NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The NICE scope defined the population as people with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab. The company, in line with the main clinical trial for pembrolizumab (KEYNOTE-002), included people with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab and if BRAF V600 mutation positive, a BRAF or MEK inhibitor. What is the Committee's view on the expected place of pembrolizumab within the treatment pathway? What is the Committee's view on the expected efficacy of pembrolizumab in people with BRAF V600 mutation positive who have not had treatment with a BRAF inhibitor?

- The scope included dabrafenib and vemurafenib as comparators for pembrolizumab. The company did not compare pembrolizumab with dabrafenib or vemurafenib because it considered that pembrolizumab would be used after ipilimumab and, if BRAF V600 mutation positive disease, after a BRAF inhibitor. The company considered that established clinical practice in the UK is best supportive care (BSC) which includes chemotherapy treatment such as dacarbazine, and which the company stated has not shown any benefit in terms of overall survival (OS). The ERG agreed with the company's approach. Does the Committee agree that BSC is the appropriate comparator? Is it reasonable to assume that chemotherapy treatments are equivalent to BSC?
- KEYNOTE-002 included centres in Argentina, US and Europe (not in the UK). The ERG considered that the trial was generalizable to UK clinical practice even though there were no participating centres in the UK. The trial included 77% of people with BRAF wild type disease and 54% of people with PD-1L positive disease. What is the Committee's view on the generalisability of KEYNOTE-002 to clinical practice in the NHS?
- KEYNOTE-002 included a treatment group who had 2 mg/kg of pembrolizumab (the licensed dose) and another who had 10 mg/kg of pembrolizumab (the unlicensed dose). The company considered the efficacy of the 2 different doses of pembrolizumab to be similar. What is the Committee's view on the likelihood that the 2 doses of pembrolizumab provide similar results?
- People in KEYNOTE-002 having chemotherapy were allowed to switch to pembrolizumab after disease progression. The results of the analysis of OS did not show a statistically significant difference between pembrolizumab and chemotherapy, which the company stated was because of treatment switching. The company and the ERG considered that the 2-stage adjustment method was the most appropriate method for adjusting for treatment switching. What is the Committee's view on the OS results and does the Committee agree that the 2-stage method is the most appropriate method to adjust for treatment switching?

Cost effectiveness

- The company fitted a Gompertz curve to KEYNOTE-002 PFS data for extrapolating progression-free survival (PFS) results in the model whereas the

ERG considered that the exponential function provided a better fit. The ERG also noted that the company's assumptions in the BSC group may have underestimated the PFS results in the BSC group. The ERG amendments for modelling PFS still led to a substantial long-term PFS benefit for pembrolizumab compared with BSC. This change reduced the incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with BSC by approximately £6900. What is the Committee's view on the most appropriate approach for modelling PFS?

- Because of the lack of long-term OS data from KEYNOTE-002, the company used 3 different sources for the extrapolation of OS in its base case. The ERG stated that using these sources of data led to clinically implausible results such as a 4-year period of zero mortality risk and assuming an indefinite OS benefit for pembrolizumab compared with BSC based on the 12 months OS results in KEYNOTE-002. The ERG applied a different method for extrapolating OS data which reduced the OS benefit of pembrolizumab compared with BSC by approximately 17% and increased the ICER for pembrolizumab compared with BSC by approximately £8400. What is the Committee's view on the most appropriate approach for modelling OS?
- The company estimated the utility values based on time to death in its base case analysis and based on progression in its sensitivity analysis. Utilities values were taken from pooled analyses for the 2 treatment groups in KEYNOTE-002. The ERG noted that the 2 approaches to incorporate utility values in the model were not exclusive and should be complementary. The ERG amended this using utility values based on progression and adjusting them by including a decrement based on time to death. This increased the ICER for pembrolizumab compared with BSC by approximately £5000. The ERG also considered it more appropriate to take utility values from the non-US population in KEYNOTE-002, which increased the ICER for pembrolizumab compared with BSC by approximately £3000. What is the Committee's preferred approach to incorporating utility values in the model?
- The ERG made some amendments to the way the company included use of resources and costs in the model. In one of these amendments, the ERG modified the way in which the company modelled duration of treatment with pembrolizumab. The ERG noted that the company used PFS as a proxy to model time on treatment. In contrast, the ERG used time to stopping treatment from

KEYNOTE-002, which reduced the ICER for pembrolizumab compared with BSC by approximately £7200. What is the Committee's view on the ERG's amendments on use of resources and costs and particularly on the most appropriate way to model time on treatment?

- The results from the company's model showed that the deterministic ICER for pembrolizumab compared with BSC was £42,923 per QALY gained and the probabilistic ICER was £67,615 per QALY gained. The company noted that these results were higher than the deterministic results because of the uncertainty in the short-term PFS data from KEYNOTE-002 and the fact that in the model many patients did not have disease progression and had treatment for life. The ERG presented alternative results which incorporated all of its preferred assumptions and amendments which led to an ICER of £46,662 per QALY gained for pembrolizumab compared with BSC. The ERG cautioned that the company and the ERG's estimates were reliant on immature survival data and were affected by treatment switching, and therefore they were associated with a high degree of uncertainty. What is the Committee's view on the most plausible ICER for pembrolizumab compared with BSC and the robustness of the estimates?
- The company did a scenario analysis assuming that people having pembrolizumab stopped treatment after 2 years based on the protocol of KEYNOTE-006. The deterministic analysis led to an ICER for pembrolizumab compared with BSC of £31,764 per QALY gained and the probabilistic ICER was £33,841 per QALY gained. The company also did scenario analyses varying the assumed duration of NHS reimbursement for pembrolizumab. What is the Committee's view on this scenario analyses?

Other

- The company considered pembrolizumab to be innovative and a step-change in the management of advanced melanoma noting that it treats a life threatening and seriously debilitating condition, it meets a high unmet need and provides a significant advantage over other treatments used in the UK. Does the Committee consider pembrolizumab to be an innovative therapy?
- The company stated that pembrolizumab met all the criteria to be considered a life-extending treatment at the end of life. Is the Committee satisfied that all the

criteria have been met, the estimates presented by the company are robust enough and the assumptions used in the model are plausible, objective and robust?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating advanced melanoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab	Adults with unresectable or metastatic melanoma who have progressed after being previously treated with ipilimumab and, if BRAFV600 mutation positive, a BRAF or MEK inhibitor	As per the population of interest addressed in the key clinical trials supporting this submission, people with BRAFV600 mutation positive disease must have had a prior treatment regimen with an approved BRAF and/or MEK inhibitor.	The ERG noted that NICE has not appraised MEK inhibitors and most patients with BRAFV600 mutation positive melanoma currently have BRAF inhibitors (vemurafenib or dabrafenib). Therefore, the ERG noted that the population referenced in the company's decision problem is a more specific population than that specified in the NICE scope.
Int.	Pembrolizumab	Pembrolizumab		The ERG noted that different doses of pembrolizumab were used in clinical trials.

Com.	• Dacarbazine • Vemurafenib (for people with BRAF V600 mutation-positive disease) • Dabrafenib (for people with BRAF V600 mutation-positive disease) • BSC	BSC (including dacarbazine)	There is unanimity in placing dacarbazine and other chemotherapy agents in the position of palliation as part of BSC. The licenced indication for pembrolizumab is “monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults”. As the submission is focused on the sub-population of ‘patients who have received prior treatment with ipilimumab and if BRAFV600 mutation positive, a BRAF or MEK inhibitor’, this precludes BRAF inhibitors from being appropriate comparators to pembrolizumab in the population of interest covered within this STA.	The ERG agreed with the company that there is no evidence showing that use of palliative chemotherapy is associated with an increase in overall survival and so BSC and dacarbazine can be considered to be effectively equivalent comparators. The ERG also agreed with the company it was not meaningful to compare pembrolizumab with either vemurafenib or dabrafenib because people in KEYNOTE-022 had treatment with a BRAF inhibitor if they had BRAF V600 mutation positive disease.
Out.	• progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life.	• progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life.	In line with NICE final scope	The ERG noted the company reported evidence on all outcomes listed in the scope. It also noted that a lack of mature overall survival data and the high rates of treatment switching increased the difficulty of analysing and interpreting overall survival data.

