

Pembrolizumab for advanced melanoma not previously treated with ipilimumab

Technology appraisal guidance

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1 Guidance

- 1.1 Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only when the company provides pembrolizumab in line with the commercial access agreement with NHS England.

2 The technology

- 2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised monoclonal antibody. It acts on the programmed cell death protein-1 immune-checkpoint receptor pathway, blocking its interaction with ligand on the tumour cells. This allows reactivation of anti-tumour immunity. It has a marketing authorisation in the UK as monotherapy 'for the treatment of advanced (unresectable or metastatic) melanoma in adults'. Pembrolizumab is administered intravenously for 30 minutes at a dose of 2 mg/kg every 3 weeks until disease progression or unacceptable toxicity.
- 2.2 The most common (occurring in 1 in 10 people or more) adverse reactions with pembrolizumab in clinical trials were diarrhoea, nausea, itching, rash, joint pain and fatigue. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The acquisition cost of pembrolizumab is £1,315 per 50-mg vial (excluding VAT; company's submission). The pricing arrangement considered during guidance development was that Merck Sharp & Dohme had agreed a patient access scheme with the Department of Health. This scheme provided a simple discount to the list price of pembrolizumab with the discount applied at the point of purchase or invoice. After guidance publication in November 2015, the company agreed a commercial access agreement with NHS England that replaces the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.

3 The company's submission

The Appraisal Committee ([section 7](#)) considered evidence submitted by Merck Sharp & Dohme and a review of this submission by the Evidence Review Group (ERG; [section 8](#)).

Clinical effectiveness

- 3.1 The company presented clinical-effectiveness evidence for pembrolizumab from 2 clinical trials: KEYNOTE-006 and KEYNOTE-001. KEYNOTE-006 was a randomised, international, multicentre, phase III trial of pembrolizumab 10 mg/kg every 2 weeks (n=279) or every 3 weeks (n=277), continued until disease progression or unacceptable toxicity, compared with ipilimumab 3 mg/kg every 3 weeks, continued for 4 doses (n=278). Results were analysed at 2 planned interim analyses, after 6 months of follow-up (September 2014) and after 9–12 months of follow-up (March 2015). After the second interim analysis the study was stopped, because the primary endpoint had been met. KEYNOTE-001 was a combined phase I and II study. Evidence was presented from a sub-study of this trial, referred to as KEYNOTE-001 part D: this was a randomised, open-label study comparing pembrolizumab 2 mg/kg every 3 weeks (n=51; the licensed dose) with 10 mg/kg every 3 weeks (n=52). Both KEYNOTE-006 and KEYNOTE-001 part D included people with advanced melanoma, with or without BRAF mutations, who had not had ipilimumab before (previous treatment with 1 or 2 other therapies was permitted).
- 3.2 In KEYNOTE-006, pembrolizumab was associated with statistically significant increases in both progression-free survival (first interim analysis) and overall survival (second interim analysis), compared with ipilimumab (table 1). Pembrolizumab was also associated with statistically significantly higher overall response rates compared with ipilimumab (table 1; $p < 0.001$). Pre-specified subgroup analyses based on demographic and clinical characteristics suggested that the treatment effect associated with pembrolizumab was generally consistent across subgroups, although some variations in effect based on the line of therapy and the expression of ligands for the 'programmed death 1' protein (termed 'PD-L1 status') were seen. No significant differences in clinical effectiveness between pembrolizumab doses (that is, 10 mg/kg every 3 weeks, 10 mg/kg every 2 weeks or 2 mg/kg every 3 weeks) were seen in either KEYNOTE-006 or KEYNOTE-001 part D.

Table 1 Clinical-effectiveness outcomes in KEYNOTE-006

	Pembrolizumab		Ipilimumab n=278
	10 mg/kg every 3 weeks n=277	10 mg/kg every 2 weeks n=279	
Progression-free survival (interim analysis 1)			
Median: months (95% CI)	4.1 (2.9–6.9)	5.5 (3.4–6.9)	2.8 (2.8–2.9)
Hazard ratio versus ipilimumab (95% CI)	0.58 (0.47–0.72) p<0.00001	0.58 (0.46–0.72) p<0.00001	
Overall survival (interim analysis 2)			
Overall survival at 6 months ¹ : % (95% CI)	87.3 (82.7–90.7)	84.8 (80.0–88.5)	74.5 (68.7–79.4)
Hazard ratio versus ipilimumab (95% CI)	0.69 (0.52–0.90) p=0.00358	0.63 (0.47–0.83) p=0.00052	
Overall response (interim analysis 1)			
Overall response rate: % (95% CI)	32.9% (27.4–38.7)	33.7% (28.2–39.6)	11.9% (8.3–16.3)
Abbreviations: CI, confidence interval; n, number of patients. ¹ Median overall survival not reached.			

