Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

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

SMC No. (1120/16)

Bristol-Myers Squibb Pharmaceuticals Ltd

08 July 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 Scotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the end of life and orphan medicine process

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

Indication under review: as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.

SMC restriction: patients previously untreated with ipilimumab.

In a phase III randomised double-blind study, treatment with nivolumab extended overall survival compared with a palliative chemotherapy in patients with previously untreated advanced melanoma without a BRAF mutation. In an ongoing open label phase III study, treatment with nivolumab, at the time of primary analysis, extended overall response rate, compared with investigator's choice of chemotherapy in patients with advanced melanoma previously treated with an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) treatment or an anti-CTLA-4 treatment and a BRAF inhibitor.

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

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of nivolumab. This advice 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 views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 08 August 2016

Indication

As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Dosing Information

The recommended dose of nivolumab is 3mg/kg administered intravenously over 60 minutes every two weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

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

Product availability date

June 2015. Nivolumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 29 May 2015.

Nivolumab 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 and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity which is involved in the control of T-cell immune responses. Nivolumab therefore potentiates T-cell responses, including anti-tumour responses, by blocking PD-1 binding to PD-L1 and PD-L2 in antigen presenting cells, tumours or other cells in the tumour microenvironment.[1] Nivolumab is indicated as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. This submission relates to the monotherapy indication only; the use of nivolumab in combination with ipilimumab will be considered in a future SMC submission.

The evidence to support the use of nivolumab in patients with advanced (unresectable or metastatic) melanoma comes from three phase III, multi-centre randomised controlled studies (CheckMate 066,[2,3] CheckMate 067,[4] and CheckMate 037[3,5]) in adults (≥18 years) with an European Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

CheckMate 066 was a double-blind study designed to assess the efficacy of nivolumab compared with dacarbazine in 418 patients with previously untreated advanced melanoma without a BRAF mutation.[2] Patients were randomised equally to receive nivolumab 3mg/kg intravenous (IV) infusion every two weeks or dacarbazine 1000mg/m^2 body-surface area IV infusion every three weeks. Treatment continued until investigator-assessed disease progression (measured by Response Evaluation Criteria in Solid Tumours [RECIST] v1.1) or unacceptable adverse effects. Treatment could be continued after disease progression if a patient was experiencing a clinical benefit and did not have substantial adverse effects. Stratification was according to tumour PD-L1 status (positive versus negative or indeterminate) and metastasis stage (M0, M1a, or M1b versus M1c).[2,3] The study was unblinded at an unplanned interim database lock because of a significant difference in overall survival in favour of nivolumab, and the protocol was amended to allow patients enrolled in the dacarbazine group to receive nivolumab. The study results reported are from the double-blind part of the study before the amendment.[2]

The primary outcome measured in the intention to treat (ITT) population was overall survival. After a median follow up of 8.9 months in the nivolumab group and 6.8 months in the dacarbazine group, the median overall survival was not reached in the nivolumab group and was 10.8 months in the

dacarbazine group. The estimated overall survival rate at one year was 73% in the nivolumab group and 42% in the dacarbazine group. The hazard ratio (HR) for death was 0.42 (99.79% confidence interval [CI]: 0.25 to 0.73), p<0.001.[2,3]

The median investigator-assessed progression-free survival (PFS) was 5.1 months in the nivolumab group and 2.2 months in the dacarbazine group, HR 0.43 (95% CI: 0.34 to 0.56), p<0.001. The objective response rate (ORR) was 40% (84/210) in the nivolumab group and 14% (29/208) in the dacarbazine group, odds ratio 4.06 (95% CI: 2.52 to 6.54), p<0.001. The proportion of patients with a complete response was 7.6% (16/210) in the nivolumab group and 1.0% (2/208) in the dacarbazine group.[2]

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EuroQol-five dimension (EQ-5D) questionnaire. The adjusted completion rates at baseline for the EQ-5D utilities were 70% in the nivolumab group and 65% in the dacarbazine group. In the nivolumab group, improvements from baseline (EQ-5D utilities: 0.778 versus 0.711; EQ-5D visual analogue scale [VAS] scores: 70.9 versus 69.1) in EQ-5D utility index were noted from week 7 (0.027; n=132; p=0.011) through to week 49 (0.045; n=38; p=0.034) and in EQ-5D visual analogue scale (VAS) scores at week 25, 31, 37, 49 and 61 (p≤0.03). No quality of life changes were noted for the dacarbazine group prior to study drop-out. Assessment of quality of life in the dacarbazine group after week 13 was unfeasible due to the drop-out rate in this group.[6]

