

# Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab

Technology appraisal guidance

Published: 7 October 2015

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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# 1 Guidance

1.1 Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only:

- after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor and
- 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'. Previously, pembrolizumab was available in the NHS through the early access to medicines schemes from the UK Medicines and Healthcare products Regulatory Agency. 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 October 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's submission focused on the evidence from KEYNOTE-002, a multicentre randomised controlled trial (including centres in Argentina, US and Europe, although not in the UK). This trial compared pembrolizumab with chemotherapy in people with advanced melanoma who had had at least 2 doses of ipilimumab and whose disease had progressed within 24 weeks of the last ipilimumab dose. People with BRAF mutation-positive melanomas must have also had treatment with a BRAF inhibitor (vemurafenib or dabrafenib) or a MEK inhibitor (trametinib). People were randomised to chemotherapy chosen by an investigator (paclitaxel plus carboplatin, carboplatin alone, paclitaxel alone, dacarbazine or temozolomide; n=179) according to standard of care or current practice, or pembrolizumab 2 mg/kg (licensed dose; n=180) or 10 mg/kg (unlicensed dose; n=181) given every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent, physician's decision to stop therapy or study sponsor's decision to stop the study. After week 12, people who had chemotherapy and whose disease progressed were allowed to switch to pembrolizumab. The company reported that people in KEYNOTE-002 had had several previous treatments for advanced melanoma and that their baseline characteristics were generally balanced between the 3 treatment groups. Seventy seven percent of people in the trial had BRAF wild-type disease. The company focused on the pembrolizumab 2 mg/kg dose because it was the licensed dose.
- 3.2 The progression-free survival results were based on the interim analysis 2 (data cut-off 12 May 2014). Results based on central review showed that median progression-free survival was 2.9 months in the pembrolizumab 2 mg/kg group and 2.7 months in the chemotherapy group. The difference in progression-free survival between the treatment groups was statistically significant (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.45 to 0.73, p<0.0001). The company noted that the Kaplan–Meier results showed that the progression-free survival curves for both treatment groups separated from week 12 onwards and showed

a substantial separation by month 6. The company also noted that progression-free survival results based on investigator review were consistent with the results based on central review results (median progression-free survival was 3.7 months in the pembrolizumab 2 mg/kg group and 2.6 months in the chemotherapy group, HR 0.49, 95% CI 0.38 to 0.62,  $p < 0.0001$ ).

3.3 The overall survival results were also based on the interim analysis 2, at which time 86 out of 179 people (48%) in the chemotherapy group had switched treatment to pembrolizumab. At this time, 215 deaths had occurred. The company reported that there was not a statistically significant difference in overall survival results between pembrolizumab 2 mg/kg and chemotherapy (HR 0.88, 95% CI 0.64 to 1.22,  $p = 0.229$ ). This could be attributed to confounding because people whose disease progressed on the chemotherapy group could switch to pembrolizumab when their disease progressed. The rank-preserving structural failure time (RPSFT) adjustment method to account for treatment switching was pre-specified in the trial protocol. Also, the company explored other adjustment methods: 2-stage and inverse probability of censoring weighting (IPCW). The company stated that the RPSFT method is based on the assumption of a common treatment effect, so this method might not have been appropriate because there may have been a different treatment effect in people who switched to pembrolizumab after having had chemotherapy than in people who had pembrolizumab initially. It also stated that the overall survival results derived when adjusting for treatment switching with the RPSFT method were invalid because the results were similar to the ones before correction, and because the results implied that people having pembrolizumab died more quickly after progression than those having chemotherapy. Because of the small sample size and the high proportion of people switching treatment, the company noted that it was uncertain whether the IPCW method could be considered a valid method. It stated that the 2-stage method appeared to be the most appropriate because treatment switching occurred after disease progression and the potential relevant confounders were measured until the moment of switching. The company validated the adjusted overall survival results generated with the 2-stage method for the control group. To do this, it used the predicted overall survival using the algorithm from Korn et al. (2008; a study that evaluated historical data from different trials that included 2100 people with metastatic melanoma in an attempt to develop benchmarks for overall survival and progression-free survival as reference points for future trials), and reported a high degree of similarity to the adjusted

overall survival trial results. For the overall survival analysis, applying the 2-stage adjustment method, the company presented the results of 2 models. One model adjusted for all relevant covariates (including Eastern Cooperative Oncology Group [ECOG] status, tumour size, lactate dehydrogenase level, BRAF status, melanoma stage and age). The other model only incorporated ECOG. The company noted that both models led to similar results and it focused on the model with all relevant covariates (median overall survival in pembrolizumab group 11.4 months, median overall survival in chemotherapy group 7.9 months, HR 0.63, 95% CI 0.45 to 0.88,  $p=0.007$ ).