- 3.3 The company presented adverse event data from KEYNOTE-006, and stated that pembrolizumab was generally well tolerated. It was associated with a similar number of adverse events, but fewer drug-related grade 3–5 adverse events, serious adverse events, drug-related serious adverse events and adverse events leading to withdrawal from the trial, compared with ipilimumab (table 2). Pembrolizumab was also associated with fewer high-grade, immune-related adverse events than ipilimumab, and fewer people in the pembrolizumab groups withdrew from the trial because of immune-related adverse events (table 2). The most common treatment-related adverse events with both pembrolizumab

and ipilimumab were fatigue, diarrhoea, rash and itching. The most common grade 3–5 immune-related adverse events associated with pembrolizumab were colitis and hepatitis.

Table 2 Summary of adverse events in KEYNOTE-006

	Ipilimumab		Pembrolizumab (both arms combined)	
	n	%	n	%
n	256		555	
Patients with 1 or more AE	239	93%	539	97%
Drug-related grade 3–5 AE	51	20%	65	12%
Serious AE	77	30%	140	25%
Drug-related serious AE	45	18%	49	9%
Stopped because of an AE	34	13%	50	9%
Immune-related AEs				
Patients with 1 or more AE	47	18%	109	20%
Grade 3–5 AE	30	12%	30	5%
Stopped because of an AE	14	5%	15	3%
Abbreviations: AE, adverse event; n, number of patients.				

- 3.4 The company compared the clinical effectiveness of pembrolizumab with ipilimumab, dabrafenib, vemurafenib and dacarbazine in a series of network meta-analyses. The analyses were performed in a Bayesian framework using a fixed-effects model, and were based on data from KEYNOTE-006 and 5 other trials identified in the systematic review. The company presented results from a series of analyses, including 4 alternative network scenarios, 4 time points, and separate analyses of pembrolizumab as either a first- or second-line treatment. It stated that, for the outcomes of progression-free survival and overall survival, pembrolizumab appeared to have a similar efficacy to vemurafenib and dabrafenib, in people who have had no previous treatment. For example, in network scenario '3b' at the 6-month time point, pembrolizumab was associated with a hazard ratio for progression-free survival of 0.80 (95% credible interval [CrI] 0.32–1.92) compared with dabrafenib, and 0.67 (95% CrI 0.37–1.14)

compared with vemurafenib. The corresponding hazard ratios for overall survival were 0.96 (95% CrI 0.46–1.93) and 0.75 (95% CrI 0.40–1.34), compared with dabrafenib and vemurafenib respectively. The company highlighted that pembrolizumab was associated with greater progression-free survival and overall survival than both ipilimumab (scenario 3b, 6-month timepoint: hazard ratio for progression-free survival 0.45, 95% CrI 0.33–0.62; hazard ratio for overall survival 0.59, 95% CrI 0.41–0.84) and dacarbazine (scenario 3b, 6-month timepoint: hazard ratio for progression-free survival 0.36, 95% CrI 0.21–0.59; hazard ratio for overall survival 0.54, 95% CrI 0.30–0.91) for previously untreated disease, and was at least as effective as ipilimumab for people who have had 1 previous line of treatment (scenario 3b, 6-month timepoint: hazard ratio for progression-free survival 0.74, 95% CrI 0.48–1.12; hazard ratio for overall survival 0.80, 95% CrI 0.52–1.22).

Cost effectiveness

- 3.5 The company presented an economic model comparing pembrolizumab (2 mg/kg every 3 weeks) with ipilimumab, dabrafenib and vemurafenib. The model comprised 3 states: pre-progression, post-progression and death. The model used a cycle length of 1 week and a time horizon of 30 years (lifetime), taking the perspective of the NHS and personal social services, with costs and benefits discounted at a rate of 3.5% per year. The model included costs associated with melanoma treatment, costs in each health state (based on a study of resource use for melanoma treatment in the UK), management of adverse events and complications, and care at the end of life.
- 3.6 The proportion of people in the each health state was based on estimates of progression-free survival and overall survival:
- Progression-free survival was estimated using Kaplan–Meier curves from the KEYNOTE-006, BRIM-3 and BREAK-3 clinical trials, extrapolated to 30 years based on a Gompertz model (for pembrolizumab and ipilimumab) or a monthly risk of progression taken from NICE's technology appraisal guidance on [ipilimumab for previously untreated advanced \(unresectable or metastatic\) melanoma](#) (for dabrafenib and vemurafenib).
 - Overall survival was estimated by initially using Kaplan–Meier data from clinical trials (for the first 50–60 weeks of the model), followed by published mortality risks based on data from a pooled analysis of long-term survival data for people with melanoma

treated with ipilimumab (Schadendorf et al. [2015]; applied to pembrolizumab and ipilimumab) and NICE's technology appraisal guidance on [ipilimumab for previously untreated advanced \(unresectable or metastatic\) melanoma](#) (applied to dabrafenib and vemurafenib). Long-term survival was based on mortality rates in a published registry study (Balch et al. [2001]).