An updated survival analysis, after a median follow up of 18.5 months in the nivolumab group and 10.9 months in the dacarbazine group, has recently been presented; 38% of patients in the nivolumab group and 67% of patients in the dacarbazine group have died. The median overall survival has still not been reached in the nivolumab group and was 11.2 months in the dacarbazine group, HR 0.43 (95% CI: 0.33 to 0.57, p<0.001). The estimated two-year overall survival rates were 58% and 27% respectively.[7]

CheckMate 067 is an on-going double-blind study designed to assess the efficacy of nivolumab or nivolumab plus ipilimumab compared with ipilimumab alone in 945 patients with previously untreated advanced melanoma and known BRAF V600 mutational status.[4] The combination of nivolumab with ipilimumab is not being considered within this submission, so this treatment group is not discussed further. Patients were stratified according to tumour PD-L1 status (positive versus negative or indeterminate), BRAF mutation status (V600 mutant positive versus wild type) and metastasis stage (M0, M1a, or M1b versus M1c), then randomised to receive nivolumab 3mg/kg IV infusion every two weeks (n=315) or ipilimumab 3mg/kg IV infusion every three weeks for four doses (n=316). Treatment continued until investigator-assessed disease progression (measured by RECIST v1.1) or unacceptable adverse effects. Treatment could be continued after disease progression if a patient was experiencing a clinical benefit and did not have substantial adverse effects.[4]

The co-primary outcomes in the ITT population are PFS and overall survival. The primary outcome at the database lock reported here is the final PFS analysis. Overall survival data are not yet available. After a median follow up of 12.2 to 12.5 months, the median PFS was 6.9 months in the nivolumab group and 2.9 months in the ipilimumab group, HR 0.57 (95% CI: 0.43 to 0.76, p<0.001).[4]

The investigator-assessed ORR was 44% (138/316) in the nivolumab group and 19% (60/315) in the ipilimumab group, odds ratio 3.40 (95% CI: 2.02 to 5.72). The proportion of patients with a complete response was 8.9% (28/316) in the nivolumab group and 2.2% (7/315) in the ipilimumab group.[4]

CheckMate 037 is an on-going open-label study designed to assess the efficacy of nivolumab compared with investigator's choice of chemotherapy in 405 patients with advanced melanoma who had previously received treatment with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

treatment such as ipilimumab or ipilimumab and BRAF inhibitor (in patients with tumour that was BRAF V600 mutation positive). Patients were randomised in a 2:1 ratio to receive nivolumab 3mg/kg IV infusion every two weeks or investigator's choice of chemotherapy (dacarbazine 1000mg/m^2 IV infusion every three weeks or paclitaxel 175mg/m^2 IV infusion plus carboplatin area under the curve 6 IV infusion every three weeks). Treatment continued until investigator-assessed disease progression (measured by RECIST v1.1) or unacceptable adverse effects. Treatment with nivolumab could be continued after disease progression if a patient was experiencing a clinical benefit and did not have substantial adverse effects. Stratification was according to tumour PD-L1 status (positive versus negative or indeterminate), BRAF status (BRAF wild-type versus BRAF V600 mutant) and clinical benefit from previous anti-CTLA-4 treatment.