Abbreviations: ERG, evidence review group; Pop, population; BRAF, Protein kinase of the mitogen-activated protein kinase pathway; MEK, mitogen-activated protein kinase enzymes; Int, intervention; Com, comparators; BSC, best supportive care; STA, single technology appraisal, Out, outcomes

Source: adapted from company’s submission, in table 1

2 The technology and the treatment pathway

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dome) is a humanised monoclonal antibody which acts on the programmed death 1 protein (PD-1) immune-checkpoint receptor pathway blocking its interaction with ligand on the tumour cells and thus, allowing reactivation of antitumor 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 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 (see

2.2 The company that holds the marketing authorisation of pembrolizumab (Merck Sharp & Dohme) has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of pembrolizumab (see Table 2). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

2.3 Table 2).

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Table 2 Technology and comparators

	Pembrolizumab (Keytruda)	Chemotherapy

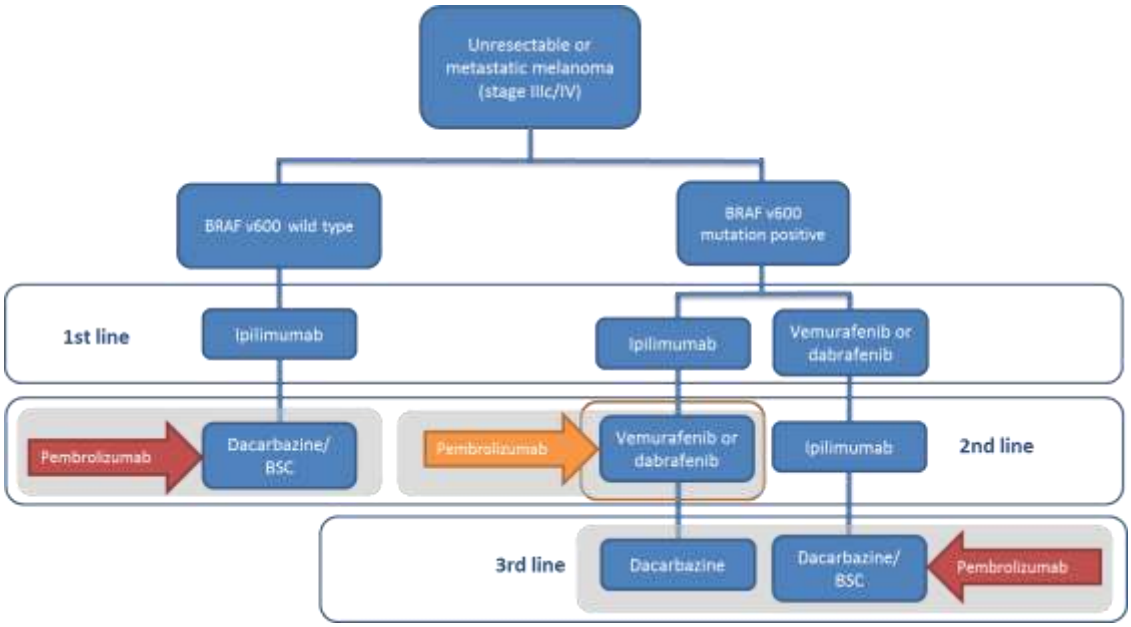
	Pembrolizumab (Keytruda)	Chemotherapy
Marketing authorisation	Monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults	Based on KEYNOTE-002: • Dacarbazine: treatment of patients with metastasized melanoma • Paclitaxel: not licensed in the UK for this indication • Carboplatin: not licensed in the UK for this indication • Temozolomide: not licensed in the UK for this indication
Administration method and dose	2 mg/kg every 3 weeks; IV until disease progression or unacceptable toxicities	Based on the mean body surface area from the KEYNOTE-002 trial: • Dacarbazine: 1000 mg/m2/day every 3 weeks • Paclitaxel: 175 mg/m2 every 3 weeks • Paclitaxel plus carboplatin: 6 (cycles 1 – 4) or 5 (cycles 5 – 10) AUC carboplatin plus 225 mg/m2 paclitaxel every 3 weeks • Carboplatin: 221.85 AUC • Temozolomide: 200 mg/m2 once daily for 5 days every 28 days
Acquisition cost	50mg vial: £1,315 50mg vial with PAS: £[redacted]	• Dacarbazine 100 mg vial: £3.29; 200 mg vial: £4.29; 500 mg vial: £16.49 • Paclitaxel 5ML vial: £3.65; 16.7 mL vial: £7.64; 25 mL vial: £11.58; 50 mL vial: £21.94 • Carboplatin 5 mL vial £3.98; 15mL vial: £9.31; 45 mL vial: £24.75; 60 mL vial: £28.55 • Temozolomide 5 mg cap: £6.52; 20 mg cap: £11.12; 100 mg cap: £44.70; 140 mg cap: £60.70; 180 mg cap: £83.10; 250 mg cap: £106.08
Average cost of a course of treatment	The average cost per cycle is £[redacted].	• Dacarbazine: £58.04 • Paclitaxel: £29.24 • Carboplatin: £116.21 • Paclitaxel plus carboplatin: £29.24 • Temozolomide: £187.98

	Pembrolizumab (Keytruda)	Chemotherapy
Abbreviations: IV, intravenous infusion; PAS, patient access scheme; AUC, area under the curve; cap, capsules See summary of product characteristics for details on adverse reactions and contraindications. Source: adapted from company's submission tables 2, 4, 75 and 76 and appendix 4 and British National Formulary (May 2015)		

2.5 Treatment options for metastatic melanoma include biological therapy, chemotherapy, radiotherapy or surgery. Some people whose disease presents with a protein kinase of the mitogen-activated protein kinase pathway (BRAF) gene mutation will have targeted therapy. NICE technology appraisals guidance 269 and 321 recommend vemurafenib and dabrafenib as options for treating locally advanced or metastatic BRAF V600 mutation-positive unresectable or metastatic melanoma respectively. NICE technology appraisal guidance 268 recommends ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have had prior therapy and NICE technology appraisal guidance 319 recommends ipilimumab as an option for treating previously untreated advanced (unresectable or metastatic) melanoma.

2.6 Pembrolizumab can be used after treatment with ipilimumab. The company's proposed place of pembrolizumab within the treatment pathway in this appraisal is after treatment with ipilimumab and BRAF inhibitors (vemurafenib or dabrafenib) if the disease is BRAF V600 mutation positive (see Figure 1). The company noted that chemotherapy treatment with dacarbazine is only considered when immunotherapy and targeted therapy are not suitable. The Evidence Review Group (ERG) noted that NICE has not made recommendations for mitogen-activated protein kinase enzymes (MEK) inhibitors at the moment. The ERG also considered that the treatment pathway presented by the company reflects current treatment options as recommended by current NICE guidance.

Figure 1 Treatment pathway



Source: Company's response to clarification, figure 15, page 61

3 Comments from consultees

3.1 A professional group noted that people with advanced unresectable melanoma have initial treatment with ipilimumab or BRAF inhibitors if the disease is BRAF V600 mutation positive. It explained that approximately a third of people with BRAF V600 mutation positive disease have low volume, indolent disease and have initial treatment with ipilimumab instead of a BRAF inhibitor. A small proportion of people with advanced melanoma may have initial treatment with chemotherapy with the aim of debulking (that is, reducing the size) of the tumour before having immunotherapy. The professional group also noted that after treatment with ipilimumab people may have treatment with chemotherapy (dacarbazine) or if the disease is BRAF V600 mutation positive, treatment with a BRAF inhibitor. Therefore, it considered that pembrolizumab will be a treatment option after ipilimumab and its direct comparators would be chemotherapy (dacarbazine) and BRAF inhibitors.

3.2 The professional group noted that pembrolizumab should only be given by oncologists, specialists in melanoma, in secondary care and that it was

not expected that any additional resources or requirements would be needed above what already exists in clinical practice. However the professional group highlighted that because of the current practice to continue treatment with pembrolizumab once every 3 weeks for up to 2 years in people whose disease responds to treatment, this is likely to represent a large volume of additional work for pharmacy and chemotherapy day unit teams.

3.3 The professional group noted that although KEYNOTE-001 and KEYNOTE-002 trials were not done in the UK (although KEYNOTE-001 part B2 included some UK centres), they are generalizable to UK clinical practice. It also noted that although long-term data is needed, pembrolizumab appeared to be an effective treatment for advanced melanoma and its adverse effects profile was manageable.

4 Clinical-effectiveness evidence

Overview of the clinical trials

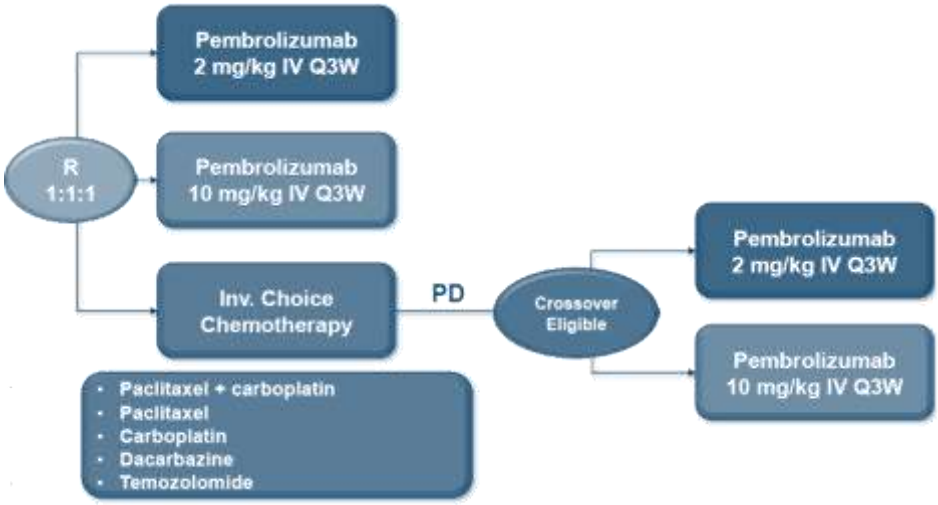
4.1 The company did a systematic literature review and identified 2 clinical trials, KEYNOTE-001 part B and KEYNOTE-002, of pembrolizumab in the population considered in this appraisal, that is, people with unresectable or metastatic melanoma that has progressed after treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF or MEK inhibitor. The company considered KEYNOTE-002 to be most relevant to the decision problem. The company also presented supportive evidence from a clinical trial (KEYNOTE-006) that studied pembrolizumab in people with advanced (unresectable stage III or IV) melanoma untreated with ipilimumab. For further details of KEYNOTE-006 see company's submission, page 94 onwards.

