pembrolizumab 50mg powder for concentrate for solution for infusion (Keytruda®)  
SMC No. (1086/15)

Merck Sharp and Dohme Ltd

9 October 2015

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 full submission assessed under the end of life and orphan equivalent process

**pembrolizumab (Keytruda®)** is accepted for use within NHS Scotland.

**Indication under review**: as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. This submission relates to use in adults previously untreated with ipilimumab.

In a phase III randomised open-label study, treatment with pembrolizumab (at unlicensed doses) extended median progression free survival and overall survival compared with other immune therapy in patients with advanced melanoma previously untreated with ipilimumab.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pembrolizumab. This advice is contingent upon the continuing availability of the patient access scheme 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.

SMC has also assessed pembrolizumab as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously treated with ipilimumab and has advised that it is not recommended for use within NHS Scotland in this setting (SMC No.1087/15).

Chairman,
Scottish Medicines Consortium
Indication
As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults (untreated with ipilimumab).

Dosing Information
The recommended dose is pembrolizumab 2mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

Product availability date
July 2015.

Pembrolizumab meets end of life and orphan-equivalent criteria.

Summary of evidence on comparative efficacy
Pembrolizumab 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. Pembrolizumab 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. Pembrolizumab has received marketing authorisation as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. In this submission, the submitting company has requested that SMC considers the use of pembrolizumab for patients with unresectable or metastatic melanoma untreated with ipilimumab. The company submitted separately for patients with advanced (unresectable or metastatic) melanoma previously treated with unresectable or metastatic melanoma untreated with ipilimumab. SMC has previously accepted pembrolizumab for patients with unresectable or metastatic melanoma who have received prior therapy and as first-line use. Vemurafenib and dabrafenib are licensed as monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. SMC accepted vemurafenib and dabrafenib for restricted use as first-line therapy.

The evidence to support pembrolizumab in advanced melanoma in patients who have not received previous ipilimumab therapy comes from one pivotal study (KEYNOTE-006). This was a randomised, controlled, open-label, phase III study in 834 patients with advanced melanoma which compared two doses of pembrolizumab with ipilimumab. Eligible patients were aged at least 18 years and had histologically confirmed unresectable stage III or IV melanoma. They
had received no more than one previous systemic therapy for advanced disease which excluded CTLA-4, PD-1 or PD-L1 inhibitors. Patients had known BRAF V600 mutational status. No prior BRAF inhibitor treatment was required for patients with normal lactate dehydrogenase (LDH) levels and no clinically significant tumour-related symptoms or evidence of rapidly progressive disease. Patients had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1.\textsuperscript{2}

Patients were randomised in a ratio of 1:1:1 to receive pembrolizumab 10mg/kg intravenously (IV) every 3 weeks or every 2 weeks, or ipilimumab 3mg/kg IV every 3 weeks (for four doses, until disease progression or unacceptable toxicity). Treatment with pembrolizumab was continued for up to 24 months until disease progression or unacceptable toxicity occurred. If a patient had been treated for at least 6 months and achieved a complete response they could discontinue pembrolizumab at least two doses after the complete response was confirmed. Randomisation was stratified by ECOG performance status (0 versus 1), line of therapy (first versus second), and PD-L1 expression (positive versus negative).\textsuperscript{2}

There were two co-primary outcomes: progression-free survival (PFS), defined as the time from randomisation until documented disease progression according to Response Evaluation Criteria in Solid Tumours [RECIST] or death from any cause, and overall survival (OS), defined as the time from randomisation until death from any cause. At the time of the first interim analysis (cut-off date 3 September 2014), after a median follow-up of 7.9 months, there had been PFS events in 57\% (157/277) of the pembrolizumab every 3 weeks group, 56\% (157/279) of the pembrolizumab every 2 weeks group and 68\% (188/278) of the ipilimumab group. Median PFS was 4.1 months, 5.5 months and 2.8 months respectively. The hazard ratio for PFS for the comparison of pembrolizumab every 3 weeks versus ipilimumab was 0.58 (95\% confidence interval [CI]: 0.47 to 0.72) and for pembrolizumab every 2 weeks versus ipilimumab was 0.58 (95\% CI: 0.46 to 0.72), p<0.001 for both comparisons.\textsuperscript{2}