The co-primary outcomes of ORR (assessed by an independent review committee) and overall survival were compared in the nivolumab group and the investigator's choice of chemotherapy group. The primary outcome reported here is ORR; overall survival data are not yet available.[3,5] At the time of the primary analysis for ORR, 120 patients had received nivolumab and 47 patients had received investigator's choice of chemotherapy and had at least six months of follow-up (per-protocol population). After a median follow up of 8.4 months of treatment in the per-protocol population, the ORR in the nivolumab group was 32% (38/120): 3.3% of patients had a complete response and 28% of patients had a partial response. In addition, 23% of patients had stable disease, 35% of patients had progressive disease and response was not established in 10% of patients. In the investigator's choice of chemotherapy group, the ORR was 11% (all partial responses). In addition, 34% of patients had stable disease, 32% had progressive disease and response was not established in 23% of patients.[5]

In the intention-to-treat analysis (182 patients at this time point), median PFS was 4.7 months in the nivolumab group and 4.2 months in the chemotherapy group (HR 0.82 [99.99% CI: 0.32 to 2.05], descriptive comparison). The six-month PFS rates were 48% and 34% respectively.[5]

Summary of evidence on comparative safety

Treatment-related adverse events, grade 3 and 4 adverse events, serious adverse events and adverse events leading to study drug discontinuation are presented in table 1. Generally nivolumab had similar or better tolerability than the comparator treatment.[2,4-5]

Table 1. Treatment-related adverse events in the phase III studies[2,4-5]

	CheckMate 066		**CheckMate 067**		**CheckMate 037**	
	nivolumab n=206	dacarbazine n=205	nivolumab n=313	ipilimumab n=311	nivolumab n=268	ICC n=102
TR adverse event	74%	76%	82%	86%	68%	79%
Grade 3 and 4 TR adverse event	12%	18%	16%	27%	9%	31%
TR serious adverse event	9.2%	8.8%	NR	NR	5%	9%
Adverse event leading to study drug discontinuation	6.8%	12%	7.7%	15%	2.6%	6.9%

TR: treatment-related, ICC: investigator's choice of chemotherapy, NR: not reported

In CheckMate 066, the most common treatment-related adverse events reported in patients taking nivolumab (versus patients taking dacarbazine) were fatigue (20% versus 15%), pruritus (17% versus 5.4%), nausea (17% versus 42%), diarrhoea (16% versus 16%), rash (15% versus 2.9%), vitiligo (11% versus 0.5%), constipation (11% versus 12%) and asthenia (10% versus 12%).[2]

In CheckMate 067, the most common treatment-related adverse events reported in patients taking nivolumab (versus ipilimumab) were fatigue (34% versus 28%), rash (26% versus 33%), pruritus (19% versus 35%), diarrhoea (19% versus 33%), nausea (13% versus 16%) and decreased appetite (11% versus 13%).[4]

Similar adverse events were reported for CheckMate 037.[5]

Summary of clinical effectiveness issues

In patients with advanced (unresectable or metastatic) melanoma, current treatment depends on BRAF mutational status. In patients with advanced melanoma without a BRAF mutation, the current first-line treatment is ipilimumab. In patients with BRAF V600 mutant positive disease, targeted therapy with vemurafenib or dabrafenib are generally used first-line and ipilimumab second-line. In patients who have received prior treatment with ipilimumab, treatment options are limited to palliative chemotherapy such as dacarbazine. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, as prognosis for patients with metastatic melanoma remains relatively poor. Pembrolizumab, another monoclonal antibody which binds to the PD-1 receptor, has been accepted for use by SMC in patients who have not received previous treatment with ipilimumab. Nivolumab meets SMC end of life and orphan equivalent criteria.

The primary outcome in the pivotal CheckMate 066 was overall survival; the difference for nivolumab compared to dacarbazine was statistically significant and clinically relevant. The two other phase III studies, CheckMate 067 and CheckMate 037, have so far each reported positive results for the surrogate primary outcomes of PFS and ORR respectively. Overall survival analyses from these two studies are awaited.

CheckMate 066 was stopped at an unplanned interim analysis on the advice of the data monitoring committee because of the survival benefit associated with nivolumab; the median overall survival in the nivolumab group has not been reached.[2,7] The data monitoring committee was assessing survival monthly, introducing the possibility of informative bias. However, the European Medicines Agency (EMA) considered that the magnitude of the effect seen suggests that bias is unlikely.[3]

CheckMate 037 is an open-label study, therefore tumour assessments were performed centrally. The open-label nature of the study may have led to the high drop-out rate in the investigator's choice of chemotherapy group; 133 patients were allocated to this treatment group but only 102 patients (77%) received treatment. In the nivolumab group, 99% of randomised patients (268/272) received treatment.[3]