KEYNOTE-002

4.2 KEYNOTE-002 was a randomised, multicentre (including centres in Argentina, US and Europe although not in the UK) controlled trial which compared pembrolizumab with chemotherapy in people with advanced

melanoma who have had at least 2 doses of ipilimumab and whose disease was refractory to ipilimumab, that is, had progressed within 24 weeks of the last ipilimumab dose. People with BRAF V600 mutation positive melanoma must have had treatment with a BRAF (vemurafenib or dabrafenib) or MEK (trametinib) inhibitor. People had investigator choice of chemotherapy (paclitaxel plus carboplatin, carboplatin alone, paclitaxel alone, dacarbazine or temozolomide) (n=179) according to standard of care or current practice, pembrolizumab 2 mg/kg (licensed dose) (n=180) or 10 mg/kg (unlicensed dose) (n=181) every 3 weeks until disease progression (according to Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1]), 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 (confirmed by central review of imaging scan) were allowed to switch to pembrolizumab (see Figure 2).

Figure 2 Study design of KEYNOTE-002



Source: company's submission figure 5, page 44

4.3 The co-primary outcomes in KEYNOTE-002 were progression-free survival (PFS) that is, time from randomisation to the first documented disease progression (based on assessment from central imaging vendor using RECIST 1.1) or death by any cause, whichever occurred first, and

overall survival (OS) that is, time from randomisation to death by any cause. If imaging at 12 weeks (or first tumour assessment) showed progressed disease or tumour assessment indicated disease progression according to RECIST 1.1, treatment with pembrolizumab was continued until a repeat assessment 4 – 6 weeks later confirmed progressed disease. Data from people who had not died at the time of the final analysis were censored, that is, excluded from the analysis from this point onwards, at the date of the last follow-up. The population used for the analyses of PFS and OS was the intention-to-treat population, that is, people were included in the treatment group to which they were allocated at randomisation. The company did 2 sensitivity analyses of PFS applying different censoring rules to evaluate the robustness of the results (for further details see company's submission, table 13). The company stated that it also did a supportive analysis of OS in which data were censored at the time of treatment switch and adjusted the OS data in the chemotherapy group for treatment switching. The rank-preserving structural failure time (RPSFT) adjustment method for treatment switching was pre-specified in the trial protocol and the company also explored other adjustment methods (2-stage and inverse probability of censoring weighting [IPCW]) (see section 4.10).

4.4 Secondary outcomes included overall response rate (defined as the proportion of people who had either a complete response or partial response based on RECIST 1.1), response duration (defined as time from first documented evidence of complete response or partial response until disease progression or death), adverse effects and subgroup analyses for OS, PFS and overall response rate. Exploratory outcomes included health-related quality of life using the European Organisation for Research and Treatment Cancer Quality of Life Questionnaire (EORTC-QLQC30) and Euroqol 5 dimensions questionnaire (EQ-5D).

4.5 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 (see Table 6 and company's submission, Table 15).

ERG comments

4.6 The ERG reported that the company had identified all relevant trials of pembrolizumab and considered that only KEYNOTE-002 was relevant to the decision problem. The ERG considered KEYNOTE-002 to be well designed and to have low risk of bias. The ERG also considered that the trial was generalizable to UK clinical practice even though there were no participating centres in the UK.

4.7 The ERG 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 Eastern Cooperative Oncology Group (ECOG) status 0 – 1 and were considered to be fit enough for having further immunotherapy following treatment with ipilimumab.

Clinical trial results

KEYNOTE-002

4.8 The PFS and OS results were based on the interim analysis 2 (data cut-off 12 May 2014), 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. Results of the pembrolizumab 10 mg/kg group (unlicensed dose) are not presented here (for full results please see company's submission, appendix 6).

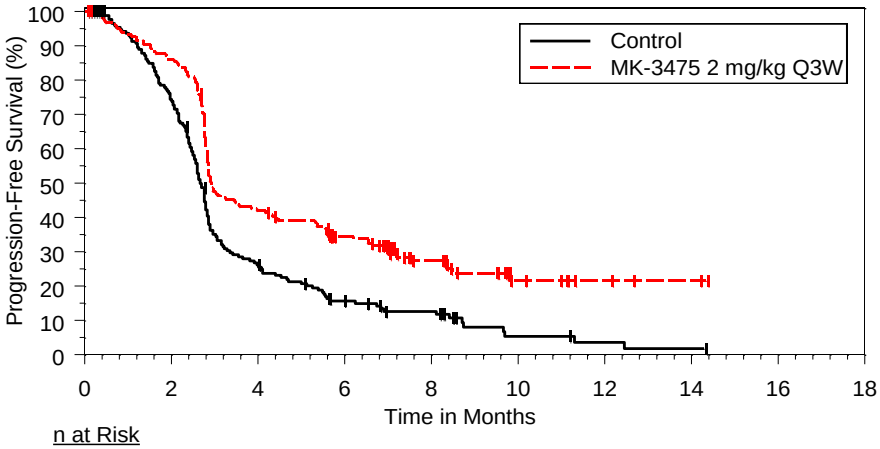
4.9 The company presented the results of the PFS analyses based on central review and investigator review. Results based on central review showed that median PFS was 2.9 months in the pembrolizumab 2 mg/kg group and 2.7 months in the chemotherapy group. The difference in PFS between the treatment groups was statistically significant (hazard ratio

[HR] 0.57, 95% CI 0.45 to 0.73, p<0.0001). The company noted that the Kaplan-Meier results showed that the PFS curves for both treatment groups separated from week 12 onwards and showed a substantial separation by month 6 (see Table 3 and Figure 3). The company stated that the results of the sensitivity analyses of PFS when using different censoring rules were consistent with the primary analyses results. The company also noted that PFS results based on investigator review were consistent with the results based on the investigator results (see Table 3).

Table 3 Summary of PFS results in KEYNOTE-002

	Pembrolizumab 2 mg/kg (N=180)	**Chemotherapy (N=179)**
PFS (IRO [central review] per RECIST 1.1)		
HR - Treatment compared with Control (95% CI)	0.57 (0.45 to 0.73)	
Median in months (95% CI)	2.9 (2.8 to 3.8)	2.7 (2.5 to 2.8)
p value†	<0.0001	
6 month PFS rate (%) (95% CI)	34.3 (27.4 to 41.3)	15.6 (10.5 to 21.5)
PFS (INV assessment)		
HR - Treatment compared with Control (95% CI)	0.49 (0.38 to 0.62)	
Median in months (95% CI)	3.7 (2.9 to 5.4)	2.6 (2.4 to 2.8)
p value†	<0.0001	
6 month PFS rate (%) (95% CI)	38.9 (31.6 to 46.1)	15.2 (10.2 to 21.0)
Abbreviations: PFS, progression-free survival; IRO, Integrated radiology and oncology analysis (central review); HR, hazard ratio; CI, confidence interval; INV, investigator assessment †Based on the stratified log-rank test. Source: adapted from company's submission, table 19 and table 22		

Figure 3 Kaplan Meier analysis of PFS based on central assessment in KEYNOTE-002



n at Risk										
Control	179	128	43	22	15	4	2	1	0	0
MK-3475 2 mg/kg Q3W	180	153	74	53	26	9	4	2	0	0

Source: company's submission, figure 8

4.10 The company stated that OS results did not show a statistically significant difference between pembrolizumab 2 mg/kg and chemotherapy because people whose disease progressed on the chemotherapy group could switch to pembrolizumab (HR 0.88, 95% CI 0.64 to 1.22, p=0.229). The company noted that because the RPSFT adjustment method had been pre-specified in the study protocol before the availability of trial information needed to determine the clinical validity of the approach, it also applied additional adjustment methods (2-stage and the IPCW) (see Table 4). The company stated that because the RPSFT method is based on the assumption of a common treatment effect, this method might not be appropriate because people who switched to pembrolizumab after having had chemotherapy may have a different treatment effect than people who had pembrolizumab initially. The company also stated that the OS results when adjusting for treatment switching with the RPSFT method were invalid because the results were similar to the ones before correction (see Figure 4) and because the results implied that people having pembrolizumab died more quickly after progression than those having chemotherapy. The company also noted that because of the small sample size and the high proportion of people switching treatment, it was

uncertain whether the IPCW method could be considered a valid method. The company stated that because treatment switch occurred after disease progression and the potential relevant confounders were measured until the moment of switching; the 2-stage method appeared to be the most appropriate. The company validated the adjusted OS results generated with the 2-stage method for the control group with the predicted OS using the Korn et al. (2008) algorithm (a study that evaluated historical data from different trials which included 2100 people with metastatic melanoma to attempt to develop benchmarks for OS and PFS as reference points for future trials), and reported a high degree of similarity. For the OS analysis applying the 2-stage adjustment method, the company presented the results of 2 models; 1 which adjusted for all relevant covariates (including ECOG status, tumour size, lactate dehydrogenase level [LDH], BRAF status, melanoma stage and age) and another model which only incorporated ECOG. The company noted that both models led to similar results.