At the time of the second interim analysis (cut-off date 3 March 2015), after a minimum follow-up of 12 months in all patients, there had been deaths in 33\% (92/277) of the pembrolizumab every 3 weeks group, 30\% (85/279) of the pembrolizumab every 2 weeks group and 40\% (112/278) of the ipilimumab group. Median OS had not been reached in any group. The hazard ratio for OS for the comparison of pembrolizumab every 3 weeks versus ipilimumab was 0.69 (95\% CI: 0.52 to 0.90, p=0.0036) and for pembrolizumab every 2 weeks versus ipilimumab was 0.63 (95\% CI: 0.47 to 0.83, p=0.00052). Based on these statistically significant results, the data and safety monitoring committee recommended that the study was unblinded and that patients in the ipilimumab group who had disease progression could receive pembrolizumab.\textsuperscript{2}

The secondary outcome of objective response rate (defined as the percentage of patients with complete or partial responses according to RECIST) was achieved by 33\% (91/277) of the pembrolizumab every 3 weeks group, 34\% (94/279) of the pembrolizumab every 2 weeks group and 12\% (33/278) of the ipilimumab group. The difference between pembrolizumab every 3 weeks and ipilimumab was 17\% (95\% CI: 9.5 to 26) p<0.001, and between pembrolizumab every 2 weeks and ipilimumab was 16\% (95\% CI: 7.8 to 24) p<0.001. There were complete responses in 6.1\% (17/277), 5.0\% (14/279) and 1.4\% (4/278) patients respectively, and partial responses in 27\% (74/277), 29\% (80/279) and 10\% (29/278) patients respectively. The duration of response (defined as the time from first documented response to radiologic progression according to RECIST) had not been reached in the pembrolizumab every 3 weeks group or the ipilimumab group, and was 251 days in the pembrolizumab every 2 weeks group.\textsuperscript{2}
Since the pembrolizumab doses used in the KEYNOTE-006 study were not the licensed dose, the company’s submission included results from the KEYNOTE-001 study. This included an open-label extension which explored the efficacy and safety of pembrolizumab 2mg/kg (licensed dose) or 10mg/kg every 3 weeks in patients with advanced or metastatic melanoma. This supportive evidence indicated comparable efficacy of the 10mg/kg every 3 weeks and 2mg/kg every 3 weeks doses.¹ ³

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

During KEYNOTE-006, there was a difference in the duration of exposure to study drugs due to the administration schedules, with a mean duration of 151 days in the pembrolizumab every 3 weeks group, 164 days in the pembrolizumab every 2 weeks group and 50 days in the ipilimumab group. Adverse events, considered by the investigator to be related to treatment, were reported in 73% (202/277), 80% (221/278) and 73% (187/256) of patients respectively with grade 3, 4 or 5 adverse events in 10% (28/277), 13% (37/278) and 20% (51/256) of patients respectively. Discontinuation due to adverse events was reported in 10% (29/277), 7.2% (20/278) and 14% (37/256) patients respectively, and there was permanent discontinuation due to adverse events in 6.9%, 4.0% and 9.4% of patients respectively.²

The most frequently reported adverse events, considered to be treatment-related by the investigator, reported in the pembrolizumab every 3 week or every 2 weeks or ipilimumab groups respectively, were: fatigue (19%, 21% and 15%); diarrhoea (14%, 17% and 23%); rash (13%, 15% and 14%); pruritus (14%, 14% and 25%); asthenia (11%, 11% and 6.3%); nausea (11%, 10% and 8.6%); arthralgia (12%, 9.4% and 5.1%) and vitiligo (11%, 9.0% and 1.6%).²

A number of additional adverse events of special interest, with possible immune-related mechanisms, were also reported regardless of whether they were considered to be treatment-related. The following were reported in the pembrolizumab every 3 week or every 2 weeks or ipilimumab groups respectively: hypothyroidism (8.7%, 10% and 2.0%); hyperthyroidism (3.2%, 6.5% and 2.3%); colitis (3.6%, 1.8% and 8.2%); hepatitis (1.8%, 1.1% and 1.2%); hypophysitis (0.7%, 0.4% and 2.3%); pneumonitis 1.8%, 0.4% and 0.4%); type 1 diabetes mellitus (0.4%, 0.4% and 0); uveitis (1.1%, 0.4% and 0); myositis (0.7%, 0 and 0.4%) and nephritis (0.4%, 0 and 0.4%).²

Summary of clinical effectiveness issues

In patients with advanced (unresectable or metastatic) melanoma, current treatment depends on BRAF mutational status. In patients with no BRAF mutation, the current treatment is ipilimumab which has been shown to extend OS. In patients with BRAF mutation, targeted therapy with vemurafenib or dabrafenib can be used first-line. These agents have been accepted for use or restricted use by SMC. Nivolumab, another monoclonal antibody which binds to the PD-1 receptor, has recently received marketing authorisation for advanced melanoma but has not yet been reviewed by SMC. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area as current treatment options are limited, overall prognosis remains poor and further new treatments are still urgently needed. Pembrolizumab meets SMC end of life and orphan equivalent criteria.
Pembrolizumab has received marketing authorisation as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. In this submission, the submitting company has requested that SMC considers the use of pembrolizumab for patients with unresectable or metastatic melanoma untreated with ipilimumab. The company submitted separately for patients with advanced (unresectable or metastatic) melanoma previously treated with ipilimumab, and SMC has advised that pembrolizumab is not recommended for use in this indication.