RECIST v1.1 is the regulatory standard for measuring tumour response and has been used in the three pivotal studies. However, these criteria may not fully capture the benefits of immune mediated treatment. Some patients may initially have progressive disease that subsequently responds to treatment with nivolumab: this delayed response is not captured by RECIST v1.1.[5]

The comparator used in CheckMate 066, dacarbazine, is less relevant to patients with previously untreated advanced melanoma without a BRAF mutation because of the use of ipilimumab in Scottish

practice. The CheckMate 067 study has demonstrated a PFS benefit associated with nivolumab over ipilimumab in patients with previously untreated advanced melanoma (and known BRAF mutational status). Patients with wild-type BRAF status (68% of the study population) would currently be offered ipilimumab and there was a significant benefit associated with nivolumab over ipilimumab in this subgroup. Patients with BRAF V600 mutant tumours (32% of the study population) would currently be offered dabrafenib or vemurafenib first line and ipilimumab second line. There was no direct evidence presented comparing nivolumab with the BRAF inhibitors and no clinical evidence presented for the use of nivolumab after a BRAF inhibitor in patients who have not had ipilimumab. The CheckMate 037 study compared nivolumab with investigator's choice of chemotherapy (dacarbazine or paclitaxel plus carboplatin) in patients who had previously received ipilimumab or ipilimumab and BRAF inhibitor (in patients with tumour that was BRAF V600 mutation positive). In current Scottish practice, palliative chemotherapy such as dacarbazine is a relevant comparator in this patient group. The proportion of patients in CheckMate 037 with BRAF V600 mutation positive tumours was low. Further data have been requested by the Committee for Medicinal Products for Human Use (CHMP) to confirm the benefit of nivolumab in this subgroup.[3]

Covariate adjusted indirect comparisons via parametric survival modelling of patient level data were carried out to support the economic analysis and allow nivolumab to be compared with ipilimumab and the BRAF inhibitors with respect to overall survival and PFS in patients with advanced (unresectable or metastatic) melanoma. Data from CheckMate 066 were used to represent nivolumab and data from three other studies were used to represent the comparators. The outcomes presented were time to progression (TTP) pre- and post-100 days, pre-progression survival (PrePS) and post-progression survival (PostPS). TTP and PrePS were used to inform long-term extrapolation of PFS. TTP, PrePS and PostPS were used to inform the long-term extrapolation of overall survival. A number of assumptions have been made in order for such analyses to be performed. For the comparison between nivolumab and ipilimumab:

- Equivalence of dacarbazine and gp100 melanoma peptide vaccine (gp100)
- Line of treatment is not independently prognostic and does not independently impact treatment effectiveness.
- No difference between treatment effects by BRAF mutation status
- Equivalence of ipilimumab 3mg/kg + gp100 and ipilimumab 3mg/kg

For the comparison of nivolumab with the BRAF inhibitors, it was assumed that vemurafenib and dabrafenib were equivalent. As patient level data were not available, the published Kaplan-Meier curves were estimated using digitisation software and pseudo patient level data were created. The results of the comparison between nivolumab and ipilimumab favour nivolumab for the outcome TTP post-100 days. PostPS was similar for the two interventions and PrePS could not be adjusted due to the limited amount of data available from CheckMate 066. The results for the comparison between nivolumab and the BRAF inhibitors suggest that, initially, the BRAF inhibitors may increase overall survival and PFS due to the speed of their mechanism of action but, in the long-term, nivolumab is expected to increase survival. The number of assumptions and the multiple modelling necessary to perform these indirect comparisons suggests that the results should be treated with caution. The submitting company advised that a network meta-analysis could not be performed and, therefore, all the available evidence, including the direct evidence available from CheckMate 067, was not considered, possibly introducing bias.