- 3.4 The most common adverse events in the pembrolizumab 2 mg/kg group were fatigue (38.8%), itching (23.5%), constipation (21.3%), diarrhoea (20.8%), nausea (19.7%), anaemia (17.4%), cough (17.4%), decreased appetite (16.3%) and joint pain (15.2%). The most common adverse events in the chemotherapy group were fatigue (48.0%), nausea (41.5%), anaemia (26.3%), vomiting (22.8%), decreased appetite (22.8%), constipation (20.5%), hair loss (20.5%), diarrhoea (19.9%) and cough (15.8%). The company stated that the results showed that the overall safety profile of pembrolizumab as an immune therapy for advanced melanoma was favourable compared with chemotherapy.

## Cost effectiveness

- 3.5 The company did a de novo economic model to assess the cost effectiveness of pembrolizumab compared with best supportive care in people with unresectable or metastatic melanoma previously treated with ipilimumab and whose disease had progressed within 24 weeks of the last dose. The population in the model differed from the scope in that people with BRAF mutation-positive disease had also had treatment with a BRAF inhibitor (vemurafenib or dabrafenib) in line with KEYNOTE-002. Best supportive care included systemic therapies such as dacarbazine, paclitaxel, paclitaxel plus carboplatin, carboplatin or temozolomide. The model structure was a partitioned survival model with 3 states: pre-progression, post-progression and death. The cycle length was 1 week, the time horizon was 30 years (assumed to be lifetime), and costs and outcomes were discounted at a 3.5% rate. Data from KEYNOTE-002 were used to estimate the baseline characteristics, the proportion of people in the different states, the proportion experiencing adverse events, and utility values. The average age of the cohort in the model was 60 years.

- 3.6 The company assumed that all chemotherapy treatments had equal efficacy in terms of progression-free survival and overall survival. The company used progression-free survival results based on central review assessment. It applied standard parametric curve fitting using the Gompertz distribution for extrapolating progression-free survival in the pembrolizumab group. It stated that, because progression-free survival results were affected by the fact that the first radiological tumour response assessment was done in week 12, it applied a 2-part curve fit: Kaplan–Meier curves were used until week 13 and parametric curves were fitted from this point onwards. The company also stated that the proportional hazard assumption could not be rejected so it incorporated it in the extrapolation of the data. For the best supportive care group, the company directly used Kaplan–Meier data until the final date when any patient was seen to still have progression-free disease (week 62). At this point, all remaining patients were assumed to have died or have disease progression. The company highlighted that using progression-free survival to represent disease status within the model may have underestimated pre-progression survival and overestimated post-progression survival. The company acknowledged that because of the relatively short-term progression-free survival data from KEYNOTE-002, the extrapolation of these results added uncertainty to the cost-effectiveness results.
- 3.7 The company reported that, because overall survival data from KEYNOTE-002 were immature and standard parametric curve fitting resulted in survival estimates that were not clinically plausible, alternative methods were needed to extrapolate survival beyond the trial period. The company used the following sources for the extrapolation of overall survival in its base case:
- from 0 to 1 year: KEYNOTE-002 data
  - from 1 year to 10 years: ipilimumab (previously treated) survival curve (as published in Schadendorf et al. [2015], a study that included a pooled analysis of long-term survival data for ipilimumab in unresectable or metastatic melanoma)
  - from year 10 onwards: Balch et al. (2001) registry data from the American Joint Committee on Cancer registry plus general population mortality.
- 3.8 The company got the utility values from EQ-5D questionnaire data from KEYNOTE-002. The company noted that utility values decreased when patients were closer to the time of death so utility values were calculated based on time

to death. The company reported that there were no statistically significant differences in utility values between the pembrolizumab and chemotherapy groups at baseline so it pooled the utility values from both treatment groups in the model. The company also calculated pooled utility values for pre-progression and post-progression states and used them in sensitivity analyses.

