nivolumab plus ipilimumab (n=314)</th>
<th>Ipilimumab (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (February 2015)</td>
<td>Event accrual rate, % (n/N)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48% (151/314)</td>
<td>74% (234/315)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>11.5 months</td>
</tr>
<tr>
<td></td>
<td>2.9 months</td>
<td></td>
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<tr>
<td></td>
<td>Hazard ratio versus ipilimumab (99.5% CI)</td>
<td>0.42 (0.31 to 0.57), p&lt;0.001</td>
</tr>
</tbody>
</table>

PFS = progression-free survival, CI = confidence interval

Tumour responses were assessed as secondary outcomes. Investigator-assessed objective response rates (ORR), defined as complete and partial responses as per RECIST, were 58% (181/314) and 19% (60/315) in the nivolumab plus ipilimumab and ipilimumab monotherapy groups respectively, odds ratio 6.11 (95% confidence interval [CI]: 3.59 to 10.38), p<0.001. In the nivolumab plus ipilimumab group, ORR comprised complete responses in 11% (36/314) and partial responses in 46% (145/314) of patients. In comparison, complete responses were achieved in 2.2% (7/315) and partial responses in 17% (53/315) of ipilimumab-treated patients. The median times to objective response were similar across the treatment groups (2.76 to 2.79 months). Median duration of response was not reached in any group.³

The study assessed quality of life through the completion of several tools: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), the EuroQol 5D (EQ-5D), and the Work Productivity and Activity Impairment: General Health Questionnaire (WPAI: GH).³ Global health status measured with the EORTC QLQ-C30 tended to deteriorate over the first six months. However, no changes from baseline for any treatment group at any time-point exceeded the minimal clinically important change of 10 points. No clinically important changes from baseline was observed for any treatment group in the EQ-5D utility index, EQ-5D visual analogue scale, or in the functional and symptom scales within the EORTC QLQ-C30.⁵ Results have not been reported for the WPAI: GH. Results from week 67 were considered less reliable due to small sample sizes from reduced completion rates.

CHECKMATE 069 was a multi-centre, randomised, double-blind, controlled study with patient eligibility criteria similar to CHECKMATE 067. Patients were randomised (stratified by BRAF mutation status) in a 2:1 ratio to nivolumab plus ipilimumab (n=95) or to ipilimumab monotherapy (n=47). Dosing regimens were as used in CHECKMATE 067. Treatment continued until unacceptable toxicity, withdrawal of consent or if the investigator considered the patient was no longer obtaining clinical benefit. Upon un-blinding of treatment, patients in the nivolumab plus ipilimumab group discontinued treatment and those in the ipilimumab group could commence nivolumab monotherapy.⁴

The primary outcome measure was ORR measured by RECIST 1.1 analysed in the BRAF mutation negative population (n=109). The confirmed investigator-assessed ORR was 61% (44/72) in the nivolumab plus ipilimumab group and 11% (4/37) in the ipilimumab group. The odds ratio of an objective response was 13.0 (95% CI: 3.9 to 54.5), p<0.001. A significant benefit for PFS in the BRAF mutation negative population was found for the nivolumab plus ipilimumab regimen; hazard ratio was 0.40 (95% CI: 0.23 to 0.68), p<0.001. Median PFS was not reached in the nivolumab plus ipilimumab group and was 4.4 months for ipilimumab. Exploratory analysis of the cohort with BRAF V600 mutation-positive disease found ORR rates...
of 52% (12/23) and 10% (1/10) in the combination and ipilimumab groups respectively. There had been 19/33 PFS events, median PFS was 8.5 months and 2.7 months respectively and hazard ratio was 0.38 (95% CI: 0.15 to 1.00).\(^4\)

Patient-reported outcomes were assessed using the EQ-5D questionnaire and the EORTC QLQ-C30. There were no clinically important changes in Global Health status as measured by the EORTC QLQ-C30 in either treatment group over the six months of assessment. Changes from baseline in EQ-5D did not exceed the minimum clinically important difference for improvement, except for patients given ipilimumab monotherapy (from week 25 for the utility index, and from week 19 for the visual analogue scale).\(^6\)