Nivolumab is given as an IV infusion every two weeks and, according to the marketing authorisation, treatment should continue as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. The optimal duration of treatment is unknown. The submitting company has advised that a maximum of two years duration of therapy is appropriate, based on the phase I study of nivolumab showing that patients continue to respond to nivolumab post study discontinuation.[8]

Clinical experts consulted by SMC considered that nivolumab is a therapeutic advancement because of its improved efficacy and tolerability compared with ipilimumab and dacarbazine. For patients who have not previously received ipilimumab, the introduction of nivolumab would offer an alternative to ipilimumab, with an improved PFS. Ipilimumab is given by IV infusion every three weeks for a maximum of four infusions. In the first line setting in patients with BRAF V600 mutant-disease, nivolumab is an alternative to the oral BRAF inhibitors, dabrafenib and vemurafenib. For patients who have previously received ipilimumab and, if appropriate, a BRAF inhibitor, nivolumab offers an alternative to palliative chemotherapy such as dacarbazine. Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the patient and/or service delivery due to the method of administration and duration of therapy.

Patients should be monitored for immune-related adverse events, including pneumonitis, colitis, hepatitis, nephritis, renal dysfunction, endocrinopathies or rash.[1]

Summary of 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, 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:

- Metastatic melanoma is an incurable cancer with a poor life expectancy. It affects a disproportionate number of young adults and often leads to complex and severe symptoms.
- Despite recent advances in systemic therapy, the overall prognosis remains poor. After failure of BRAF inhibitors, and in patients without BRAF mutations, immunotherapy is the treatment of choice.
- There is an unmet need for patients who have previously been treated with ipilimumab (pembrolizumab is not approved by SMC in this setting). Clinicians emphasised that nivolumab would also be of benefit for previously untreated patients where immunotherapy is indicated. Nivolumab and pembrolizumab were discussed as being the most active immunotherapy agents in advanced melanoma.
- PACE participants highlighted that nivolumab has been shown to improve overall survival compared to chemotherapy and improve response rates compared to ipilimumab or chemotherapy.
- Clinicians described how both nivolumab and pembrolizumab were easier to manage with regards to treatment-related toxicities compared to ipilimumab.
- Nivolumab can lead to a rapid response which may then enable some patients to return to work and normal everyday activities. This is particularly important because the age group affected is predominantly of working age.
- Clinicians emphasised that nivolumab has been shown to be active irrespective of being used first or second-line and they would welcome the widest possible positioning to enable them to individualise care for their patients.

Additional Patient and Carer Involvement
We received a patient group submission from the Melanoma Action Support Scotland (MASScot). The patient group has not received any pharmaceutical company funding in the past two years. A representative from the patient group also participated in the PACE meeting. The keys 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, using a semi-Markov survival model over a 40 year time horizon, for two patient subgroups with advanced (unresectable or metastatic) melanoma. For BRAF mutation-negative patients, nivolumab was compared against ipilimumab or dacarbazine. For BRAF mutation-positive patients, nivolumab was compared against ipilimumab, dabrafenib or vemurafenib.

In terms of model structure, health states were defined by four different measures relevant to the evaluation of the clinical and cost-effectiveness of nivolumab compared to its comparators. Disease progression status was modelled using three health states: progression free survival, progressed disease and death. Utility was captured through the three disease progression status health states and the inclusion of two time to death health states: ≥30 days before death and <30 days before death. Resource use and cost were modelled through four health states: first year, second year, third and subsequent years after treatment initiation, 12 weeks before death and death. Medicines costs were captured through two health states: on and off treatment. The same overall model structure is applied to all treatments within both the BRAF-mutation positive and BRAF-mutation negative subgroups. Patients treated with nivolumab were assumed to be treated for a maximum of two years.

The sources of the clinical data used in the analysis included a covariate adjusted indirect comparison which compared nivolumab with ipilimumab and the BRAF inhibitors using parametric survival modelling of patient level data. Long-term melanoma registry data were used to capture overall survival (OS) from year 2 onwards for dacarbazine and the BRAF inhibitors. Pooled ipilimumab data from phase II and phase III studies were used to model survival from year 3 onwards for nivolumab and ipilimumab. Adverse event data for each medicine were also estimated from relevant phase III studies.

Utility estimates were taken from the CheckMate 066 study which captured EQ-5D data. Patient utility declined in the model as patients moved closer to death and as their disease progressed. The model also included a utility decrement for adverse events.