- 3.7 Utility values were estimated using EuroQol EQ-5D data from KEYNOTE-006, by assuming that quality of life decreases as people approach the last months of life. The utility scores decreased from 0.82, for people who were more than 360 days before death, to 0.33 for people in the 30 days before death.
- 3.8 The company's base-case results are summarised in table 3. These results were based on the discount in the patient access scheme for pembrolizumab and the list prices for all other drugs, and therefore were not used for decision-making; they are included here for illustration only. Results from the company's model including the patient access schemes for pembrolizumab and all 3 comparators were presented by the ERG; these results are commercial in confidence and cannot be reported here.

Table 3 Results of the company's base-case analysis (including pembrolizumab patient access scheme, list price for all comparators; not used for decision-making)

BRAF mutation-positive disease							
	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY)
Dabrafenib	£71,029	3.41	2.17	-	-	-	-
Pembrolizumab	£76,689	5.08	3.14	£5660	1.67	0.97	£5852
Vemurafenib	£83,384	2.74	1.73	£6695	-2.34	-1.40	Dominated
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated
BRAF mutation-negative disease							
	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY)
Pembrolizumab	£76,689	5.08	3.14	-	-	-	-
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years.

Dominated: provides fewer QALYs at greater cost than the comparator.

- 3.9 In a deterministic sensitivity analysis, the model results for all comparisons were most sensitive to the extrapolation of progression-free survival for pembrolizumab (shape and treatment effect in the Gompertz model). In the probabilistic sensitivity analysis, the total costs associated with pembrolizumab increased by £10,996 compared with the deterministic results, and the total QALYs decreased by 0.02, whereas the results for ipilimumab, dabrafenib and vemurafenib did not change substantially. The company stated that the change in the results for pembrolizumab was caused by uncertainty in the extrapolation of progression-free survival from the KEYNOTE-006 trial, which led to a small number of iterations with high treatment costs. The company also presented 33 scenario analyses, to explore the effects of key assumptions on the model results. These analyses explored the effects of varying the progression-free survival and overall survival estimates, time horizon, utility estimates, treatment and terminal care costs, treatment duration for pembrolizumab, and the discounting rate. The company stated that these analyses showed that the cost effectiveness of pembrolizumab was robust to most sources of uncertainty.

ERG comments

- 3.10 The ERG stated that KEYNOTE-006 was well designed and well conducted. It considered that the population was representative of patients seen in the UK NHS, and patient characteristics were well balanced across treatment groups. However, it noted 3 key concerns about this trial:
- The dosage of pembrolizumab (10 mg/kg every 3 weeks) did not match the licensed dose (2 mg/kg every 3 weeks). The ERG noted that the European Public Assessment Report (EPAR) states that no differences between the licensed dose and the studied dose are to be expected. Although this was largely based on data from patients who had previous therapy with ipilimumab, the ERG cautiously accepted this conclusion.
 - The trial was stopped early, so the overall survival data were immature. The ERG was unclear whether the true impact of pembrolizumab on survival will be identified.

- The trial specified a maximum treatment duration of 24 months. The ERG considered that the effect of this rule on clinical outcomes is unknown.

- 3.11 The ERG considered that the clinical assumptions used in the company's network meta-analysis were reasonable, but the methods of the analysis were flawed. It stated that the populations in the control arms were not comparable, the analysis did not correctly reflect changing hazard ratios over time, and the methods used to adjust for treatment switching in the key trial for vemurafenib may not have been adequate. The ERG considered that the network meta-analysis did not provide valid treatment effect estimates, particularly for pembrolizumab compared with dabrafenib and vemurafenib.
- 3.12 The ERG's critique of the company's economic model suggested that the model was generally consistent with the NICE reference case. However, it highlighted that the structure of the model led to counterintuitive results – specifically, that pembrolizumab would become less cost effective if its effectiveness at delaying disease progression increased. The ERG stated that this was because delaying disease progression was associated with additional treatment costs but no increase in quality of life. In addition, the ERG expressed concerns about the modelling of overall survival, progression-free survival, treatment costs and quality of life. It considered that there were limitations in the methods of extrapolation for both progression-free survival and overall survival. In particular, for overall survival, the ERG stated that there was a risk of selection bias in the data taken from the study by Schadendorf et al. (2015), and there were limitations in the algorithm used to adjust for patient characteristics and the long-term survival data (from Balch et al. [2001]) used to project long-term survival. The ERG highlighted that the company's estimates for mortality risk in people treated with pembrolizumab changed erratically during the course of the model and were not clinically plausible. For the analysis of progression-free survival, the ERG noted limitations including the use of centrally assessed progression, the company's choice of censoring rule, inappropriate use of the proportional hazards assumption and incomplete adjustment for differences in patient characteristics between the dabrafenib, vemurafenib and pembrolizumab trials. The ERG described concerns about the duration of treatment, the weight distribution of the population, and the administration costs of ipilimumab, which meant that the costs of treatment were not accurately estimated. It considered that there were important limitations in the estimation of utility, because of the use of EQ-5D data based on patients from all regions (rather than UK or European patients only) and the assumption that