- 3.9 The company included costs reflecting the clinical management of unresectable or metastatic melanoma. This included costs of treatment, monitoring and follow-up, management of complications and adverse events, and terminal care. The incidence of adverse events was based on KEYNOTE-002, and their associated costs were taken from NICE technology appraisal guidance on [ipilimumab for previously untreated advanced melanoma](#).
- 3.10 The results from the company's cost-effectiveness analysis of pembrolizumab compared with best supportive care showed that pembrolizumab provided 1.19 additional quality-adjusted life years (QALYs) at an additional cost of £50,995 compared with best supportive care. This led to an incremental cost-effectiveness ratio (ICER) of £42,923 per QALY gained. The company did deterministic sensitivity analyses and found that the variables with the highest impact on the ICER were the curve fit parameters for progression-free survival data and the HR for overall survival from the 2-stage treatment switching adjustment method.
- 3.11 The company did probabilistic sensitivity analyses to assess the uncertainty around the variables included in the model. The results led to a probabilistic ICER of £67,615 per QALY gained for pembrolizumab compared with best supportive care. The company noted that these results were higher than the deterministic results because of the uncertainty in the progression-free survival data from KEYNOTE-002 and the fact that, in the model, many patients did not have disease progression and had treatment for life. The cost-effectiveness acceptability curves showed that there was a probability of about 50% of pembrolizumab being cost effective at a maximum acceptable ICER of £50,000 per QALY gained.

## Evidence review group comments

- 3.12 The ERG considered that KEYNOTE-002 was generalisable to UK clinical

practice even though there were no participating centres in the UK. It noted that the company stated that people in KEYNOTE-002 had more advanced disease and a worse prognosis than expected in clinical practice in England. However, the ERG considered that it could also be argued that people in KEYNOTE-002 had a better prognosis because they had ECOG status 0–1 and were considered to be fit enough to have further immunotherapy after treatment with ipilimumab.

- 3.13 The ERG agreed with the company that the difference in median progression-free survival between treatment groups in KEYNOTE-002 could be affected by the timing of the first scheduled response assessment (week 12). The ERG also agreed that it was likely that median progression-free survival rates underestimated the treatment effect of pembrolizumab compared with chemotherapy. It noted that the company explored different methods to adjust overall survival data from KEYNOTE-002 for treatment switching, and agreed with the company that the 2-stage adjustment method was the most appropriate.
- 3.14 The ERG considered that the exponential distribution provided a better fit to Kaplan–Meier progression-free survival data from KEYNOTE-002 than the Gompertz distribution used by the company in its model. The ERG also noted that the Gompertz distribution usually overestimates progression-free survival results in the long term. It noted that assuming that all patients in the best supportive care group died or had disease progression at week 62 without any projection underestimated the progression-free survival results in the best supportive care group. The ERG considered that this overestimated the benefit of pembrolizumab in terms of progression-free survival compared with best supportive care by about 30%. The ERG considered that progression-free survival by investigator assessment was more representative of clinical practice than progression-free survival results by central review. Therefore, it applied the progression-free survival results by investigator assessment using an alternative censoring rule in its exploratory analyses and used exponential models for extrapolating the results in both treatment groups. It found that this still led to a substantial long-term progression-free survival benefit for pembrolizumab compared with best supportive care (net extended progression-free survival benefit with pembrolizumab compared with best supportive care of 4.18 months compared with the company's estimate of 5.35 months). This reduced the ICER for pembrolizumab compared with best

supportive care by approximately £6900.