Medicines costs were included in the analysis, as were costs associated with administration, treatment initiation, end of life care, pre-palliative care disease management, palliative-care disease management and adverse events. The economic model also included the cost of subsequent use of ipilimumab. This cost was applied to 29.7% and 22.2% of patients who discontinued treatment in the BRAF mutation negative and positive analysis respectively. The subsequent use of ipilimumab cost was not included in the model for patients who were initiated on ipilimumab at the start of the analysis.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a discount is offered on the cost of the medicine. SMC would wish to present the with-PAS incremental cost-effectiveness ratios (ICERs), costs and quality adjusted life years (QALYs) 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 ICERs can be presented.

For BRAF mutation negative patients, the base case results presented as an incremental analysis, indicated that the ICER for nivolumab versus dacarbazine was £23,613 per QALY without PAS. Ipilimumab was excluded from the incremental analysis due to extended dominance and the pairwise ICER versus ipilimumab was £24,483 without PAS. A PAS is in place for ipilimumab and this was included in the analysis by using an estimate of the relevant price of ipilimumab.

In terms of the comparison versus ipilimumab, the without-PAS ICER was most sensitive to treatment duration and treatment discontinuation as follows: no maximum treatment duration (£79,257), 25% of patients who remain on treatment at 2 years discontinue at 2 years (£65,305), 100% of patients that discontinue at 2 years have registry OS for life (£60,432), 50% of patients who remain on treatment at 2 years discontinue at 2 years (£51,528), maximum treatment duration of 5 years (£44,962). For the comparison against dacarbazine, the without-PAS ICER was most sensitive to: no maximum treatment duration (£52,877), 25% of patients who remain on treatment at 2 years discontinue at 2 years (£45,487), 10 year time horizon (£43,353), 50% who remain on treatment at 2 years patients discontinue at 2 years (£38,147), maximum treatment duration of 5 years (£34,628).

For BRAF mutation positive patients, the base case result presented as pairwise comparisons indicated that the ICER for nivolumab versus ipilimumab was £17,362 without PAS. For comparisons against vemurafenib and dabrafenib the without-PAS ICERs were £4,832 and £6,209 respectively. A PAS is in place for ipilimumab, vemurafenib and dabrafenib and were included in the analysis by using an estimate of the relevant PAS price of each medicine.

In relation to the BRAF mutation positive patients, the ICER versus ipilimumab, dabrafenib and vemurafenib was most sensitive to no maximum treatment duration which generated without-PAS ICERs of £59,623, £35,789 and £34,538 respectively, and 25% of patients who remain on treatment at 2 years discontinue at 2 years of £48,904, £28,318 and £27,035 respectively. For the comparison against ipilimumab, the analysis was also sensitive to 100% of patients discontinue at 2 years have OS registry for life £40,578 without PAS. For comparisons against dabrafenib and vemurafenib, the analysis was also most sensitive to 50% of patients who remain on treatment at 2 years discontinue at 2 years which generated without-PAS ICERs of £20,898 and £19,583 respectively.

The main weaknesses were:

- The model assumed patients were not treated with nivolumab for longer than 2 years, which was not included in the clinical studies. Discussion at SMC indicated that a stopping rule at 2 years would be potentially difficult to implement and that patients who respond would most likely continue on treatment. However, the economic model was sensitive to this assumption as, when the proportion of patients who remained on treatment beyond two years was increased, the ICER increased significantly, as shown. The company submitted a clinical consensus letter which supports the stopping rule used in the economic model. The letter was signed by five clinicians including two clinicians from Scotland. The SMC clinical experts indicated that it was a plausible assumption but was associated with some uncertainty.

- In terms of the comparison against dabrafenib and vemurafenib in the BRAF mutation positive subgroup, similar weaknesses were noted with the indirect comparison which generated PFS and OS estimates for the BRAF inhibitors. In addition, the SMC Statistical Advisor noted that the BRAF inhibitors generate more favourable PFS and OS estimates in year 1, whereas nivolumab generates improved PFS and OS over the long term when the extrapolated curves are taken into account. OS and PFS were modelled using a state transition approach for nivolumab, while an area under the curve structure was used to model these outcomes for the BRAF inhibitors. It was difficult to determine whether the different approaches caused bias; however, the company was able to reference a published study in order to support the methods adopted in the economic evaluation.