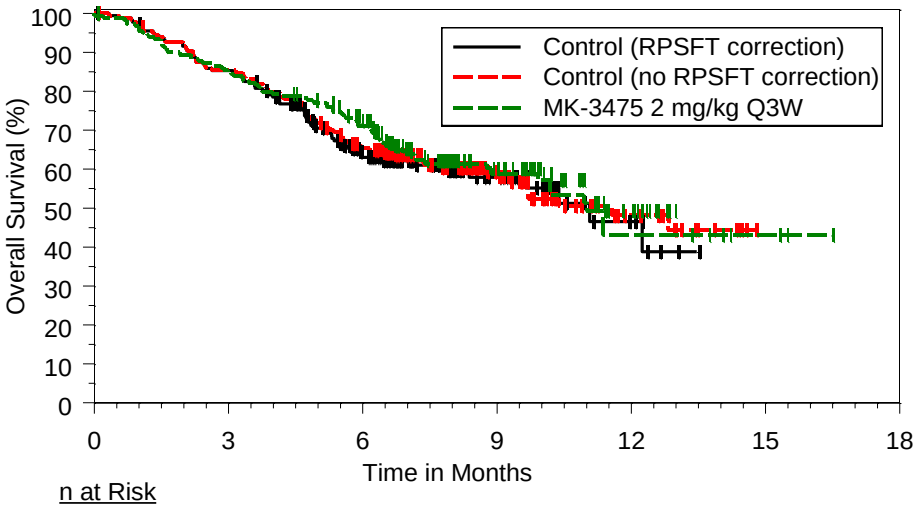
Table 4 Summary of OS results in KEYNOTE-002

	Pembrolizumab 2 mg/kg (N=180)	Chemotherapy (N=179)
OS Median in months (95% CI)		
Unadjusted for crossover	11.4 (10.2 to NR)	11.6 (9.0 to 16.3)
Control: RPSFT correction		11.1 (9.7 to NR)
Control (2-stage correction - simple model		7.8 (5.3 to 9.7)
Control (2-stage correction – all covariates)		7.9 (5.4 to 9.7)
Control (IPCW)		7.5*
OS rate at Month 3 (%) **(95% CI)**	85.5 (79.4 to 89.9)	85.3 (79.2 to 89.8)
HR: pembrolizumab 2mg/kg compared with control (95% CI); p value		
Unadjusted for crossover	0.88 (0.64 to 1.22); p=0.229	
Control: RPSFT correction	0.81 (0.50 to 1.23); p=0.229	
Control (2-stage correction - simple model	0.63 (0.45 to 0.88); p=0.006	
Control (2-stage correction – all covariates)	0.63 (0.45 to 0.88); p=0.007	
Control (IPCW correction)	0.68 (0.48 to 0.96); p=0.028	

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; RPSFT, Rank-preserving structural failure time; IPCW, Inverse probability of censoring weighted; NR, Not reached.

Source: adapted from company's submission, table 19

Figure 4 Kaplan Meier analysis of OS using the RPSFT adjustment method in KEYNOTE-002



n at Risk							
Control (RPSFT correction)	179	151	84	29	8	1	0
Control (no RPSFT correction)	179	151	110	49	17	1	0
MK-3475 2 mg/kg Q3W	180	153	119	56	18	3	0

Source: company's submission, figure 11, page 82

4.11 At the time of the secondary interim analysis (data cut-off date 12 May 2014), the median time to response was 13 weeks in both treatment groups. The median duration of response was not yet reached in the pembrolizumab group and was 37 weeks in the chemotherapy group. The company noted that because of the small number of people at risk at the median, the median response duration for the chemotherapy group should be interpreted with caution. Overall response rate assessed by central review was statistically significantly higher with pembrolizumab than with chemotherapy (21.1% in the pembrolizumab group and 4.5% in the chemotherapy group, $p<0.0001$). Results based on investigator assessment were consistent with results based on central review (see Table 5).

Table 5 Summary of secondary outcomes results in KEYNOTE-002

	Pembrolizumab 2 mg/kg (N=180)	Chemotherapy (N=179)
ORR analysis (IRO [central review] per RECIST 1.1)		
ORR – ITT (%) (95% CI)	21.1 (15.4 to 27.8)	4.5 (1.9 to 8.6)
Difference in % compared with Control (95% CI) (p value) ‡	12.8 (7.0 to 20.6) (p<0.0001)	
Response duration (IRO [central review] per RECIST 1.1)		
People with a response (n)	38	8
Median in weeks (range)	NR (6+ to 50+)	37 (7+ to 41)
Non-progressing (non-progressed disease) n (%)	35 (92)	5 (63)
Median time to response in weeks (range)	13 (12 to 30)	13 (12 to 18)
Abbreviations: IRO, Integrated radiology and oncology analysis (central review); CI, confidence interval; ORR, overall response rate; ITT, intention to treat; NR: Not reached. ‡ Based on stratified on Miettinen & Nurminen method. Source: adapted from company's submission, table 19		

4.12 The company noted that results on health-related quality of life using the EORTC QLQ-30 showed that there was a statistically significant lower reduction in the least squares mean change from baseline with pembrolizumab than with chemotherapy (the difference in least squares mean change from baseline at week 12 was 6.57, p=0.011). It stated that the pembrolizumab group had a smaller proportion of people whose health-related quality of life deteriorated and a larger proportion of people whose health-related quality of life remained stable compared with the chemotherapy group. The ERG noted that the company stated that a score change of 10 points was considered clinically meaningful and thus the ERG stated that there was no clinically meaningful difference in health-related quality of life measured by the EORTC QLQ-C30.

ERG comments

4.13 The ERG agreed with the company that the difference in median PFS between treatment groups in KEYNOTE-002 could be affected by the

timing of the first scheduled response assessment (week 12) and that it was likely that median PFS rates underestimated the treatment effect of pembrolizumab compared with chemotherapy.

4.14 The ERG noted that the company explored different methods to adjust OS data from KEYNOTE-002 for treatment switching and agreed with the company that the 2-stage adjustment method was the most appropriate. This was because treatment switching occurred after disease progression, all relevant confounders were measured until that point and the adjusted OS results for the chemotherapy group could be validated using an external source (the Korn algorithm). The ERG accepted the company's rationale in response to clarification that the assumption of a common treatment effect, which is necessary for applying the RPSFT method, did not hold, showing that people who initially had treatment with pembrolizumab showed a different treatment effect to people who switched to pembrolizumab on disease progression. The ERG also agreed with the company that the IPCW method was not appropriate because of the relatively small number of patients in KEYNOTE-002 and the high proportion of people who switched treatment.

KEYNOTE-001 part B

4.15 The company also presented evidence on KEYNOTE-001 part B. This was a multicentre (including the UK), open-label trial in which pembrolizumab was studied in people with locally advanced or metastatic melanoma (irrespective of previous treatment with ipilimumab [part B1] and that had progressed after treatment with ipilimumab [part B2]). In part B2 (n=173) people had disease that progressed within 24 weeks of the last ipilimumab dose and, if BRAF V600 mutation positive, they must have had treatment with a BRAF inhibitor (vemurafenib or dabrafenib) or MEK inhibitor (trametinib). Treatment allocation was randomised in 2 groups: pembrolizumab 2mg/kg every 3 weeks (the licensed dose) (n=89) and pembrolizumab 10 mg/kg every 3 weeks (unlicensed dose) (n=84). The

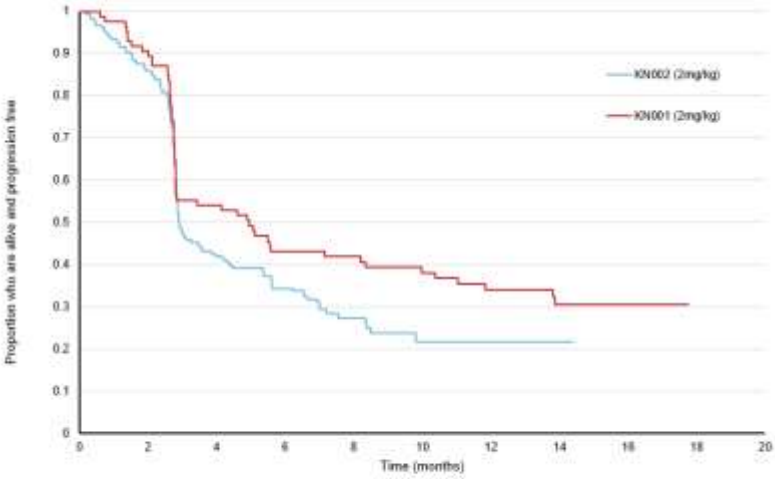
company stated that patients' baseline characteristics were generally balanced between the 2 treatment groups (see Table 6).

4.16 The primary efficacy outcome in KEYNOTE-001 part B2 was response rate based on immune-related response criteria assessed by investigators. In a supportive analysis, response rate was also assessed based on RECIST 1.1 by central reviewers. Secondary outcomes included disease control rate, response duration, PFS based on both immune-related response criteria and RECIST 1.1 and overall survival OS (for full details on the results of KEYNOTE-001 part B2 see company's submission, table 30).

Meta-analyses and indirect comparison

4.17 The company did not do a meta-analysis of KEYNOTE-001 part B2 and KEYNOTE-002 because the treatment effect of pembrolizumab was higher in KEYNOTE-001 part B2 and results in terms of PFS and OS were too different between the 2 trials (see Figure 5 and Figure 6). The company noted that these differences were associated with differences in study design and baseline characteristics because people in KEYNOTE-002 had disease with poorer prognosis and more severe metastases. Table 6 summarises the patients' baseline characteristics in KEYNOTE-001 part B2 and KEYNOTE-002.