3.15 The ERG stated that the company's approach to modelling overall survival (using 3 different sources of data) led to clinically implausible results such as a 4-year period of zero mortality risk and a sudden increase in mortality from zero to non-zero at 10 years. It was concerned that the company applied the overall survival hazard ratio from the trial to the whole time horizon (including to the background mortality from all causes from UK life tables), and that this led to an indefinite overall survival gain in the pembrolizumab group compared with best supportive care from 10 years to 30 years. The ERG applied a different method for extrapolating overall survival data in the model based on a previous approach developed during NICE's technology appraisal guidance on [ipilimumab for previously treated advanced \(unresectable or metastatic\) melanoma](#). The ERG's method used a mixed exponential model with 2 subgroups of people (1 subgroup had a high risk of mortality, the other subgroup [about 10–15% of the total population] had much longer survival) as seen in clinical practice. The ERG used the American Joint Committee on Cancer registry data. It generated expected survival profiles matched for the subgroups of people with stage IV melanoma (M1a, M1b and M1c) for each treatment group in KEYNOTE-002. It used the subsequent curves in both extrapolation phases of the company's model (that is, from year 1 onwards) using the point at which the American Joint Committee on Cancer registry data matched profiles corresponded to a common mortality rate in both the KEYNOTE-002 data and the projection model. This meant that, beyond the observed trial period, most patients having pembrolizumab stopped treatment rapidly because of disease progression or adverse events, so future survival was largely determined by the conventional treatment options covered in the registry data. Using this method for extrapolating overall survival data led to a reduction in the estimated survival gain of about 17%, and increased the ICER for pembrolizumab compared with best supportive care by approximately £8400.

3.16 The ERG applied other amendments to the company's model, including the approach used to incorporate utility values and the way the company included resources use and costs in the model. The ERG noted that, although individual amendments had substantial effects on the ICER, the net effect when implementing all the changes was small. It noted that this led to an overall change in the ICER of less than £4000, so the ICER for pembrolizumab compared with best supportive care including all of the ERG's preferred

amendments was £46,662 per QALY gained.

3.17 Full details of all the evidence are in [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 unresectable, metastatic melanoma after progression 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 clinical management of advanced (unresectable or metastatic) melanoma in the NHS and the place of pembrolizumab within the treatment pathway. It was aware of the disparity between the wording of the marketing authorisation for pembrolizumab, the definition of the population in the scope and the decision problem addressed by the company in its submission. The Committee noted the broad wording of the marketing authorisation for pembrolizumab (that is, the treatment of advanced [unresectable or metastatic] melanoma in adults), and the narrower population in the scope (that is, people with advanced [unresectable stage III or IV] melanoma whose disease has progressed after previous treatment with ipilimumab). It further noted that the decision problem addressed by the company in its submission was even narrower, based on the population included in the clinical trial evidence available for pembrolizumab from KEYNOTE-002 (that is, people with unresectable or metastatic melanoma whose disease has progressed after ipilimumab and, if the disease is BRAF V600 mutation positive, a BRAF or MEK inhibitor). The Committee heard from the company that, when preparing the submission, the marketing authorisation was expected to specify that pembrolizumab would be indicated after progression with ipilimumab, and if BRAF V600 mutation-positive disease, after a BRAF or MEK inhibitor, and that this had been the approach taken when pembrolizumab was made available via the early access to medicines scheme in the NHS. The Committee questioned whether in clinical practice pembrolizumab would always be used after a BRAF or MEK inhibitor in people with BRAF V600 mutation positive disease, as in KEYNOTE-002 and the company submission, or whether pembrolizumab would sometimes be considered as an alternative to a BRAF or MEK inhibitor. It heard from the clinical experts that, after disease progression with ipilimumab, most people with BRAF V600 mutation-positive disease would

have a BRAF or MEK inhibitor but that, in a few people, pembrolizumab might be preferred because of slow-growing disease and the expectation of a longer survival. However, the Committee was aware that the company had not submitted any evidence for the efficacy of pembrolizumab compared with BRAF inhibitors. It considered that it could not make recommendations for a population for whom there was no evidence of the relative clinical effectiveness of pembrolizumab. Therefore, the Committee accepted the company's approach to the decision problem. It concluded that, on the basis of the evidence submitted, it could only make recommendations for pembrolizumab after treatment with ipilimumab and, for BRAF V600 mutation-positive disease, after both ipilimumab and a BRAF or MEK inhibitor.