utility did not change when disease progressed. The ERG highlighted that 75–90% of the cost differences between treatments in the company's model could be attributed to direct treatment costs, and that 87.5% of the health gain with pembrolizumab occurred after 12 months. It therefore considered that the key factors affecting results of the model were drug costs, duration of treatment and overall survival.

3.13 The ERG presented a series of exploratory analyses to address their principal concerns about the company's model (see section 3.12). In particular, it changed the modelling of overall survival (using methods developed for NICE's technology appraisal guidance on [ipilimumab for previously treated advanced \(unresectable or metastatic\) melanoma](#)), progression-free survival and treatment duration, and amended the treatment costs and utility scores. It also presented 2 scenario analyses, in which the duration of progression-free survival was extended by 3 or 6 years for people whose disease had not progressed after 2 years; the ERG presented results for all analyses using the patient access scheme price for pembrolizumab and the list prices for ipilimumab, dabrafenib and vemurafenib (summarised below) and also using patient access schemes for all drugs (commercial in confidence; cannot be reported here). The ERG's amendments, combined, increased the costs associated with pembrolizumab by £6593 and reduced the total QALYs by 0.18. The amendments also reduced the costs and QALYs associated with ipilimumab (by £2558 and 0.17 respectively), increased the costs and QALYs for vemurafenib (by £7027 and 0.5 respectively), and increased the costs but reduced the QALYs for dabrafenib (by £3,238 and 0.02 respectively). Both of the scenario analyses substantially increased the costs associated with pembrolizumab, but had no effect on the other treatments.

3.14 Full details of all the evidence are [available](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pembrolizumab, having considered evidence on the nature of advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab and the value placed on the benefits of pembrolizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee discussed the current management of advanced melanoma in the NHS, and the potential place of pembrolizumab in the treatment pathway. It was aware of the disparity between the wording of the marketing authorisation for pembrolizumab and the definition of the population in the scope; it understood that this appraisal specifically considered pembrolizumab for melanoma that had not been previously treated with ipilimumab, and that ipilimumab-treated melanoma was considered in a separate appraisal. The Committee understood that ipilimumab is the most common treatment option for advanced (unresectable or metastatic) melanoma that does not have a BRAF V600 mutation (BRAF mutation-negative or 'wild type' disease). For melanoma with BRAF V600 mutations (BRAF mutation-positive disease), the Committee heard from the clinical experts that the treatment strategy has changed in recent years. In the past, a clear distinction was made between rapidly progressing tumours (which would usually be treated with a BRAF inhibitor – that is, dabrafenib or vemurafenib), and more slowly progressing disease (which may be treated with an immunotherapy agent such as ipilimumab). More recently, the long survival benefit shown in a percentage of patients treated with ipilimumab (based on 5-year overall survival data) has led to an increasing emphasis on immunotherapy. The Committee also heard from the clinical experts that pembrolizumab appeared to have a faster onset of action and higher response rate than ipilimumab, and may also be more suitable for treating higher-volume disease. Consequently, although some people with rapidly progressing BRAF mutation-positive melanoma will continue to have BRAF inhibitors as a first-line treatment, the clinical experts expected that pembrolizumab would be considered for more people than just those who, in the past, would have had treatment with ipilimumab. The Committee was aware that dacarbazine is now used only after the other available treatments, if at all, because it has not been shown to improve survival compared with supportive

care. The Committee concluded that ipilimumab, dabrafenib and vemurafenib were appropriate comparators for people with advanced melanoma that has not previously been treated with ipilimumab.