During the SMC assessment process, overall survival data from CHECKMATE 069 was published. In an exploratory analysis after a median follow-up of two years, 37% (35/95) of nivolumab plus ipilimumab patients and 47% (22/47) of ipilimumab patients had died. Median overall survival had not been reached in either treatment group and two-year overall survival was estimated as 64% and 54% in the nivolumab plus ipilimumab and ipilimumab treatment groups, respectively, \(p=0.26.\)\(^7\)

*Other data were also assessed but remain commercially confidential.*

### Summary of evidence on comparative safety

In CHECKMATE 067, treatment-related adverse events (AEs) were reported in 96% of nivolumab plus ipilimumab patients, 82% of nivolumab monotherapy patients and in 86% of ipilimumab patients. Treatment-related AEs led to discontinuation in 29%, 7.7% and 13% of patients respectively.\(^3\)

Nivolumab plus ipilimumab was associated with a greater incidence of grade 3 or 4 treatment-related AEs: 55% versus 16% and 27% respectively. The incidence of individual grade 3 or 4 AEs that may adversely impact on daily well-being was less than 10% in all treatment groups. Diarrhoea was reported in 9.3% of nivolumab plus ipilimumab patients, 2.2% of nivolumab patients and in 6.1% of ipilimumab patients. Colitis was reported in 7.7%, 0.6% and 8.7% of patients respectively. The incidence of fatigue was 4.2%, 1.3% and 1.0% respectively.\(^3\)

Immune-mediated AEs were managed with immune-modulators in 83%, 47% and 56% of patients in the nivolumab plus ipilimumab, nivolumab, and ipilimumab monotherapy groups respectively. These AEs tended to be successfully managed with immune-modulators, with the exception of endocrine events (eg hypothyroidism) where there were low resolution rates (range: 29% to 40%).\(^3\)

Adverse events reported in the CHECKMATE 069 study were similar in pattern to the phase III study; gastrointestinal AEs (particularly colitis and diarrhoea) were the most frequently reported AE in the nivolumab plus ipilimumab group, and immune-related AEs tended to resolve with immunosuppressant therapy (with the exception of endocrine-related AEs). It was noted that most AEs occurred while patients were taking the two immune-oncology agents in combination rather than during the nivolumab monotherapy phase.\(^4\)
Summary of clinical effectiveness issues

Melanoma is the third most common type of skin cancer diagnosed in the UK. NHS Scotland cancer statistics show that melanoma was diagnosed in 1,248 people (3.9% of all cancer incidence) and there were 176 deaths due to melanoma in 2014. Incidence of melanoma increased by 22% over the previous ten years, and mortality increased by 2.3%. Median at diagnosis of melanoma is in the range of 65 to 69 years.

The submitting company requested that SMC considers nivolumab plus ipilimumab when positioned for use for the first-line treatment of advanced melanoma. The management of advanced melanoma is changing in NHS Scotland in response to the availability of immunotherapy and targeted therapies. Patients with BRAF V600 mutation-negative disease are offered immunotherapy with ipilimumab or the PD-1 receptor antibody, pembrolizumab. In patients with BRAF V600 mutation-positive disease, immunotherapy or the BRAF inhibitors vemurafenib or dabrafenib are recommended as per extant SMC advice for these agents. Patients not considered suitable for immunotherapy (eg requiring rapid disease control) or targeted therapy, may be offered palliative chemotherapy (eg dacarbazine). Clinical experts consulted by SMC have advised that the most relevant comparator in current practice is pembrolizumab. They considered BRAF inhibitors to be less relevant as comparators. At the time of this submission, nivolumab monotherapy was not considered a relevant comparator although this treatment has now been accepted for restricted use by SMC. Estimates of median overall survival with pembrolizumab treatment are available from the phase I KEYNOTE-001 study, and ranged from 23 to 32 months. The combination regimen of nivolumab plus ipilimumab meets SMC end-of-life and orphan-equivalent criteria.

The CHECKMATE studies compared nivolumab plus ipilimumab combination therapy with ipilimumab monotherapy. Until the decision by SMC to accept pembrolizumab for use in NHS Scotland, ipilimumab was considered the standard of care for patients requiring immunotherapy for their advanced disease. In CHECKMATE 067, nivolumab plus ipilimumab treatment was associated with clinically and statistically significant improvement in PFS compared with ipilimumab monotherapy. CHECKMATE 069 demonstrated superior radiological tumour response rates with nivolumab plus ipilimumab therapy when compared with ipilimumab. Overall survival data in both studies are immature. Furthermore, overall survival data from CHECKMATE 069 are confounded by patient crossover from ipilimumab to nivolumab monotherapy.