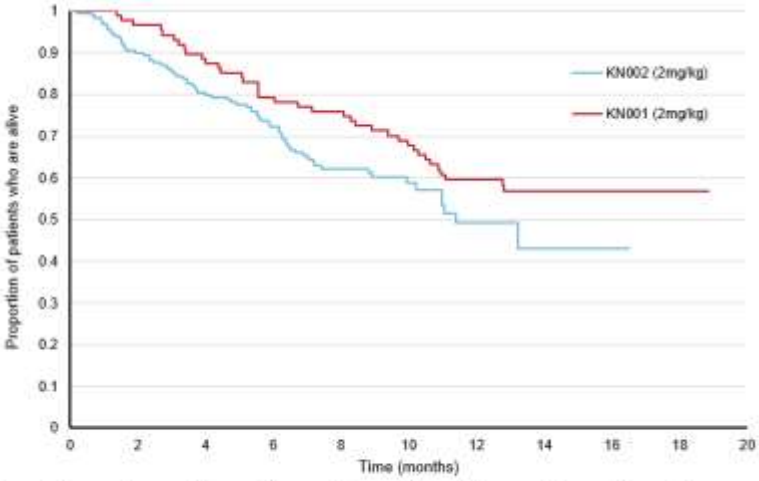
Figure 5 PFS results in the pembrolizumab group in KEYNOTE-002 and KEYNOTE-001 part B2



Time (Months)	0	2	4	6	8	10	12	14	16
KN002	180	153	84	56	27	10	10	10	0
KN001	89	77	45	35	33	30	23	16	16

Source: company's submission, figure 21

Figure 6 OS results in the pembrolizumab group in KEYNOTE-002 and KEYNOTE-001 part B2



Time (Months)	0	2	4	6	8	10	12	14	16	18
KN002	180	161	143	120	81	40	22	7	0	0
KN001	89	85	76	69	66	56	51	40	40	40

Source: company's submission, figure 21

Table 6 Patients baseline characteristics in KEYNOTE-001 part B2 and KETYNOTE-002

Patient characteristic	KEYNOTE-002: ITT population				KEYNOTE-001 (Part B2): ApaT population		
	Pembrolizumab 2mg/kg Q3W	Pembrolizumab 10mg/kg Q3W	Chemotherapy	Total	Pembrolizumab 2mg/kg Q3W	Pembrolizumab 10mg/kg Q3W	Total
	n=180	n=181	n=179	n=540	n=89	n=84	n=173
Age, median (range)	62.0 (15 to 87)	60.0 (27 to 89)	63.0 (27 to 87)	61.5 (15 to 89)	59.0 (18 to 88)	62.5 (27 to 86)	61.0 (18 to 88)
Male	58%	60%	64%	61%	54%	68%	61%
ECOG performance status							
0 [normal activity]	54%	54%	55%	55%	66%	68%	67%
1 [symptoms but ambulatory]	44%	46%	45%	45%	34%	32%	33%
BRAF status							
Mutant	24%	22%	23%	23%	13%	23%	18%
Wild type	76%	78%	77%	77%	87%	77%	82%
LDH level							
Normal	55%	58%	60%	58%	55%	66%	60%
Elevated (≥110% ULN)	43%	40%	38%	40%	44%	35%	39%
M-stage							
M0	<1%	<1%	1%	<1%	16%	12%	14%
M1a	5%	7%	8%	7%	8%	13%	10%
M1b	12%	9%	8%	10%	16%	16%	16%
M1c	82%	83%	82%	83%	57%	56%	57%

Patient characteristic	KEYNOTE-002: ITT population				KEYNOTE-001 (Part B2): ApaT population		
	Pembrolizumab 2mg/kg Q3W	Pembrolizumab 10mg/kg Q3W	Chemotherapy	Total	Pembrolizumab 2mg/kg Q3W	Pembrolizumab 10mg/kg Q3W	Total
	n=180	n=181	n=179	n=540	n=89	n=84	n=173
No. of lines of previous therapies							
0	<1%	0%	0%	<1%	0%	0%	0%
1	22%	31%	26%	27%	33%	23%	28%
2	44%	37%	44%	41%	35%	40%	38%
≥3	33%	33%	30%	32%	33%	37%	35%

Abbreviations: ITT, intention to treat; ApaT, all patients as treated; ECOG, Eastern Cooperative Oncology Group; BRAF, Protein kinase of the mitogen-activated protein kinase; LDH, Lactate Dehydrogenase; ULN, upper limit of normal

Source: ERG report, table 5

4.18 The company reported that there is no evidence comparing pembrolizumab or chemotherapy with best supportive care (BSC) in people with metastatic melanoma after progression with ipilimumab and thus, it did not do an indirect comparison of pembrolizumab and BSC.

ERG comments

4.19 The ERG agreed with the company that a meta-analysis of results from KEYNOTE-002 and KEYNOTE-001 part B2 was not appropriate because of the differences in patient populations. It also agreed that an indirect comparison of pembrolizumab and BSC was not possible because there was no evidence on which to base this.

Adverse effects of treatment

4.20 The company presented results of adverse effects based on the all patients as treated (APaT) population from KEYNOTE-002 and Table 7 summarises these. The most common adverse effects in the pembrolizumab 2 mg/kg group were fatigue (38.8%), pruritus (23.5%), constipation (21.3%), diarrhoea (20.8%), nausea (19.7%), anaemia (17.4%), cough (17.4%), decreased appetite (16.3%) and arthralgia (that is, joint pain) (15.2%). The most common adverse effects in the chemotherapy group were fatigue (48.0%), nausea (41.5%), anaemia (26.3%), vomiting (22.8%), decreased appetite (22.8%), constipation (20.5%), alopecia (20.5%), diarrhoea (19.9%), and cough (15.8%). The company stated that the results showed the overall favourable safety profile of pembrolizumab as an immune therapy for advanced melanoma and compared with chemotherapy. For further details on adverse effects in KEYNOTE-002 see company's submission, tables 48 – 52 and appendix 11. For details of adverse effects in KEYNOTE-001 part B2 see company's submission, tables 53 and 54.

Table 7 Summary of adverse effects in KEYNOTE-002

	Pembrolizumab 2 mg/kg (n=178)	Chemotherapy (n=171)
Exposure, days		
Median (range)	112.5 (1 to 499)	61 (1 to 335)
Mean (SD)	144.2 (107.7)	75.5 (66.4)
With 1 or more AEs	172 (96.6%)	167 (97.7%)
Grade 3-5 AE	83 (46.6%)	88 (51.5%)
Any grade drug-related AE	121 (68.0%)	138 (80.7%)
Drug-related Grade 3-5 AE	20 (11.2%)	45 (26.3%)
Serious AE	79 (44.4%)	57 (33.3%)
Serious drug-related AE	14 (7.9%)	17 (9.9%)
Death	11 (6.2%)	8 (4.7%)
Drug-related AE leading to death	1 (0.6%)	0 (0.0%)
AE leading to discontinuation	18 (10.1%)	20 (11.7%)
Drug-related AE leading to discontinuation	5 (2.8%)	10 (5.8%)
Serious AE leading to discontinuation	15 (8.4%)	14 (8.2%)
Serious drug-related AE leading to discontinuation	5 (2.8%)	4 (2.3%)
Abbreviations: SD, standard deviation; AE, adverse effects Source: company's submission, table 47		

ERG comments

4.21 The ERG noted that pembrolizumab had a better safety profile than chemotherapy showing fewer adverse effects and drug-related adverse effects of any grade, grade 3 or higher and leading to stopping treatment. The ERG also noted that immune-related adverse effects with

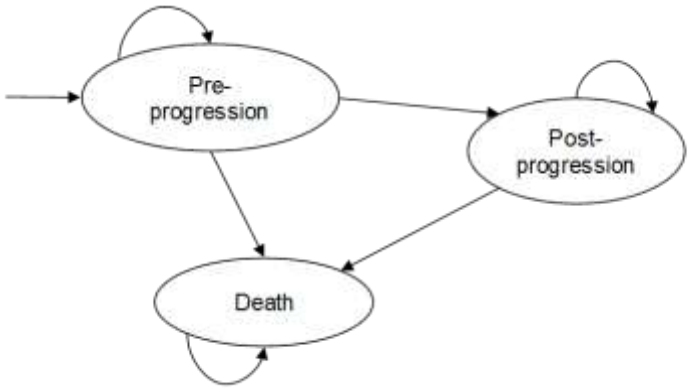
pembrolizumab were generally reversible when treatment was stopped and when treated with corticosteroids. The ERG received clinical advice highlighting that specialists working in oncology services may be not familiar with some adverse effects associated with pembrolizumab and their management may require the involvement of specialists other than oncologists. The ERG however acknowledged that the management of some of these adverse effects has become more common because of experience with treatment with ipilimumab.

5 Cost-effectiveness evidence

Model structure

5.1 The company did a de novo economic model to assess the cost effectiveness of pembrolizumab compared with BSC in people with unresectable or metastatic melanoma previously treated with ipilimumab and who had progressive disease within 24 weeks of the last dose. The population in the model differed from the scope in that people with BRAF V600 mutation positive disease had also had treatment with a BRAF inhibitor (vemurafenib or dabrafenib) in line with KEYNOTE-002. BSC 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 (see Figure 7). 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.