- 4.2 The Committee considered how pembrolizumab might be used in clinical practice, and in particular whether treatment may be limited to a fixed duration. It noted that the KEYNOTE-006 trial protocol specified a maximum treatment duration of 2 years, and heard from the company that although the 2-year point had not yet been reached, the maximum treatment duration will be adhered to as follow-up continues. The Committee understood that the trial had been unblinded early, after which people in the ipilimumab group could start treatment with pembrolizumab. The Committee heard from the clinical experts that there is no evidence to indicate the optimum duration of treatment with pembrolizumab. The clinical experts considered the likely treatment duration in clinical practice and stated that if a maximum duration were specified, consideration should be given to whether pembrolizumab could be restarted if the disease progressed. The Committee was aware that in KEYNOTE-006, people could stop treatment if they had a complete response and could restart treatment if their disease progressed, but that there was limited evidence on the clinical effectiveness of this approach. The Committee highlighted that the marketing authorisation for pembrolizumab specifies that treatment should continue until disease progression or unacceptable toxicity. The Committee concluded that, consistent with the limited evidence available, it was appropriate to appraise pembrolizumab in line with its marketing authorisation. However, it appreciated that there is uncertainty about the optimum duration of treatment with pembrolizumab.
- 4.3 The Committee discussed the clinical needs of people with advanced melanoma. It heard from the patient experts that melanoma has a major effect on people's health and quality of life. Having a choice of treatments would be particularly valuable to people with this condition, allowing them and their doctors to choose treatments that take into account their individual needs and preferences and giving them a feeling of more control over their condition. For example, when considering different treatment options, some people might take into account their preferences for oral or intravenous administration, fixed-duration or continuous treatment, or different side-effect profiles. The Committee heard from the patient experts that treatment with ipilimumab can be associated with severe side effects, and this may be a major consideration.

The Committee concluded that the availability of an effective new treatment option with an acceptable tolerability profile would be valuable for people with advanced melanoma.

- 4.4 The Committee considered the generalisability of the KEYNOTE-006 trial. It understood that the percentage of people with BRAF mutation-positive melanoma in this trial (35%) was likely to reflect the use of pembrolizumab if it becomes established in clinical practice. The Committee noted that the dosage of pembrolizumab in KEYNOTE-006 was 10 mg/kg every 2 or 3 weeks, but that the dosage specified in the marketing authorisation is 2 mg/kg every 3 weeks. It heard from the clinical experts that they expect the 2-mg/kg dose to be as effective as 10 mg/kg, and there is no evidence for a dose-response effect over this range. The Committee reviewed evidence from the KEYNOTE-001 trial comparing the 10-mg/kg and 2-mg/kg doses, and considered that it had not seen any evidence to suggest a difference in effectiveness. The Committee concluded that the clinical-effectiveness evidence presented was broadly generalisable to clinical practice in the NHS.
- 4.5 The Committee considered the results of the KEYNOTE-006 trial. It noted that pembrolizumab provided significant improvements in progression-free survival, overall survival and overall response rates compared with ipilimumab. However, it noted that the trial was stopped early (because the primary endpoints had been met). Consequently, the evidence available was based on a limited duration of follow-up and the overall survival data were immature (that is, fewer than half of the people in the trial had died). It therefore considered that the long-term benefits of pembrolizumab were very uncertain. The Committee acknowledged that further survival data were expected to be available soon, but that there were no data beyond 2 years at the time of the appraisal. The Committee heard from the clinical experts that pembrolizumab was expected to provide a long-term survival benefit consistent with that shown in the ipilimumab trials. It recognised that this expectation is biologically plausible and that there is currently no evidence to suggest pembrolizumab will differ from ipilimumab in this respect. However, it emphasised that there was not enough clinical evidence to directly support this conclusion. The Committee concluded that pembrolizumab is likely to provide improved clinical effectiveness compared with ipilimumab in the short term, but that the long-term benefits of pembrolizumab are highly uncertain. The Committee considered that the choice

of treatment should be made on an individual basis, taking into account the potential risks and benefits of each treatment.

- 4.6 The Committee discussed the adverse effects associated with pembrolizumab. The Committee heard about the experiences of people with melanoma and clinicians treating them, which suggested that pembrolizumab is often better tolerated than ipilimumab. It heard that pembrolizumab causes less-severe adverse effects and leads to fewer hospitalisations. The Committee considered that although evidence from KEYNOTE-006 suggested that pembrolizumab was better tolerated than ipilimumab, the difference was not as dramatic as the individual experiences reported by the experts. It did, however, note that a higher dose (10 mg/kg) was used in the trial, and that this dose might be associated with greater toxicity than the licensed 2-mg/kg dose. The Committee concluded that pembrolizumab is likely to offer a better tolerability profile than ipilimumab.
- 4.7 The Committee considered the clinical effectiveness of pembrolizumab compared with dabrafenib and vemurafenib. The Committee noted that there was no direct clinical trial evidence comparing pembrolizumab with dabrafenib or vemurafenib. The company had carried out a network meta-analysis, but the Committee considered that this had a number of methodological flaws. The clinical experts indicated that in clinical practice dabrafenib and vemurafenib are not considered to have different effectiveness and are broadly interchangeable. The Committee understood that the choice between pembrolizumab and dabrafenib or vemurafenib may be made partly on clinical grounds, taking into account disease progression and the preferences of the person having treatment. The Committee considered that the company's meta-analysis did not provide robust evidence to compare pembrolizumab with dabrafenib and vemurafenib; it therefore concluded that the effectiveness of pembrolizumab compared with dabrafenib and vemurafenib is highly uncertain, and there is not enough evidence to reliably assess their comparative effectiveness. The Committee reiterated that people with melanoma and clinicians should discuss the potential risks and benefits of each treatment when considering therapy options.