The pivotal KEYNOTE-006 study included two relevant co-primary outcomes: PFS and OS, which were both statistically significantly longer in the pembrolizumab groups compared with ipilimumab. PFS results were based on the first interim analysis, and OS results on the second interim analysis and since pre-specified efficacy results were achieved, the study was stopped early. However, median OS had not been reached in any group and subsequent OS analysis would be confounded by crossover of patients from ipilimumab to pembrolizumab on disease progression after the second interim analysis.

The doses of pembrolizumab used in KEYNOTE-006 (10mg/kg IV every 2 or 3 weeks) do not reflect the licensed dose (2mg/kg IV every 3 weeks). Supportive evidence from the KEYNOTE-001 study indicated comparable efficacy of the 10mg/kg every 3 weeks and 2mg/kg every 3 weeks doses in patients with unresectable or metastatic melanoma who have not received previous treatment with ipilimumab.

The KEYNOTE-006 study population had known BRAF mutational status and 36% of patients were mutation positive and 64% mutation negative. The study did not enrol patients with BRAF mutations who had not received previous BRAF inhibitor treatment if they had high LDH and symptomatic or rapidly progressive disease. In these patients, the most effective sequence of treatment is unclear and so the study results may not be extrapolated to these patients in clinical practice. Of those with BRAF mutations, approximately half had received previous BRAF inhibitors. Subgroup analysis found that regardless of the disease BRAF mutation status, the treatment effect of pembrolizumab compared with ipilimumab for PFS and OS were consistent with the benefit in the full study population.

There are no studies directly comparing pembrolizumab with vemurafenib and dabrafenib. The company presented several Bayesian network meta-analyses (NMA) which estimated treatment effects of pembrolizumab relative to ipilimumab, vemurafenib and dabrafenib in patients with advanced melanoma who were ipilimumab-treatment naive. These data were used to support a scenario analysis in the economic case. The networks of evidence consisted of six studies and outcomes compared were OS and PFS. Several assumptions were made with respect to some treatment arms having similar outcomes to enable the formulation of a connected network (eg different doses of the same agent, or different agents combined into a single node in the network); this was explored in various scenarios. Given the limitations of the NMA, the results were supportive for sensitivity analyses within the economic case only.

For patients who have not previously received ipilimumab, the introduction of pembrolizumab would offer an alternative medicine to ipilimumab, with an improved PFS and OS. Both pembrolizumab and ipilimumab are given by IV infusion every three weeks. Since pembrolizumab is given until disease progression, there may be service implications compared with ipilimumab, which is given for a maximum of four infusions. The most common adverse events associated with pembrolizumab were immune-related and included pneumonitis, colitis, hepatitis, nephritis and endocrinopathies. These are mostly reversible and can be managed with dose interruptions, corticosteroids and supportive care. Patients treated with
pembrolizumab must be given a Patient Alert Card and be informed about the risks associated with treatment. Please refer to the Summary of Product Characteristics for further information. Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to its novel mechanism of action and objective and progression-free response rates.

**Summary of patient and clinician engagement**

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of pembrolizumab, as an end of life and orphan medicine, in the context of treatments currently available in NHS Scotland, specifically as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults (untreated with ipilimumab).

The key points expressed by the group were:

- Metastatic melanoma is an incurable cancer that affects a disproportionate number of young adults and often leads to complex and severe symptoms. It has a particularly severe impact on patients/families/carers’ daily life.

- Despite recent advances in systemic therapy, overall prognosis remains poor.

- BRAF inhibitors represent a treatment option in only 50% of people who suffer from metastatic melanoma and they serve to delay but not avoid the progression of the disease. When BRAF inhibitors fail, patients need a potential rescue that acts as quickly as possible because the cancer exhibits a rebound effect in this situation. Pembrolizumab may offer an improved response rate over ipilimumab and so is likely to provide a more effective rescue option.