Figure 7 Company's model structure



Source: company's submission, figure 25

ERG comments

5.2 The ERG considered that the company's model structure was appropriate and generally well implemented.

Model details

5.3 Data from KEYNOTE-002 were used to estimate the baseline patients' characteristics, the proportion of people in the different states, the proportion experiencing adverse effects, and utility values. The average age of the cohort in the model was 60. People had treatment with pembrolizumab or chemotherapy until disease progression and subsequent therapies were not considered in the model. The definitions of the health states were based on KEYNOTE-002. Progressed disease was defined based on RECIST v1.1. Non-progressed disease included patients whose disease had complete response, partial response and stable disease. Transitions between states were derived from the proportion of patients that were reflected by the areas under the PFS and OS curves in KEYNOTE-002. The area between the PFS and OS curves represented the proportion of people in the post-progression state. The company noted that because the model was based on data from KEYNOTE-002 in which people had disease refractory to ipilimumab (that is, had progressed within 24 weeks of the last ipilimumab dose; which is a

subgroup of the overall population who had had treatment with ipilimumab), it was likely that the model results underestimated the true OS benefit associated with pembrolizumab. For modelling the impact of treatment on costs and quality of life, the analysis was based on time spent alive. The model included time-to-death sub-health states to capture patients' quality of life, each associated with a specific utility value, and these were: less than 30 days to death, 30 to 89 days to death, 90 to 179 days to death, and more than 180 days to death (for further details see company's submission, figure 26).

5.4 The company assumed that all chemotherapy treatments had equal efficacy in terms of PFS and OS. The company applied standard parametric curve fitting for extrapolating PFS. The company stated that because PFS 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 Gompertz function was selected because the company considered that it provided the best fit to PFS data. The company stated that the proportional hazard assumption could not be rejected and it incorporated it on the extrapolation of the data. The company highlighted that using PFS to represent disease status within the model may underestimate pre-progression survival and overestimate post-progression survival. The company applied different PFS extrapolation methods in scenario analyses (see Table 8).

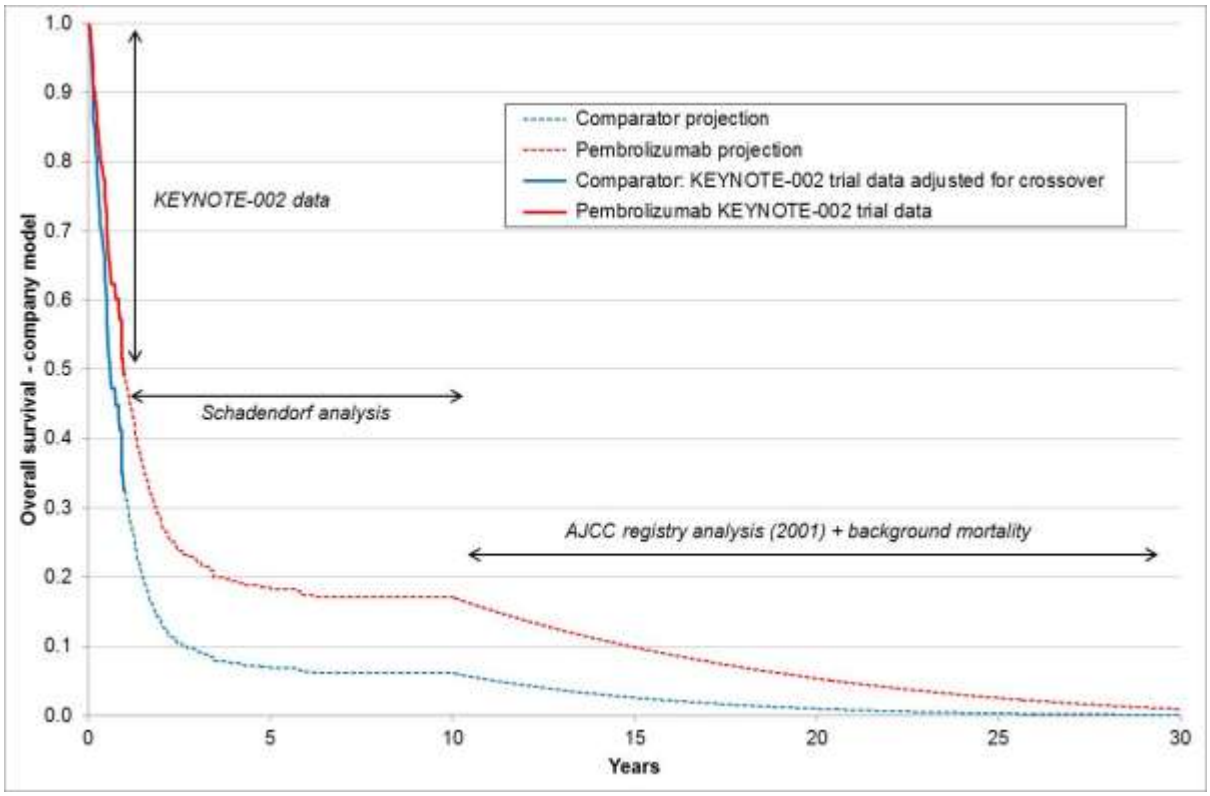
5.5 The company reported that because OS data from KEYNOTE-002 were immature, and standard parametric curve fitting resulted in survival estimates that were not clinically plausible, alternative methods were needed to extrapolate survival beyond the trial period. The company noted that because pembrolizumab had shown similar outcomes to ipilimumab for previously treated metastatic melanoma, it could be assumed that pembrolizumab had a similar survival profile to ipilimumab in the long term. The company applied different methods for adjusting for treatment switching (2-stage approach, IPCW and RPSFT) and

considered the 2-stage method to be the most appropriate (see section 4.10). It also reported that 3 clinical experts agreed that it was reasonable to assume that pembrolizumab was associated with similar survival to ipilimumab, that the projections obtained appeared clinically plausible, and that there was a need to adjust for treatment switching. The company used the following sources for the extrapolation of OS in its base case (see Figure 8):

- 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 + general population mortality

The company used alternative extrapolation methods in scenario analyses (see Table 8). For further details on the extrapolation options see company's submission pages 161 – 166.

Figure 8 Overall survival in company's model



Source: ERG report, figure 8

Table 8 Summary of company's extrapolation options for PFS and OS data

Pembrolizumab	BSC
1. Trial data + ipilimumab extrapolation from Schadendorf 2015 (relative rate of survival) (company's base case) • PFS Kaplan-Meier data from KEYNOTE-002 trial used for the first 12 weeks, and a parametric curve (best fit: Gompertz distribution) is fit to the KEYNOTE-002 pembrolizumab group from week 13. • Summary of the data used for OS: ○ 0 to 1 year: KEYNOTE-002 trial data ○ 1 year to 10 years: ipilimumab (previously treated) survival curve (as published in Schadendorf et al. [2015]) ○ 10 years onwards: Balch et al. (2001) registry data + general population mortality	**1. Chemotherapy from KEYNOTE-002, 2-part curve fit (company's base case)** • PFS Kaplan-Meier data from KEYNOTE-002 used for the first 12 weeks. A parametric curve (best fit: Gompertz distribution) is fit to the chemotherapy arm of KEYNOTE-002 from week 13. • For OS, survival is modelled based upon the curve fit selected for pembrolizumab adjusted for crossover using the 2-stage method. No external data is used outside of the trial.
2. Trial data + ipilimumab extrapolation from MDX010-020 (using relative rate of survival) • PFS Kaplan-Meier data from KEYNOTE-002 used for the first 12 weeks, and a parametric curve (Gompertz distribution) fitted to the KEYNOTE-002 pembrolizumab group from week 13. • Summary of the data used for OS: ○ 0 to 1 year: KEYNOTE-002 trial data ○ 1 year to 1.5 years: ipilimumab survival curve (previously treated) (i.e. MDX010-20 trial Kaplan-Meier data) ○ 1.5 to 5 years: curve fit to MDX010-020 data (as in NICE technology appraisal guidance 268 on ipilimumab for previously treated advanced melanoma) ○ 5 years onwards: Balch et al. (2001) registry data + general population mortality	**2. gp100 from MDX010-020 trial as a proxy for BSC** • For PFS, the comparator group (gp100) PFS curve from MDX010-20 trial (as in NICE technology appraisal guidance 268 on ipilimumab for previously treated advanced melanoma). • Summary of the data used for OS: ○ 0 to 1 year: comparator group (gp100) from MDX010-020 Kaplan-Meier data ○ 1 to 5 years – curve fit to comparator group (gp100) from MDX010-020 data ○ 5 years onwards: Balch et al. (2001) registry data + general population mortality Korn model to adjust for differences in patient characteristics

3. Hazard ratio using KEYNOTE-002 on external data
• PFS Kaplan-Meier data from KEYNOTE-002 used for the first 12 weeks, and a parametric curve (Gompertz distribution) fitted to the KEYNOTE-002 pembrolizumab group from week 13.
• For OS, the hazard ratio between the pembrolizumab and the chemotherapy groups from the 2-stage adjustment analysis applied to a selected external dataset (gp100 from MDX010-020 trial as in NICE technology appraisal guidance 268 on ipilimumab for previously treated advanced melanoma).
	3. Korn dataset (OS only)
	• Summary of the data used for OS:
	  ○ 0 to 5 years: Korn Kaplan-Meier data
	  ○ 5 years onwards: Balch 2001 registry data + general population mortality
	Korn model to adjust for differences in patient characteristics.

4. Trial data + ipilimumab extrapolation from Schadendorf 2015 – Treatment naïve cohort (relative rate of survival)
• PFS Kaplan-Meier data from KEYNOTE-002 trial used for the first 12 weeks, and a parametric curve (best fit: Gompertz distribution) fitted to the KEYNOTE-002 pembrolizumab group from week 13.
• Summary of the data used for OS:
  ○ 0 to 1 year: KEYNOTE-002 trial data
  ○ 1 year to 10 years: ipilimumab (previously untreated) survival curve (as published in Schadendorf et a;. [2015])
  ○ 10 years onwards: Balch et al. (2001) registry data + general population mortality
This is based upon clinical advice that long-term survival with pembrolizumab would be expected to be at least as good or better than that seen with ipilimumab.	