Improved efficacy over ipilimumab monotherapy is balanced by increased incidence of adverse events. The pattern of toxicity, eg immune-related reactions such as hepatitis, colitis and endocrinopathies, was similar to those known for the individual agents. Despite increased adverse events, health-related quality of life was not significantly worse when compared with ipilimumab monotherapy.

The CHECKMATE 067 study recruited patients with or without BRAF V600 mutation. In the study, 32% of patients had BRAF V600 mutation positive disease; this seems to be an under-representation of the general patient population in which 40 to 50% of advanced melanomas have this mutation. Furthermore, in practice, patients with BRAF V600 mutated disease are
likely to be given a BRAF inhibitor as first-line treatment; no direct comparative evidence is available for nivolumab plus ipilimumab with the BRAF inhibitors.

Both studies did not recruit patients with poorer performance status; data of efficacy and safety are available for patients with ECOG performance status 0 or 1 only. Given the toxicity associated with the combination regimen, it may be that only fitter patients may be considered for nivolumab plus ipilimumab in practice.

A significant proportion of patients allocated to ipilimumab in CHECKMATE 067 subsequently received pembrolizumab (29% at the February 2015 data cut-off). This is not a treatment option for patients in Scotland and may, therefore, reduce the generalisability of mature overall survival data when available.

Tumour responses in both studies were assessed using RECIST 1.1. This methodology may not fully capture the benefits of immune checkpoint inhibitors; some patients may initially have pseudo-progression that subsequently responds to treatment. Both CHECKMATE studies conducted initial planned tumour assessments 12 weeks after commencing randomised treatment, and allowed continuation of randomised treatment after progression if there was clinical benefit.

The summary of product characteristics notes that increased PFS in comparison with nivolumab monotherapy is only established in patients with low PD-L1 expression and 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”. Currently PD-L1 expression is not routinely tested in NHS Scotland.

The CHECKMATE 067 and 069 studies are considered to provide robust evidence for the efficacy and safety of the nivolumab plus ipilimumab regimen against ipilimumab (comparisons with nivolumab monotherapy were descriptive only). Direct comparative data with pembrolizumab are lacking. To support the economic case, the company conducted a frequentist, fixed-effects network meta-analysis (NMA) of nivolumab plus ipilimumab combination regimen with pembrolizumab monotherapy, using ipilimumab monotherapy as the common comparator. The network comprised three clinical studies of patients with advanced melanoma and outcomes compared were overall survival and progression-free survival.

The results of the NMA suggest that nivolumab plus ipilimumab is associated with improved PFS versus pembrolizumab monotherapy and ipilimumab monotherapy, and improved overall survival versus ipilimumab monotherapy. There was a numerical advantage for overall survival for nivolumab plus ipilimumab versus pembrolizumab. This is not unexpected given the immaturity of overall survival data from the constituent studies.

There were several weaknesses with the NMA. The literature search conducted by the company did not include pembrolizumab in the search strategy; studies were identified by consulting UK health-technology submissions for pembrolizumab. Studies included in the network providing evidence for pembrolizumab included a heterogeneous patient population including both those previously treated with ipilimumab and those who were ipilimumab naïve. The internal validity of the NMA results relies on the assumption that the treatment effect of pembrolizumab 2mg/kg versus 10mg/kg is not affected by prior treatment history. If considered valid, then the results of the NMA can be cautiously generalised to the Scottish population.
A NMA with the BRAF inhibitors was not considered feasible by the company, which cited issues such as non-proportional hazards with the BRAF inhibitor studies. A naïve indirect comparison of nivolumab plus ipilimumab with the BRAF inhibitors was presented. Point estimates of treatment differences were not presented, but incorporated directly into the economic analysis.

Clinical experts consulted by SMC considered that nivolumab plus ipilimumab combination therapy is a therapeutic advancement with improved tumour response and progression-free survival. In addition, the combination is active in patients with low levels of PDL-1. They considered that the place in therapy of nivolumab plus ipilimumab is in patients fit enough to tolerate the increased toxicity associated with the regimen.