Cost effectiveness

- 4.8 The Committee considered the company's model, which compared pembrolizumab with ipilimumab in BRAF mutation-negative disease, and with ipilimumab, vemurafenib and dabrafenib in BRAF mutation-positive disease, for people with advanced (unresectable or metastatic) melanoma that had not been previously treated with ipilimumab. The Committee considered that the Evidence Review Group (ERG) had identified a number of important uncertainties in the economic modelling, and it expressed concerns about some of the company's assumptions. In particular, it highlighted that:
- The model results were strongly influenced by extrapolated survival benefits after 12 months. However, there were potential issues with the methods of extrapolation, as highlighted by the ERG (see [section 3.12](#)); in particular, the Committee noted the ERG's view that the proportional hazards assumption was not appropriate, there were limitations in the use of data from Schadendorf et al. (2015) and Balch et al. (2001), and the modelled overall survival was consequently not plausible.
 - The results for dabrafenib and vemurafenib were highly uncertain because of the substantial uncertainty in the comparative clinical effectiveness of these treatments (see section 4.7).
 - The predicted total costs associated with adverse effects seemed low given the number of events in clinical trials; these costs were not plausible and were unlikely to reflect the costs in clinical practice.
- 4.9 The Committee reviewed the exploratory analyses that the ERG presented to address some of its concerns about the company's modelling (see [section 3.13](#)). The Committee noted that the ERG's exploratory analyses, combined, decreased the cost effectiveness of pembrolizumab. It understood that the ERG's scenario analyses primarily aimed to 'stress-test' the model, and considered that the second scenario (in which progression-free survival was extended by 6 years for some people; see section 3.13) was at the upper end of the plausible range for the cost-effectiveness estimate. The Committee concluded that there were a number of uncertainties in the economic modelling, but considered that the company's and ERG's analyses provided sufficient information on which to base a decision.

- 4.10 Having reviewed the company's base case, the scenario and sensitivity analyses, and the exploratory analyses from the ERG, and taking into account all 4 patient access schemes, the Committee concluded that the most plausible incremental cost-effectiveness ratios (ICERs) for pembrolizumab (compared with ipilimumab in BRAF mutation-negative disease, and with ipilimumab, dabrafenib and vemurafenib in BRAF mutation-positive disease) were less than £50,000 per quality-adjusted life year (QALY) gained. The exact ICERs are confidential and cannot be reported here, because this could allow the discounts in the patient access schemes for ipilimumab, dabrafenib and vemurafenib to be back-calculated.
- 4.11 The Committee discussed the innovative aspects of pembrolizumab. It noted that the company stated that pembrolizumab is innovative because it has a novel mechanism of action and is expected to provide a durable response for a significant number of people with a high unmet need. The Committee understood that an improved tolerability profile of pembrolizumab compared with ipilimumab may be valuable for some people with melanoma, although it recalled that the benefit in the trial was not as dramatic as the individual experiences reported by the experts (see section 4.6). It also noted that a long-term survival benefit, similar to ipilimumab, had not yet been confirmed. The Committee concluded that pembrolizumab is innovative, but it could not identify any specific health-related benefits that had not been captured in the QALY calculation.
- 4.12 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.
- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
 - There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
 - The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded

that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

- 4.13 The Committee considered that the life expectancy of people with advanced melanoma that has not previously been treated with ipilimumab is short. It understood that the median survival for people with previously untreated melanoma that is treated with ipilimumab, dabrafenib or vemurafenib ranges from about 14 to 20 months. The Committee considered that the extension to life offered by pembrolizumab was somewhat uncertain. It highlighted that the median overall survival was not reached in the KEYNOTE-006 trial, so the estimates of survival gain were dependent on extrapolation. However, the Committee noted that the estimates for overall survival gain presented by the company and the ERG were consistently greater than 3 months. It therefore concluded that pembrolizumab was likely to provide a survival gain of at least 3 months. Although this is subject to some uncertainty, the Committee considered that it was plausible, objective and robust enough for this criterion to be met. The Committee noted that the company estimated the population for which pembrolizumab is indicated to be about 1300 people, and concluded that this represented a small patient population. The Committee therefore concluded that pembrolizumab meets all the criteria to be considered a life-extending, end-of-life treatment.
- 4.14 Taking into account the most plausible ICERs, the uncertainties in the clinical and cost-effectiveness evidence and the supplementary advice for appraising life-extending, end-of-life treatments, the Committee concluded that, on balance, pembrolizumab could be considered a cost-effective use of NHS resources for people with advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab.
- 4.15 The Committee was aware of NICE's [position statement](#) about the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism. It acknowledged 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal of pembrolizumab. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the cost effectiveness of pembrolizumab for

treating advanced melanoma that has not been previously treated with ipilimumab.