Abbreviations: PFS, progression-free survival; OS, overall survival; HR, hazard ratio Source: adapted from company's submission, table 63	

ERG comments

5.6 The ERG noted that the company used the Gompertz distribution for extrapolating PFS data in the pembrolizumab group from week 13 onwards. In contrast to what the company stated in its submission (see section 5.4), the ERG noted that for the BSC group the company directly used Kaplan-Meier data until the final date when any patient was observed to still have progression-free disease (week 62), at which point all remaining patients were assumed to have died or have disease progression. The company applied the extrapolation method stated in section 5.4 (that is, PFS Kaplan-Meier data from KEYNOTE-002 used for the first 12 weeks and a Gompertz parametric curve fitted to the PFS data from chemotherapy group of KEYNOTE-002 from week 13 onwards) in scenario analyses. The ERG considered that the exponential distribution provided a better fit to Kaplan-Meier data from KEYNOTE-002 than the Gompertz function used by the company in its model. The ERG also noted that the Gompertz function usually overestimates PFS results in the long term and that assuming that all patients in the BSC group died or had disease progression at week 62 without any projection underestimated the PFS results in the BSC group. The ERG considered that this overestimated the benefit of pembrolizumab in terms of PFS compared with BSC by approximately 30%. The ERG noted that the company used the PFS results by central review in its model and requested the PFS results by investigator assessment using an alternative censoring rule (censor patients lost to follow-up and who withdraw from the trial at the time recorded and patients alive and still at risk of the target event at the date of data cut-off, and not when last seen). The ERG stated that PFS by investigator assessment was more representative of clinical practice and used these results in its exploratory analyses. It applied exponential models to the PFS results in both treatment groups and found that this still led to a substantial long-term PFS benefit for pembrolizumab compared with BSC (net extended PFS benefit with pembrolizumab compared with BSC of 4.18 months compared with company's estimate of 5.35 months).

Table 12, scenario R6 shows the impact of this amendment on the incremental cost-effectiveness ratio (ICER).

5.7 The ERG noted that the company estimated OS in its base case analysis in 3 times phases based on 3 different sources and explored each of these separately:

- From 0 to 1 year: KEYNOTE-002 data. The ERG compared the survival of people in the pembrolizumab group with the survival of people who switched treatment to pembrolizumab after disease progression and found a similar benefit in both groups. Therefore, it concluded that correction for treatment switching was justified.
- From 1 to 10 years: Schadendorf et al. (2015) data. The ERG noted that in Schadendorf et al. selected treatment groups from different trials of ipilimumab were pooled and that the company directly used the results in the model. The ERG noted that this did not take into account the diminishing number of patients who had progression-free disease in the model and the reduction in the number of patients in the pembrolizumab group because of patients stopping treatment. The ERG also stated that using these data led to a period from 6 to 10 years in which there were no deaths from any cause and considered this to be implausible and a misrepresentation of the data. It also noted that the company assumed that the multiple heterogeneity observed in the pooled analysis in Schadendorf et al. did not influence long-term survival. After examination of the references used in the Schadendorf et al. analysis the ERG considered that there was a large risk of uncontrolled selection bias which would affect the estimation of long-term survival.
- From 10 to 30 years: Balch et al. (2001) registry data + general population mortality. The ERG noted that there were several problems with the Balch et al. analysis:
  - It was based on the American Joint Committee on Cancer registry data which have been subsequently updated and reported in Balch

et al. (2009). The updated analyses showed that the average life expectancy of people with melanoma was influenced by the subgroup of stage IV melanoma (that is, M1a, M1b, M1c)

- It did not include patients who had had treatment with ipilimumab and therefore applied to a different population from that included in either treatment group in KEYNOTE-002
- Survival was measured from the time of diagnosis and the use of these data would depend on being able to identify the time from diagnosis for all patients in KEYNOTE-002.

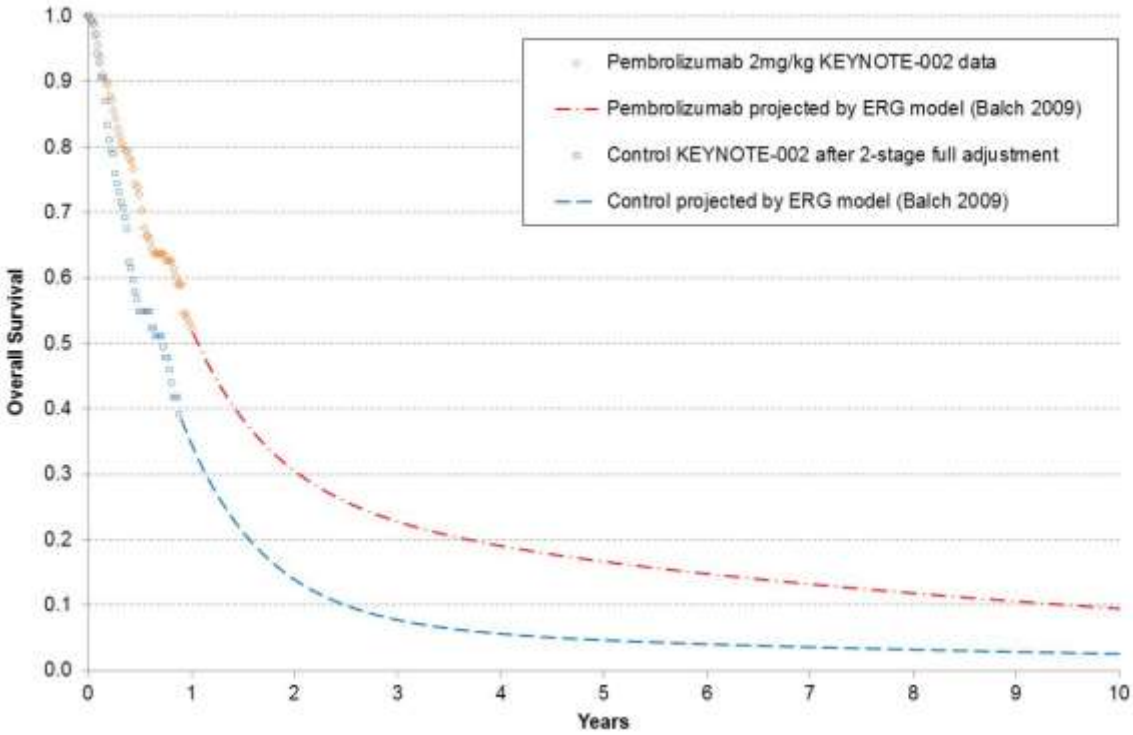
The ERG stated that using these 3 different sources of data led to clinically implausible results such as a long period of zero mortality risk and a sudden increase in mortality from zero to non-zero at 10 years. It was concerned that the company applied the OS HR from the trial to the whole time horizon (including to the background mortality from all causes from UK life tables) and that this led to an indefinite OS gain in the pembrolizumab group compared with BSC from 10 to 30 years. The ERG did sensitivity analyses removing the zero mortality risk period (see Table 12, scenario R8) and revising the mortality rates to be equal in both treatment groups beyond 10 years to reflect that OS in the pembrolizumab group will eventually become similar to that in the BSC group (see Table 12 scenario R9).

5.8 The ERG explored the company's alternative methods for extrapolating OS summarised in Table 8 and noted that they all used data from Schadendorf et al. (2015), Balch et al. (2001) or both. Therefore the ERG also considered these scenarios not to be appropriate.

5.9 The ERG applied a different method for extrapolating OS data in the model based on a previous approach taken for ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. The ERG's method used a mixed exponential model with 2 subgroups of patients (1 subgroup had a high risk of mortality, and the other subgroup [approximately 10-15% of the total population] had much longer survival) as observed in clinical practice. The ERG used the American Joint

Committee on Cancer registry data and 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 and 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 (see Figure 9). This resulted in a situation in which beyond the observed trial period, most patients having pembrolizumab stopped treatment rapidly because of disease progression or adverse effects, and future survival was therefore largely determined by the conventional treatment options covered in the registry data. Using this method for extrapolating OS data led to a reduction on the estimated survival gain of approximately 17% (see Table 12, scenario R10).

Figure 9 ERG's long-term projection of OS



Source: ERG report, figure 14

Health-related quality of life

5.10 The company obtained the utility values from EQ-5D data from KEYNOTE-002. Utility values were calculated based on time to death and progression-based states. The company reported that there were no statistically significant differences in utility values between the pembrolizumab and chemotherapy groups at baseline. Therefore, the company used pooled utility values from both treatment groups in the model. The company noted that utility values decreased when patients were closer to the time of death. The company focused the analysis of the intervals related to time to death of less than 180 days on people with observed death dates. However, for the category of 180 days or more to death, people with censored death date of 180 days or longer were also included because their EQ-5D data related to a survival of at least 180 days. The company adjusted the EQ-5D data by age using the values from Kind et al. (1999) and applied utility decrements because of grade 3 – 5 and relevant adverse effects. The company also calculated pooled utility values for pre-progression (0.74) and post-progression states (0.68) for both treatment groups and applied them in sensitivity analyses. Table 9 shows a summary of the utility values used in the model.