A disadvantage for both patients and the service with the nivolumab plus ipilimumab regimen is the administration of nivolumab every two weeks (in the nivolumab monotherapy phase) whereas pembrolizumab is administered every three weeks. Clinical services will be familiar with managing the immune-related toxicities associated with immunotherapy although the increased incidence of these toxicities with the combination regimen may have additional service delivery implications.

*Other data were also assessed but remain commercially confidential.*

**Patient and clinician engagement (PACE)**

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of nivolumab in combination with ipilimumab, as an end-of-life and orphan-equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:
- Advanced melanoma is an aggressive and debilitating disease which commonly affects a younger population. The majority of patients have multiple metastases and develop incapacitating symptoms which can affect normal daily activities, with a resultant deterioration in quality of life.
- The aim of treatment with nivolumab and ipilimumab is to allow as many patients as possible to achieve durable disease control, and PACE participants viewed this treatment as another major advance in order to achieve that aim.
- PACE participants noted that the company positioning for first line use is unhelpful and may deny some patients the opportunity for a long term response.
- While the increased rate of toxicities with the combination regimen was noted, it was highlighted that clinicians are gaining a greater understanding in managing the adverse effects associated with immunotherapies.
- This regimen may enable some patients to return to work and maintain normal every day activities such as caring for children or elderly relatives. This is particularly important because the age group affected is predominantly of working age.

**Additional Patient and Carer Involvement**

We received a patient group submission from Melanoma Action and Support Scotland (MASScot). MASScot have not received any pharmaceutical company funding in the last two
years. A representative from MASScot participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

**Summary of comparative health economic evidence**

The submitting company presented a cost-utility analysis comparing nivolumab plus ipilimumab versus ipilimumab alone or pembrolizumab alone as first-line treatment in patients with advanced melanoma.

Clinical expert responses indicate that the relevant comparators in this indication are:
- Pembrolizumab in BRAF negative patients and some BRAF positive patients
- BRAF inhibitors (vemurafenib and dabrafenib) in BRAF positive patients (although this was considered to be less relevant as a comparator). A limited cost-utility analysis of nivolumab plus ipilimumab versus BRAF inhibitors was presented.

A cohort semi-Markov model was used to synthesise the evidence and predict costs and outcomes over a 40 year horizon. The model was structured as three linked Markov models: a three-state Markov model predicted overall survival (OS) and progression free survival (PFS), a treatment resource use Markov model to capture treatment costs, and a two-state on/off treatment Markov model to capture adverse events and treatment related disutility. This model structure is sufficient to capture the important health outcomes and costs for this decision.

Key clinical evidence was taken from the CheckMate 067 study with supporting evidence taken from the NMA of nivolumab plus ipilimumab combination regimen with pembrolizumab monotherapy reported in the clinical effectiveness section, and from a published pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in advanced melanoma.

OS estimates were based on parametric survival analysis of Checkmate 067 data for nivolumab plus ipilimumab combination therapy. For ipilimumab monotherapy, parametric survival analysis of Checkmate 067 data was used to predict survival over the first two years and the published pooled analysis data were used for the remaining time period. OS estimates for the pembrolizumab comparator were made under a proportional hazards assumption using a hazard ratio derived from the NMA. PFS estimates for both combination therapy and ipilimumab monotherapy were derived from parametric survival analysis of CheckMate 067 data. PFS for pembrolizumab was predicted using a hazard ratio derived from the NMA. A Gompertz curve for OS was selected for both combination therapy and ipilimumab monotherapy using goodness of fit statistics and visual fit criteria, in accordance with guidelines for parametric survival analysis. It should be noted that the choice of a Gompertz curve generates very high long-term survival estimates. OS and PFS for the comparison with BRAF inhibitors were taken from the naïve indirect comparison of nivolumab plus ipilimumab with the BRAF inhibitors reported in the clinical effectiveness section. OS and PFS in the dabrafenib comparison were assumed to be equivalent to those in the vemurafenib comparison.