- 4.2 The Committee discussed the relevant comparators for pembrolizumab and noted that the company considered conventional chemotherapy to be the appropriate comparator for pembrolizumab. The Committee heard from the clinical experts that conventional chemotherapy, including dacarbazine, remained the only treatment option after treatment with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor. It also heard that there is no proven survival benefit associated with these therapies. The Committee concluded that conventional chemotherapy was an appropriate comparator for pembrolizumab at this stage of the disease.
- 4.3 The Committee discussed the clinical need of people with advanced melanoma after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor. It heard from the patient expert that metastatic melanoma is associated with severe emotional stress and anxiety about the future for the patient and their family, and a reduced quality and length of life. The patient expert and clinical experts also explained that ipilimumab, which is used earlier in the pathway, can be associated with severe side effects that affect normal activities and that these may be so severe the patient sometimes needs hospital admission. The patient expert also noted that, in contrast, pembrolizumab offers a much more manageable side effect profile that means people with metastatic melanoma can continue their normal lives and activities, including employment. The patient expert also highlighted that, once the disease progresses after ipilimumab, the lack of further therapy options that can extend survival is devastating, so having an additional option such as pembrolizumab provides hope for the future. The Committee concluded that the availability of a new treatment that slows disease progression and

improves quality of life when other therapies have failed is very important to patients and their families.

- 4.4 The Committee considered that the key clinical evidence came from KEYNOTE-002. The Committee noted that KEYNOTE-002 had not included any UK sites but had included centres in the USA, Argentina, and some European countries. It heard from the clinical experts that historically there had been a difference in outcomes in people with advanced melanoma in the UK compared with some other countries, possibly related to later diagnosis. However, the clinical experts explained that, because of recent advances in managing malignant melanoma in the NHS, including earlier diagnosis and the availability of new treatments, this has changed. The Committee also noted that 23% of people in KEYNOTE-002 had BRAF V600 mutation-positive disease. It heard from the clinical experts that this was lower than the overall prevalence of BRAF V600 mutation-positive disease in the UK, which is about 45%. The clinical experts noted that this difference related mainly to patient selection in the trial and that the results would still be generalisable to the BRAF V600 mutation-positive population eligible to have pembrolizumab in clinical practice. Therefore, the Committee concluded that KEYNOTE-002 was generalisable to clinical practice in the NHS for those people whose disease has progressed after ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor.
- 4.5 The Committee discussed the progression-free survival results from KEYNOTE-002. It was aware that follow-up in the trial was short and therefore, the results were immature. It was aware that the company presented results based on an independent central review and an investigator assessment, and that both results were based on an interim analysis. It was also aware that the median progression-free survival for pembrolizumab was higher using the investigator assessment, which it considered could relate to the lack of blinding in the trial. However, the Committee noted that both methods showed small but statistically significant improvements in median progression-free survival with pembrolizumab compared with conventional chemotherapy. It also noted that there was a separation of the progression-free survival curves that began around 12 weeks, after which a larger difference in progression-free survival was seen between chemotherapy and pembrolizumab. The Committee heard from the clinical experts that treatment response is best assessed around 12 weeks and, after this, the progression-free survival benefit starts becoming

apparent. The Committee concluded that the evidence from KEYNOTE-002, although immature, suggested that pembrolizumab improved progression-free survival compared with conventional chemotherapy, and that the benefit became most apparent after 12 weeks.

- 4.6 The Committee discussed the overall survival results and was aware that there was no statistically significant difference seen between pembrolizumab and chemotherapy. It considered that this could relate to immaturity of the data given the short follow-up in the trial, and particularly to the fact that 48% of people in the chemotherapy group had switched to pembrolizumab. The Committee noted that the company had explored different methods of adjusting for treatment switching, and had concluded that the 2-stage adjustment method was the most appropriate. It noted that the Evidence Review Group (ERG) had agreed with the company's approach and that, when using this method, there was a statistically significant difference in median overall survival between pembrolizumab and chemotherapy of 3.5 months. The Committee concluded that, although the results were immature and there was uncertainty about the true survival benefit associated with pembrolizumab compared with conventional chemotherapy, the best available evidence from KEYNOTE-002, using the 2-stage adjustment method, suggested a difference in median overall survival of 3.5 months.
- 4.7 The Committee discussed the adverse events associated with pembrolizumab. It noted that, in KEYNOTE-002, pembrolizumab was associated with fewer adverse events than chemotherapy. It also recalled the comments from the clinical and patient experts that the adverse events of pembrolizumab were usually manageable and allowed people to continue with their normal activities (see section 4.3). The Committee concluded that the adverse events of pembrolizumab were manageable, and favourable when compared with chemotherapy.