- The structure of the economic model presented by the company may be more applicable to a population which is untreated with ipilimumab, rather than to patients who have already received ipilimumab. This was because the economic analysis accounted for subsequent ipilimumab use when estimating OS and costs and the SMC clinical experts suggested that

patients would not receive ipilimumab post-nivolumab if they had received ipilimumab as a line of therapy before nivolumab. The company has suggested that the results presented are generalisable to a 'previously treated with ipilimumab population', and provided supportive data. However, there were weaknesses with the data provided and SMC expert responses are mixed, with one expert suggesting outcomes for nivolumab may be different depending on whether or not patients have received previous treatment with another medicine. The company has provided additional sensitivity analyses for a pre-treated with ipilimumab or BRAF inhibitor population, but the robustness of these analyses is uncertain and additional sensitivity analysis was not available to enable these analyses to be taken as a potential base case in this population.

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 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 accepted nivolumab for restricted use in NHS Scotland. Use was restricted to patients previously untreated with Ipilimumab.

*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.[9] 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 therapy 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.[10] These guidelines note that new therapeutic strategies including nivolumab, pembrolizumab, ipilimumab and BRAF inhibitors vemurafenib, encorafenib and dabrafenib (with or without MEK inhibitors) 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.

A collaboration of multi-disciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer published; Diagnosis and treatment of melanoma, European consensus-based interdisciplinary guideline - update 2012.[11] It states that the two main goals of systemic therapy of metastatic disease are prolongation of survival and reduction of tumour size or load with a resultant increase in symptom-free course or a decrease in symptoms. Treatments included in the guidance are targeted therapy (vemurafenib), immunotherapy (ipilimumab) and chemotherapy (dacarbazine). The

guidance notes there are insufficient data to establish a treatment algorithm for stage IV melanoma. However general principles include:

- BRAF mutated patients should be offered treatment with BRAF inhibitors or experimental drugs blocking the MAP kinase and PI3K pathways, preferably still in the context of clinical trials designed to reduce the emergence of drug resistance.
- Patients whose disease progresses on first-line treatment and with health status of presumably six or more months should be offered ipilimumab or other immunotherapies in the context of clinical trials as they are made available.
- Non-BRAF-mutated patients and those progressive under BRAF inhibitors and immunotherapies should be considered for chemotherapy.

This guideline predates the availability of newer agents.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 72; Cutaneous Melanoma in July 2003 (and updated in February 2004).[12] This guideline was withdrawn in February 2015 and is currently under review.

Additional information: comparators

Ipilimumab, vemurafenib, dabrafenib and palliative chemotherapy such as dacarbazine. Pembrolizumab has been accepted for use by SMC for patients who have not received previous treatment with ipilimumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 6 months (£)
Nivolumab	**3mg/kg by IV infusion every two weeks**	**31,596**
Ipilimumab	3mg/kg by IV infusion every three weeks for four doses	75,000
Vemurafenib	960mg orally twice daily continuously	45,500
Dabrafenib	150mg orally twice daily continuously	36,400
Pembrolizumab	2mg/kg by IV infusion every three weeks	31,560
Dacarbazine	1000mg/m^2 IV infusion every three weeks	1,060

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMC dictionary of medicines and devices browser on 14 April 2016. Doses are based on body weight of 70kg and body surface area 1.8m^2. Dacarbazine cost has changed since previous submission. These costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment in the BRAF mutation positive subgroup to be 63 patients in year 1, rising to 73 in year 5 and estimated 11 patients would be treated in year 1 and 10 by year 5. In the BRAF mutation negative group, 68 and 80 patients were assumed to be eligible in years 1 and 5 respectively, with estimated treated patient numbers of 20 and 17 in years 1 and 5 respectively.

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.

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

References

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

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8. Topalian SL, Sznol M, McDermott DF, *et al*. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014;32(10):1020-30.

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10. Dummer R, Hauschild A, Guggenheim M. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015;26(Supplement 5):v126–v132.

11. Garbe C, Peris K, Hauschild A, *et al.* Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2012. European journal of cancer. 2012;48(15):2375-90.

12. Scottish Intercollegiate Guidelines Network. Guideline number 72; Cutaneous Melanoma. 2003. Updated February 2004. www.sign.ac.uk

This assessment is based on data submitted by the applicant company up to and including **17 June 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*.

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.