Health state utility weights were estimated using direct EQ-5D data available from CheckMate 067 to derive values for progression free and progressed disease states and also utility decrements for each treatment arm. Pembrolizumab was assumed to have the same effect as
nivolumab monotherapy as observed in the CheckMate 067 study. The same assumption was made for BRAF inhibitors.

Resource use was estimated based on an analysis of CheckMate 067 resource-use data. This included adverse events, treatment administration, end-of-life care and subsequent therapy frequencies. Pembrolizumab was again assumed to be the same as the nivolumab monotherapy arm in the CheckMate 067 study. Frequencies of subsequent therapies and adverse events were taken from the naïve indirect comparison with BRAF inhibitors.

Medicine use for nivolumab was based on a time on treatment (TOT) parametric survival analysis using CheckMate 067 data. In addition, a treatment discontinuation rule was applied. All responding patients who had neither progressed nor stopped treatment for other reasons by 18 months stopped treatment at this time point. Approximately 18% of patients stop treatment because of the stopping rule. Ipilimumab consumption was based on the observed number of doses in the CheckMate 067 study. Pembrolizumab use was based on the assumption that all responding patients are taken off treatment at 18 months. Mean number of doses of each treatment were not presented.

A Patient Access Scheme (PAS) was proposed by the submitting company for both nivolumab and ipilimumab and both have been accepted by the Patient Access Scheme Assessment Group (PASAG) for implementation in NHS Scotland. Under the PAS, a simple discount is offered on the price of nivolumab and a simple discount is also offered on the price of ipilimumab. PAS are in place for pembrolizumab, vemurafenib and dabrafenib and were included in the analysis by using an estimate of the relevant price of each medicine.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS results can be presented.

The base case analysis reports an incremental cost-effectiveness ratio (ICER) of £8,453 per quality-adjusted life year (QALY) without PAS for nivolumab plus ipilimumab in combination versus ipilimumab alone. Incremental costs were £24,209 without PAS and incremental QALYs were 2.86. In the comparison with pembrolizumab, nivolumab plus ipilimumab in combination dominates pembrolizumab (i.e. nivolumab plus ipilimumab without PAS was more effective and less expensive). Incremental costs were -£24,977 without PAS and incremental QALYs were 1.42. In comparison with vemurafenib, the base case analysis reports an ICER of £9,881 without PAS. Incremental costs were £46,764 without PAS and incremental QALYs were 4.73. In comparison with dabrafenib, an ICER of £10,762 without PAS was reported. Incremental costs were £50,933 without PAS and incremental QALYs were 4.73.

Sensitivity analyses presented by the company indicate that the results are sensitive to OS parameters, the discount rate applied to health benefits and the hazard ratio used for pembrolizumab. Scenario analyses showed results are sensitive to the assumed functional forms in the survival analysis for OS and TOT. Using an alternative Weibull OS curve, the ICER vs. ipilimumab was £18,714 without PAS and combination therapy remained dominant compared to pembrolizumab without PAS. Treatment discontinuation rules also influenced results, under the least cost-effective scenario presented (complete responders are treated for a maximum of 18 months) the ICER vs ipilimumab was £25,384 without PAS. Combination therapy remained dominant versus pembrolizumab under most treatment stopping rule scenarios.
The main weaknesses in the analysis were:

- The key weakness is in the data available to estimate long-term survival. Only a maximum 28 months of follow-up data are available from Checkmate 067 to inform survival estimates over a 40-year time horizon. This introduces significant uncertainty both from sampling variance and structural uncertainty arising from the choice of functional form of the survival model. Interpretation of ICERs based on longer term projections should be cautious.
- No direct comparison is available for pembrolizumab and, therefore, the comparison relies on an indirect comparison. There is a high degree of uncertainty in the estimates from the indirect comparison. The hazard ratio for OS between pembrolizumab and the combination reported in the indirect treatment comparison described above was not statistically significantly, although there was a numerical advantage in OS and evidence of improved PFS in favour of combination therapy. However, the company has subsequently provided an analysis which removed non-significant differences in OS and combination therapy remained dominant versus pembrolizumab without PAS.
- No direct comparison is available for BRAF inhibitors. A naive indirect comparison was presented but there is significant uncertainty around the resulting estimates.
- There is some concern that the treatment discontinuation rules applied in the base case do not reflect actual clinical practice. Without the discontinuation rule, the predicted medicine consumption for nivolumab would likely be significantly higher. A sensitivity analysis provided by the company explores an alternative 24 month discontinuation rule. The ICER compared to ipilimumab for the 24 month discontinuation rule scenario for all responders was £7611 without PAS. In the comparison with pembrolizumab, combination therapy continued to dominate without PAS. The company also provided sensitivity analysis which removed the stopping rule from the economic analysis which generated an ICER of £32k versus ipilimumab and remained dominant versus pembrolizumab without PAS.