## Cost effectiveness

- 4.8 The Committee considered the company's model, which compared pembrolizumab with best supportive care in people with advanced (unresectable or metastatic) melanoma after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor. The Committee considered that a 3-state model structure was appropriate for

decision-making. It also accepted the company's use of data from the chemotherapy group in KEYNOTE-002 as a proxy for best supportive care based on the Committee's previous conclusion that conventional chemotherapy was an appropriate comparator for pembrolizumab in its expected place in the treatment pathway (see section 4.2).

- 4.9 The Committee noted that the company's economic analysis resulted in a deterministic incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with best supportive care of about £43,000 per quality-adjusted life year (QALY) gained, and a probabilistic ICER of about £68,000 per QALY gained. The Committee expressed concerns about the substantial difference between these figures and discussed possible reasons for the difference. It understood that the variables with the biggest impact on the results were the parameters used to extrapolate progression-free survival and the hazard ratio for overall survival from the 2-stage adjustment method used to extrapolate the overall survival results.
- 4.10 The Committee was aware that the company used a Gompertz distribution for extrapolating progression-free survival from the time of assessment (week 12) onwards in the pembrolizumab group, and that it assumed all people having chemotherapy had progressed or died by the end of the trial (week 67). The Committee noted the comments from the ERG that the Gompertz distribution is associated with a long tail in the progression-free survival curve and that this tends to overestimate progression-free survival in the long-term. It also noted that the confidence intervals were wide because there was a very small proportion of the cohort still at risk at the end of the tail in the progression-free survival curve, which would have a particular impact on the probabilistic cost-effectiveness estimate. The ERG also considered that the company's assumption that all people in the chemotherapy group had disease progression or died at week 67 overestimated the relative progression-free survival benefit associated with pembrolizumab. It also noted that it was more appropriate to use exponential models for extrapolation in both treatment groups. The Committee was concerned that the progression-free survival results were immature, and that it was uncertain how many and for how long people would have progression-free disease. However, it accepted that, when using a Gompertz distribution, the progression-free survival results appeared too optimistic because it was unlikely that people would have life-long progression-free disease.

- 4.11 The Committee noted that the company had used a 3-stage approach to modelling overall survival based on different data sources. It also noted the comments from the ERG that this provided clinically implausible results such as: a 4-year period of zero mortality risk followed by a sudden increase in the mortality risk occurring after 10 years, and an overall survival benefit of pembrolizumab compared with best supportive care that persisted indefinitely. The Committee noted that the ERG had implemented amendments to the company's model in line with its preferred assumptions. It also noted that it provided an exploratory analysis incorporating a different approach to modelling overall survival using trial results, together with a mixed-exponential model based on registry data. The Committee expressed the view that the ERG's overall approach was generally more clinically plausible than the company's model using 3 separate sources.
- 4.12 The Committee noted that, even when incorporating multiple amendments such as changes to the utility values and costs, the cumulative effect of all ERG amendments on the ICER was modest, increasing the ICER for pembrolizumab compared with best supportive care by about £4000, to £47,000 per QALY gained. The Committee was aware that the ERG had not presented probabilistic cost-effectiveness results and recalled its previous concerns about the wide difference between the company's deterministic and probabilistic results (see sections 4.9 and 4.10). The Committee heard from the ERG that, because its approach for modelling progression-free survival used an exponential model instead of a Gompertz model, it was likely that the ERG's deterministic and probabilistic analyses would be much more similar. The Committee therefore considered that, despite the differences between the company's model and the ERG's preferred approach, the ICERs were not very different. It concluded that the most plausible ICER for pembrolizumab compared with best supportive care was likely to be less than £50,000 per QALY gained.
- 4.13 The Committee discussed the innovative nature of pembrolizumab. It noted that the company stated that pembrolizumab was innovative and a step-change in the management of advanced melanoma because it treats a life-threatening and seriously debilitating condition, meets a high unmet need and provides a significant advantage over other treatments used in the UK. The Committee agreed with the company that pembrolizumab is innovative because it meets a high unmet medical need, and because of its low toxicity and favourable adverse effects profile compared with other treatments for metastatic melanoma.