- The clinical trials required to satisfy the regulatory authorities are often still at a relatively early stage of follow up and therefore may not fully capture the long term benefits of immunotherapy treatment options. The full impact on disease control (or possibly cure) may not become apparent until long after the course is finished.

- Ipilimumab and pembrolizumab have a different adverse effect (AE) profile. While both have similar rates of Grade 3 and 4 AEs, it was noted that AEs associated with pembrolizumab are mainly thyroid and skin related which can be detected early and managed relatively easily. This is particularly important as it allows some patients to continue to fulfil their wider societal role while on treatment.

**Summary of comparative health economic evidence**

The submitting company presented a cost-utility analysis which compared pembrolizumab with ipilimumab in patients with advanced (unresectable or metastatic) melanoma. The analysis considered patients with both BRAF V600 wild type and BRAF V600 positive mutations, and the company has positioned pembrolizumab for patients who are untreated with ipilimumab.
The company used a partitioned survival Markov model over a 40 year time horizon to assess the cost-effectiveness of pembrolizumab versus the comparator. In terms of model structure, patients entered the model in the pre-progression health state and could transition to post-progression or death. Patients in the post-progression health state could also transition to death. The economic model also included six time-to-death sub-health states in order to capture the decrease in utility as patients moved closer to death.

The sources of the clinical data used in the analysis were the KEYNOTE-006 study, published studies, previous health technology assessments and registry data.

Baseline utility estimates were taken from the KEYNOTE-006 study and utility values decreased as patients moved towards death.

Medicines and administration costs were included in the analysis, as were costs associated with background disease management, medical resource use, adverse events and palliative care.

A Patient Access Scheme (PAS) was submitted by the company and accepted by the Patient Access Scheme Assessment Group (PASAG) for implementation in NHS Scotland. Under the PAS, a simple discount was given on the price of the medicine.

With the PAS and for all patients independent of BRAF V600 status, the ICER for pembrolizumab versus ipilimumab was £8,343 per QALY gained. This result was based on an incremental cost of pembrolizumab versus ipilimumab of £3,716 and an incremental QALY gain of 0.44. The economic analysis was most sensitive to using the lower bound of the PFS Gompertz distribution shape estimate for pembrolizumab (£250,398), using the lower bound of the PFS Gompertz treatment effect estimate for pembrolizumab (£22,567), applying the hazard ratio for the efficacy of pembrolizumab 2mg/kg every 3 weeks compared with the pembrolizumab 10mg/kg every 3 weeks dose from the KEYNOTE-001 study (£16,361), assessing the impact of vial sharing (£11,883), using OS and PFS estimates from the NMA (£11,711). A PAS is in place for ipilimumab and this was included in these analyses by using an estimate of the relevant price of ipilimumab.

The company also provided subgroup analyses which included vemurafenib and dabrafenib as comparators in patients with BRAF V600 positive mutations. However, following discussions at the New Drugs Committee (NDC) and consideration of SMC expert responses, ipilimumab was considered the appropriate comparator for patients with both BRAF V600 wild type and positive mutations. Given this, dabrafenib and vemurafenib were not considered such relevant comparators in the positive mutations subgroup. However, the results of these analyses are presented below for information:

- With the PAS for pembrolizumab the ICER for pembrolizumab versus vemurafenib was £12,042 per QALY gained. A PAS is in place for vemurafenib and this was included in the analyses by using an estimate of the relevant price of vemurafenib.
- With the PAS of pembrolizumab the ICER for pembrolizumab versus dabrafenib was £19,040 per QALY gained. A PAS is in place for dabrafenib and this was included in the analysis by using an estimate of the relevant price of dabrafenib.

The main weaknesses were
- In order to model PFS and OS, the company used a piecewise approach in which multiple data sources were combined to generate estimates for pembrolizumab and ipilimumab. Therefore, the approach was subject to a number of adjustments and
assumptions which increased the uncertainty in the economic model. The SMC statistical advisor highlighted further weaknesses with the survival modelling which included the appropriateness of the published study and registry data used to support the analysis. SMC expert responses have indicated that the OS estimates for the treatments considered in the analysis were overestimated. However, the company did provide a large number of alternative scenarios to model the extrapolated outcomes within the submission and this provided some reassurance that the ICER remained under £30,000 per QALY. Further analysis was also provided which altered the shape parameter of the PFS Gompertz function by one standard deviation (rather than the lower bound noted above which produced a very high ICER) and this resulted in an ICER of £43,172.