The Committee considered the benefits of nivolumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as nivolumab is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was able to accept nivolumab for restricted use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.*

### Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published a guideline on Melanoma: assessment and management of melanoma on 29 July 2015. For systemic anticancer treatment this recommends targeted treatment with dabrafenib and vemurafenib as options for treating unresectable or metastatic BRAF V600 mutant positive melanoma and immunotherapy with ipilimumab as an option for treating unresectable or metastatic melanoma that has been previously treated or not. These agents are recommended only if manufacturers provide them with discounts agreed in patient access schemes. Cytotoxic chemotherapy with dacarbazine can be considered for patients with stage IV metastatic melanoma if immunotherapy or targeted therapies are not suitable. Further chemotherapy should not be
routinely offered to patients with stage IV metastatic melanoma who have been previously treated with dacarbazine, except in the context of a clinical trial.

The European Society for Medical Oncology (ESMO) published Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, in 2015. These guidelines note that new therapeutic strategies including nivolumab, pembrolizumab, ipilimumab and BRAF inhibitors vemurafenib, encorafenib and dabrafenib (with or without MEK inhibitors such as cobimetinib and trametinib) demonstrate notable anti-tumour activity. These treatment options should be used in preference to chemotherapy and may be considered in the first and second line treatment setting. Tumour tissues should be screened for the BRAF V600 mutation. The preferred first-line therapies are still a matter for debate. Response rates to combination therapy with BRAF inhibitors and MEK inhibitors are higher however some responses to PD-1 inhibitors are durable.

**Additional information: comparators**

Pembrolizumab, ipilimumab, BRAF inhibitors (dabrafenib and vemurafenib), and palliative chemotherapy such as dacarbazine are currently used in NHS Scotland. Nivolumab monotherapy has recently been recommended for use by SMC.

### Cost of relevant comparators

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<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost for initial 26 weeks (£)*</th>
</tr>
</thead>
</table>
| nivolumab plus           | **Initial phase** *(four doses)*  
                          | nivolumab 1mg/kg IV infusion every three weeks  
                          | ipilimumab 3mg/kg IV infusion every three weeks  
                          | **Second phase**  
                          | nivolumab 3mg/kg IV infusion every two weeks  | 99,576 |
| ipilimumab               | 3mg/kg by IV infusion every three weeks for four doses                      | 75,000                      |
| vemurafenib              | 960mg orally twice daily continuously                                        | 45,500                      |
| nivolumab                | 3mg/kg by IV infusion every two weeks                                        | 36,862                      |
| dabrafenib               | 150mg orally twice daily continuously                                       | 36,400                      |
| pembrolizumab            | 2mg/kg by IV infusion every three weeks                                      | 35,505                      |
| trametinib plus dabrafenib** | trametinib 2mg orally once daily continuously  
                          | dabrafenib 150mg orally twice daily continuously                            | 65,520                      |
| dacarbazine              | 1,000mg/m² IV infusion every three weeks                                     | 1,260                       |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online (June 2016), except for nivolumab (from dictionary of medicines and devices browser) on 27 June 2016. Doses are based on body weight of 70kg and body surface area 1.8m². These costs do not take any patient access schemes into consideration. *costs include doses given up to and including day 182 **SMC advice issued September 2016
The submitting company estimated there would be 96 patients eligible for treatment with nivolumab in year 1 and 112 patients in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.
References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Bristol Myers Squibb Pharma EEIG. Summary of product characteristics - Opdivo 10 mg/mL concentrate for solution for infusion. 11 May 2016 [cited 11 July 2016]; Available from: www.medicines.org.uk

This assessment is based on data submitted by the applicant company up to and including 12 August 2016.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place
for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.