However, it could not identify any specific health-related benefit that had not been already captured in the QALY calculation.

4.14 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 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.

4.15 The Committee discussed whether pembrolizumab met all the criteria to be considered a life-extending, end-of-life treatment and whether the evidence presented was plausible, objective and robust enough to support it. The Committee agreed that the life expectancy of people with advanced melanoma after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor, who do not have any other treatments available apart from conventional chemotherapy, is normally less than 24 months. For example, life expectancy in people with metastatic melanoma was up to 9.0 months based on data from Balch et al. (2001), Korn et al. (2008) and Thirlwell and Nathan (2008), 20.9 months in the company's base-case analysis, and 17.2 months in the ERG's exploratory analyses. The Committee also agreed that, although the overall survival data are immature, the best available data from KEYNOTE-002 and using the 2-stage adjustment method for treatment switching suggested that pembrolizumab offers an extension to life compared with conventional chemotherapy of 3.5 months (see section 4.6). Finally, the Committee discussed the company's estimate for the number of people eligible to have pembrolizumab (that is, people with unresectable or metastatic melanoma whose disease has progressed after ipilimumab and, for

BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor), noting that this was about 600 in 2015, and about 300 annually thereafter. It heard from the clinical experts that these estimates were plausible and in line with the number of people who have had pembrolizumab through the early access to medicines scheme in the NHS. It concluded that this represents a small patient population. The Committee considered that, although the evidence for pembrolizumab in terms of progression-free survival and overall survival is immature and based on a short follow-up, the estimates and assumptions applied can be considered plausible, objective and robust enough to conclude that pembrolizumab meets all the criteria to be considered a life-extending, end-of-life treatment.

- 4.16 Having accepted that the supplementary advice for appraising a life-extending, end-of-life treatment applies, the Committee discussed whether pembrolizumab could be considered a cost-effective use of NHS resources. The Committee recalled its previous conclusion that, despite the differences between the company's model and the ERG's amendments, the results were not very different and that it was likely that the most plausible ICER for pembrolizumab compared with best supportive care was less than £50,000 per QALY gained. Therefore, 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) after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor.
- 4.17 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.

## Summary of Appraisal Committee's key conclusions

TA357	Appraisal title: Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab	Section
<b>Key conclusion</b>		
<p>Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only:</p> <ul style="list-style-type: none"> <li>• after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor and</li> <li>• when the company provides pembrolizumab with the discount agreed in the patient access scheme.</li> </ul>		1.1
<p>The Committee concluded that the evidence from KEYNOTE-002, although immature, suggested that pembrolizumab improved progression-free survival compared with conventional chemotherapy and that, when using the 2-stage adjustment method, pembrolizumab was associated with an overall survival benefit of 3.5 months compared with chemotherapy.</p>		4.5, 4.6
<p>The Committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with best supportive care was likely to be less than £50,000 per quality-adjusted life year (QALY) gained.</p>		4.12
<p>Having accepted that the supplementary advice for appraising a life-extending, end-of-life treatment applies, the Committee concluded that pembrolizumab could be considered a cost-effective use of NHS resources for people with advanced (unresectable or metastatic melanoma) after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor.</p>		4.16
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee concluded that the availability of a new treatment which slows disease progression and improves quality of life when other therapies have failed is very important to patients and their families.</p>	4.3
<b>The technology</b>		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee agreed with the company that pembrolizumab is innovative because it meets a high unmet medical need and because of its low toxicity and favourable adverse effects profile compared with other treatments for metastatic melanoma.	4.13
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that, on the basis of the evidence submitted, it could only make recommendations for pembrolizumab after treatment with ipilimumab and, for BRAF V600 mutation-positive disease, after both ipilimumab and a BRAF or MEK inhibitor.	4.1
Adverse reactions	The Committee concluded that the adverse effects of pembrolizumab were manageable, and favourable when compared with chemotherapy.	4.7
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee considered that the key clinical evidence came from KEYNOTE-002.	4.4
Relevance to general clinical practice in the NHS	The Committee concluded that KEYNOTE-002 was generalisable to clinical practice in the NHS for those people whose disease has progressed after ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor.	4.4
Uncertainties generated by the evidence	The Committee concluded that, because the results were immature, there was uncertainty about the true survival benefit associated with pembrolizumab compared with conventional chemotherapy.	4.6