Summary of Appraisal Committee's key conclusions

TA366	Appraisal title: Pembrolizumab for advanced melanoma not previously treated with ipilimumab	Section
Key conclusion		
<p>Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, when the company provides pembrolizumab with the discount agreed in the patient access scheme.</p> <ul style="list-style-type: none"> • Pembrolizumab is likely to provide improved short-term clinical effectiveness and a better tolerability profile compared with ipilimumab. The long-term benefits compared with ipilimumab and the effectiveness compared with dabrafenib and vemurafenib are highly uncertain. • The most plausible incremental cost-effectiveness ratios (ICERs) were less than £50,000 per quality-adjusted life year (QALY) gained. • The Committee concluded that pembrolizumab meets all the criteria to be considered a life-extending, end-of-life treatment. 		1.1, 4.14, 4.5–4.7, 4.10, 4.13
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the patient experts that melanoma has a major effect on people's health and quality of life, and that having a choice of treatments would be particularly valuable to people with this condition.	4.3
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee noted that pembrolizumab provided significant improvements in progression-free survival, overall survival and overall response rates, and a better tolerability profile, compared with ipilimumab.</p> <p>The company stated that pembrolizumab is innovative because it has a novel mechanism of action and is expected to provide a durable response for a significant number of people with a high unmet need. The Committee concluded that pembrolizumab is innovative.</p>	<p>4.5, 4.6, 4.11</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>This appraisal considered pembrolizumab for melanoma that had not been previously treated with ipilimumab.</p> <p>The Committee heard that pembrolizumab would be considered for more people than just those who, in the past, would have had treatment with ipilimumab, and concluded that ipilimumab, dabrafenib and vemurafenib were appropriate comparators.</p>	<p>4.1</p>
<p>Adverse reactions</p>	<p>The most common adverse reactions with pembrolizumab in clinical trials were diarrhoea, nausea, itching, rash, joint pain and fatigue.</p> <p>The Committee concluded that pembrolizumab is likely to offer a better tolerability profile than ipilimumab.</p>	<p>2.2, 4.6</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The company presented clinical-effectiveness evidence for pembrolizumab from 2 clinical trials: KEYNOTE-006 and KEYNOTE-001.</p> <p>The Evidence Review Group (ERG) stated that KEYNOTE-006 was well designed and well conducted, but noted 3 key concerns about the trial – the dosage of pembrolizumab, the immature survival data and the maximum treatment duration.</p>	<p>3.1, 3.10</p>

<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee noted that the dosage of pembrolizumab in KEYNOTE-006 was not the same as the marketing authorisation. It understood that the percentage of people with BRAF mutation-positive melanoma in this trial was likely to reflect clinical practice. The Committee concluded that the clinical-effectiveness evidence presented was broadly generalisable to clinical practice in the NHS.</p>	<p>4.4</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee identified 4 key uncertainties:</p> <ul style="list-style-type: none"> • the optimum duration of treatment with pembrolizumab • the long-term benefits of pembrolizumab compared with ipilimumab • the effectiveness of pembrolizumab compared with dabrafenib and vemurafenib • the extension to life offered by pembrolizumab. 	<p>4.2, 4.5, 4.7, 4.13</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No subgroups were specified in the scope. Subgroup analyses in KEYNOTE-006, based on demographic and clinical characteristics, suggested that the treatment effect was generally consistent across subgroups.</p>	<p>3.2</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>In KEYNOTE-006, pembrolizumab was associated with statistically significant increases in progression-free survival, overall survival and overall response rate, compared with ipilimumab.</p> <p>The Committee noted that the estimated overall survival gain was consistently greater than 3 months.</p> <p>The evidence was based on a limited duration of follow-up and the survival data were immature. The Committee considered that the long-term benefits of pembrolizumab were highly uncertain.</p>	<p>3.2, table 1, 4.13, 4.5</p>
<p>Evidence for cost effectiveness</p>		