- The dose used in the economics of pembrolizumab (the licensed dose of 2mg/kg every 3 weeks) did not match the dose used in the KEYNOTE-006 study of 10mg every 3 weeks. The company had provided evidence of similar efficacy between the doses but did provide a scenario analysis which used a hazard ratio for pembrolizumab 2mg/kg every 3 weeks compared with 10mg/kg every 3 weeks. The results of this analysis generated an ICER of £16,361 for pembrolizumab versus ipilimumab. In order to capture the combined uncertainty regarding the dose in the study not matching the licensed dose and the limitations with the survival analysis, the company also provided an analysis which reduced the mean PFS Gompertz distribution shape estimate for pembrolizumab by one standard deviation and also used the hazard ratio for pembrolizumab 2mg/kg every 3 weeks compared with 10mg/kg every 3 weeks. This resulted in an ICER of £46,227.

The Committee considered the benefits of pembrolizumab in the context of its decision modifiers that can be applied when encountering high cost-effectiveness ratios and where there is increased uncertainty due to the orphan equivalent status of the medicine.

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

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Melanoma Action and Support Scotland (MASScot), which is a Scottish Charitable Incorporated Organisation (SCIO).

- MASScot has not received any funding from pharmaceutical companies in the past two years.

- At this stage of advanced melanoma, the location of the tumour(s) may be causing symptoms. Secondary distant spread can be to any organ, with spread to the brain most difficult to cope with. Bone spread is very painful and can cause pathological fractures. Lung tumours can cause breathlessness.
Advanced melanoma has, over the past decade been the most common cancer in Scotland in those under 34 years of age. The knowledge that life is drawing to a close has a profound psychological effect on patients and their families, particularly in those who are parents of young children.

There is evidence that pembrolizumab can give improved progression free survival, and overall survival, when compared with currently available treatment. Extra time with family is very precious. There is evidence that side effects are likely to be similar or better than with current therapy options.

The additional benefit of return of hope can make a great deal of difference psychologically, especially to young adults.

### Additional information: guidelines and protocols

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

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 mutation 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 British Association of Dermatology issued revised UK consensus guidelines for the management of cutaneous melanoma in 2010. No chemotherapy has been shown to provide a survival benefit in patients with advanced melanoma. Dacarbazine is recommended as the standard treatment option outside of clinical studies, although it is acknowledged that the benefits are limited. This guideline predates the availability of newer agents.

The European Society for Medical Oncology (ESMO) published Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, in 2012. These guidelines note that, in randomised studies; ipilimumab and vemurafenib have produced substantial improvement in response rates and/or survival. Treatment options for the first- and second-line setting include ipilimumab, for all patients and vemurafenib, a BRAF inhibitor, for patients with BRAF-mutant melanoma. In patients with symptomatic, bulky metastases from a BRAF V600 mutated melanoma, a selective inhibitor such as vemurafenib is preferred, due to the high chance for a rapid response including the improvement of quality of life. There are insufficient data to guide decisions about treatment sequencing in patients with BRAF V600 mutated-metastatic melanoma, but emerging data suggest that BRAF inhibition is effective even following immunotherapy (i.e. ipilimumab).
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. 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.

**Additional information: comparators**

The main comparator is ipilimumab and, in patients with BRAF mutations, also vemurafenib and dabrafenib.

**Cost of relevant comparators**

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<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per 6 months (£)</th>
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<tbody>
<tr>
<td>Pembrolizumab</td>
<td>2mg/kg by intravenous infusion every three weeks</td>
<td>31,560</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>3mg/kg by intravenous infusion every three weeks for four doses</td>
<td>75,000</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>960mg orally twice daily continuously</td>
<td>45,500</td>
</tr>
<tr>
<td>Dabraefenib</td>
<td>150mg orally twice daily continuously</td>
<td>36,400</td>
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Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMS on 28 July 2015. Doses are based on body weight of 70kg. These costs do not take any patient access schemes into consideration.
Additional information: budget impact

The company estimated that 125 patients in year 1 would be eligible for pembrolizumab, rising to 126 patients in year 5. The market share estimated by the company was 15% in year 1, rising to 62% in year 5. When market share was taken into account, the company estimated that 19 patients would be treated with pembrolizumab in year 1, rising to 78 patients in year 5.

Without PAS
The company estimated the gross medicines impact to be £990k in year 1, rising to £4.1m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £344k in year 1, rising to £1.4m in year 5. These figures assumed displacement of ipilimumab at its list price.

*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.

1. Merck Sharp and Dohme. Draft summary of product characteristics Keytruda®


4. Commercial in Confidence*


This assessment is based on data submitted by the applicant company up to and including 14 August 2015.

*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.