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that the evidence from KEYNOTE-002, although immature, suggested that pembrolizumab improved progression-free survival compared with conventional chemotherapy and that, when using the 2-stage adjustment method, pembrolizumab was associated with an overall survival benefit of 3.5 months compared with chemotherapy.	4.5, 4.6
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The Committee considered that the company's model, which compared pembrolizumab with best supportive care in people with advanced (unresectable or metastatic) melanoma after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor, had a 3-state model structure that was appropriate for decision-making.	4.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was concerned that the progression-free survival results were immature and that it was uncertain how many and for how long people would have progression-free disease. However, it accepted that the company's approach to extrapolating progression-free survival using a Gompertz distribution led to progression-free survival results that appeared too optimistic because it was unlikely that people would have life-long progression-free disease.	4.10
	The Committee expressed the view that the Evidence Review Group's (ERG's) approach to modelling overall survival was generally more clinically plausible than the company's model using 3 separate sources.	4.11

<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>The company got the utility values from EQ-5D questionnaire data from KEYNOTE-002. The utility values were incorporated into the model based on time to death.</p>	3.8
	<p>The Committee could not identify any specific health-related benefit that had not been already captured in the QALY calculation.</p>	4.13
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	None	
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee understood that the variables with the biggest impact on the results were the parameters used to extrapolate progression-free survival and the hazard ratio for overall survival from the 2-stage adjustment method used to extrapolate the overall survival results.</p>	4.9
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee concluded that that the most plausible ICER for pembrolizumab compared with best supportive care was likely to be less than £50,000 per QALY gained.</p>	4.12
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of pembrolizumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.</p>	2.3

<p>End-of-life considerations</p>	<p>The Committee considered that, although the evidence for pembrolizumab in terms of progression-free survival and overall survival is immature (that is, based on a short period of follow-up), the estimates and assumptions applied can be considered plausible, objective and robust enough to conclude that pembrolizumab meets all the criteria to be considered a life-extending, end-of-life treatment.</p>	<p>4.15</p>
<p>Equalities considerations and social value judgements</p>	<p>No equality issues were raised during the appraisal process.</p>	

## 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. Because pembrolizumab was made available in the NHS through the early access to medicines scheme, NHS England has indicated that this guidance will be implemented 30 days after final 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 unresectable or metastatic melanoma after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor, 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](mailto:keiron.hughes@merck.com).

## 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  
October 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

#### **Mr Adrian Griffin**

Vice President, Health Technology Assessment and International Policy, Johnson & Johnson

#### **Dr Anne McCune**

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

#### **Dr Mohit Misra**

GP, Queen Elizabeth Hospital, London

**Ms Sarah Parry**

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

**Ms Pamela Rees**

Lay Member

**Dr Brian Shine**

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

**Dr Eldon Spackman**

Research Fellow, Centre for Health Economics, University of York

**Mr David Thomson**

Lay member

**Dr John Watkins**

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

**Professor Olivia Wu**

Professor of Health Technology Assessment, University of Glasgow

**Dr Nerys Woolacott**

Senior Research Fellow, Centre for Health Economics, University of York

## **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.

**Pilar Pinilla-Dominguez**

Technical Lead

**Zoe Charles**

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 and Implementation Group, University of Liverpool:

- Fleeman N, Bagust A, Richardson M, et al., Pembrolizumab for treating unresectable, metastatic melanoma after progression 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
- British Association of Skin Cancer Specialist Nurses
- Cancer Research UK
- Melanoma UK
- 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):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Liverpool Reviews & Implementation Group, University of Liverpool
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- 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
- 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 Louise Fearfield, Consultant Dermatologist, nominated by organisation representing British Association of Dermatologists – 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.

ISBN: 978-1-4731-1465-4

## Accreditation