<p>Availability and nature of evidence</p>	<p>The Committee considered the company's model, which compared pembrolizumab with ipilimumab, vemurafenib and dabrafenib, in people with advanced (unresectable or metastatic) melanoma that had not been previously treated with ipilimumab.</p>	<p>4.8</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee considered that the ERG had identified a number of important uncertainties in the economic modelling, and it expressed concerns about some of the company's assumptions:</p> <ul style="list-style-type: none"> • extrapolated survival benefit • clinical effectiveness of pembrolizumab compared with dabrafenib and vemurafenib • costs associated with adverse events. 	<p>4.8</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Utility values were estimated using EuroQol EQ-5D data from KEYNOTE 006, by assuming that quality of life decreases as people approach the last months of life. The utility scores decreased from 0.82, for people who were more than 360 days before death, to 0.33 for people in the 30 days before death.</p> <p>The ERG considered that there were important limitations in the estimation of utility, because of the use of EQ-5D data based on patients from all regions and the assumption that utility did not change when disease progressed.</p> <p>The Committee could not identify any specific health-related benefits that had not been captured in the calculation of quality-adjusted life years (QALYs).</p>	<p>3.7, 3.12, 4.11</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No subgroups were considered.</p>	<p>–</p>

<p>What are the key drivers of cost effectiveness?</p>	<p>In a deterministic sensitivity analysis, the model results were most sensitive to the extrapolation of progression-free survival for pembrolizumab. The company also presented 33 scenario analyses, and stated that the cost effectiveness was robust to most sources of uncertainty.</p> <p>The ERG considered that the key factors affecting results of the model were drug costs, duration of treatment and overall survival.</p>	<p>3.9, 3.12</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee concluded that the most plausible ICERs for pembrolizumab (compared with ipilimumab, dabrafenib and vemurafenib) were less than £50,000 per QALY gained. The exact ICERs are confidential and cannot be reported here.</p>	<p>4.10</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The company has agreed a patient access scheme, in which pembrolizumab is provided with a simple discount to its list price.</p> <p>The ERG presented analyses incorporating the confidential patient access schemes for pembrolizumab, ipilimumab, dabrafenib and vemurafenib. The Committee took into account all 4 patient access schemes.</p>	<p>2.3, 3.8, 4.10</p>
<p>End-of-life considerations</p>	<p>The Committee understood that the median survival for people with previously untreated melanoma is 14–20 months.</p> <p>It considered that the extension to life offered by pembrolizumab was somewhat uncertain, but the estimates presented were consistently greater than 3 months.</p> <p>It noted that the population for which pembrolizumab is indicated is small.</p> <p>The Committee concluded that pembrolizumab meets all the criteria to be considered a life-extending, end-of-life treatment.</p>	<p>4.13</p>

Equalities considerations and social value judgements	No equality issues were identified.	-
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5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 NHS England and Merck Sharp & Dohme have agreed that pembrolizumab will be available to the NHS with a commercial access agreement. The details of this commercial access agreement are confidential. Any enquiries from NHS organisations about the commercial access agreement should be directed to keiron.hughes@merck.com.
- 5.5 NICE has developed a [costing template and report](#) to estimate the national and local savings and costs associated with implementation.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review 3 years after publication. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
November 2015

7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

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

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

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

Dr Jane Adam (Chair)

Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice Chair)

Consultant Physician, University Hospitals of Leicester

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Mr Matthew Campbell-Hill

Lay Member

Mr David Chandler

Lay Member

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Ms Sarah Parry

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

Ms Pamela Rees

Lay Member

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

NICE project team

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

Ian Watson

Technical Lead

Eleanor Donegan

Technical Adviser

Bijal Joshi

Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews & Implementation Group (LRiG):

- Greenhalgh J, Mahon J, Richardson M, et al, Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab: A Single Technology Appraisal, July 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on pembrolizumab by making a submission to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Company

- Merck Sharp & Dohme (pembrolizumab)

II. Professional/expert and patient/carer groups:

- British Association of Dermatologists
- Cancer Research UK
- Melanoma Focus
- Melanoma UK
- Royal College of Pathologists
- Royal College of Physicians
- UK Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

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

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

- Mrs Kathryn Silvester-Eccles, nominated by organisation representing Melanoma UK – patient expert
- Mrs Gillian Nuttall, nominated by organisation representing Melanoma UK – patient expert
- Dr Pippa Corrie, Consultant Medical Oncologist, nominated by organisation representing National Cancer Research Institute/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians – clinical expert
- Dr Martin Highley, Consultant Medical Oncologist, nominated by organisation representing Melanoma Focus – clinical expert

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

- Merck Sharp & Dohme (pembrolizumab)

Update information

September 2017: Reference to a patient access scheme in section 1.1 has been replaced with details of a commercial access agreement. Sections 2.3 and 5.4 have been updated with the same information.

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Accreditation