Table 9 Summary of utility values in the model

Time to Overall Survival (days)	Total pooled values (pembrolizumab and BSC)	
	Mean	**95% CI**
≥180*	0.77	(0.75 to 0.79)
[90, 180)	0.62	(0.57 to 0.67)
[30, 90)	0.52	(0.45 to 0.58)
<30	0.42	(0.28 to 0.56)

* This group also includes patients whose death dates were censored and report EQ5D ≥ 180 days.
Abbreviations: CI, confidence interval
Source: adapted from company's submission, table 71

ERG comments

5.11 The ERG considered that utility values differed between people from US and people from other countries included in KEYNOTE-002 and asked the company to provide a breakdown of utility values (see Table 10). Based

on these values, the ERG amended the model using non-US utility values (see Table 12, scenario R5).

Table 10 Utility values from non-US population in KEYNOTE-002

Time to Death (days)	Pembrolizumab + Chemotherapy				
	n†	n‡	Mean	SE	95% CI
≥180*	88	195	0.73	0.02	(0.70, 0.77)
[90, 180)	36	62	0.56	0.04	(0.48, 0.64)
[30, 90)	35	44	0.44	0.04	(0.36, 0.53)
<30	12	13	0.33	0.11	(0.08, 0.57)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included
* This group also includes patients whose death dates were censored and report EQ5D during this time.
Source: company's response to clarification, table 41

5.12 The ERG noted that the 2 approaches to incorporating utility values in the model adopted by the company (that is, utility values based on progression and utility values based on time to death) were not exclusive but should be complementary. The ERG amended this using utility values based on progression and adjusting them including a decrement in the utility value based on time to death (see Table 12, scenario R12).

Use of resources and costs

5.13 The company included costs reflecting the clinical management of unresectable or metastatic melanoma which included treatment costs, monitoring and follow up, management of complications and adverse effects and terminal care. The company mainly took healthcare resource utilisation data from the MELODY study (a study of resource utilisation in 220 people with melanoma), which included inpatient, outpatient and hospice care costs of melanoma in the UK. The company noted that this study was done before ipilimumab and BRAF inhibitors were available and was not a reliable source for estimating long-term survivor costs. Therefore, these were based on clinical experts' feedback. The company

assumed that people whose disease had not progressed continued treatment and had regular check-ups every 3 months and every 3 to 6 months after 2 years. For people whose disease progressed, check-ups were assumed to take place at least every 3 months until an alternative treatment option was found. The company calculated the average number of vials of pembrolizumab per patient using the sex and weight distribution of patients from Europe included in KEYNOTE-002. The company used the composition of treatments from the chemotherapy group in KEYNOTE-002 to reflect BSC in the model and used alternative definitions of BSC (such as the composition of treatments from the MELODY study) in sensitivity analyses. The company assumed no vial sharing in its base-case analysis and that treatment was continued until disease progression or unacceptable toxicity. Treatment costs were obtained from the electronic market information tool (eMit) and the monthly index of medical specialities (MIMS) and administration costs from NHS reference costs. The incidence of adverse effects was based on KEYNOTE-002 and their associated costs were obtained from NICE technology appraisal guidance on ipilimumab for previously untreated advanced melanoma, which referred to the MELODY study as the main data source. For further details on use of resources and costs see company's submission, tables 73 – 80 and appendix 21.

ERG comments

5.14 The ERG noted that the company estimated the doses of pembrolizumab based on the distribution of the body weight of people in KEYNOTE-002 and divided the patients into weight bands according to the whole number of vials needed. The ERG stated that body weight can vary between countries and re-estimated the costs based on UK values reported in the Health Survey for England (2012) and using a log-normal distribution. The ERG also noted that the company did not vary body surface area according to sex when estimating the doses of some of the therapies considered as part of BSC and that it did not use a method for using the least expensive combination of vial sizes available. The ERG corrected

these issues and re-estimated the overall average cost per dose for each treatment. The ERG also noted that there were coding errors in the company's model in scenarios associated with the BSC group. The ERG also corrected the costing category of treatment administration for some treatments in the BSC group and based on clinical advice, it assumed that dacarbazine would be given up to a maximum of 6 cycles instead of until disease progression as per the company's model. The ERG also modified the way in which the company modelled duration of treatment with pembrolizumab. The ERG noted that the company used PFS as a proxy to model time on treatment. In contrast, the ERG used time to stopping treatment from KEYNOTE-002. For estimating duration of treatment in the BSC group the ERG used the values from the pembrolizumab group adjusted using the ratio of PFS. The results of these ERG amendments are summarised in Table 12, scenarios R1, R2, R3, R7 and R11.

Company's base-case results and sensitivity analysis

5.15 The results from the company's cost-effectiveness analysis of pembrolizumab compared with BSC showed that pembrolizumab provided 1.19 additional quality-adjusted life years (QALYs) and £50,995 additional costs compared with BSC, leading to an ICER of £42,923 per QALY gained. The company compared the results from the model with the outcomes from KEYNOTE-002, noting that these were similar, and suggested that in the short term the outcomes from the model were valid.

5.16 The company did deterministic sensitivity analyses and found that the variables that had the highest impact on the ICER were the curve fit parameters for PFS data (varying the scale in the Gompertz distribution led to ICERs between £28,593 and £125,879 per QALY gained, and varying the treatment effect in the Gompertz distribution led to ICERs between £30,600 and £66,341 per QALY gained) and the HR for OS from the 2-stage treatment switching adjustment method (the ICER ranged from £31,865 to £128,080 per QALY gained).

5.17 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 BSC. The company noted that these results were higher than the deterministic results because of the uncertainty in the PFS 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 approximately 50% of pembrolizumab being cost effective at a maximum acceptable ICER of £50,000 per QALY gained. The company also presented additional scenario analyses assuming different durations of NHS reimbursement for pembrolizumab (acquisition and administration costs) to reiterate the fact that the difference between the deterministic and the probabilistic base case ICER for pembrolizumab compared with BSC was associated with the uncertainty in the PFS data from KEYNOTE-002 that made that in the model many patients continued having treatment with pembrolizumab for many years, and therefore increasing the costs in the pembrolizumab group.

ERG comments

5.18 The ERG noted that the company's base case model results showed that 99.1% of the overall incremental cost was attributable to differences in direct treatment costs (acquisition costs and administration). The ERG also noted that approximately 72% of the estimated health gain occurred after disease progression in the company's model and therefore, the long-term projection of the KEYNOTE-002 results was the most important element of the company's model.

Company scenarios

5.19 The company re-ran its deterministic analysis and probabilistic sensitivity analysis assuming an alternative scenario in which people having pembrolizumab stopped treatment after 2 years based on the protocol of KEYNOTE-006. The deterministic analysis led to an ICER for

pembrolizumab compared with BSC of £31,764 per QALY gained and the probabilistic sensitivity analysis provided an ICER of £33,841 per QALY gained. The probability of pembrolizumab being cost effective compared with BSC at a maximum acceptable ICER of £50,000 per QALY gained under this scenario was 87%.

5.20 The company did several scenario analyses to assess uncertainty around structural and methodological assumptions in the model. The company stated that the results from all scenarios resulted in ICERs lower than £50,000 per QALY gained except for the scenarios assuming the log-normal and log-logistic curves for fitting PFS data, using less robust shorter-term data for extrapolation of survival based on proportional hazards and long-term use of chemotherapy. The company considered these scenarios to be clinically unrealistic. Table 11 includes a summary of the scenario analyses which changed the ICER by at least £5000 per QALY gained (for full results of the company's scenario analyses see company's submission, table 90).

Table 11 Company's scenario analyses

Scenario	Inc. cost	Inc. QALY	ICER
Base case	**£50,995**	**1.19**	**£42,923**
Exponential curve fit to PFS Kaplan-Meier data	£39,630	1.19	£33,357
gp100 dataset used for BSC group	£50,854	1.52	£33,424
Korn dataset used for BSC group	£51,132	1.52	£33,681
Weibull curve fit to PFS Kaplan-Meier data	£42,374	1.19	£35,667
Vial sharing allowed	£44,205	1.19	£37,208
IPCW treatment switch adjustment method	£50,533	1.05	£47,991
Progression-based utility values from KEYNOTE-002	£50,995	1.06	£48,056
Assuming same relative rate of survival as ipilimumab using MDX010-020 data	£50,767	0.91	£55,813
10 year time horizon	£45,888	0.79	£58,086
Log-normal curve fit to PFS Kaplan-Meier data	£73,056	1.19	£61,492
Using OS HR from KEYNOTE-2 2-stage on external data using gp100 data	£49,918	0.81	£61,664
Using OS HR from KEYNOTE-2 2-stage on external data using Korn data	£49,284	0.73	£67,713
Log-logistic curve fit to PFS Kaplan-Meier data	£80,880	1.19	£68,078
Abbreviations: Inc., incremental; QALY, Quality-adjusted life year; ICER, incremental cost effectiveness ratio; OS, overall survival; HR, hazard ratio; PFS, progression-free survival Source: adapted from company's submission, table 90			

ERG exploratory analyses

5.21 The ERG did several amendments and exploratory analyses using the company's model. The ERG noted that although individual amendments had substantial effects on the ICER, the net effect when implementing all the changes was small, leading to an overall change in the ICER of less than £4000 (see Table 12). The ERG cautioned that the company and the ERG's estimates were reliant on immature survival data and affected by treatment switching, which is associated with a high degree of uncertainty. The ERG highlighted that the assumptions needed for extrapolating survival results in the model should be considered with caution.

Table 12 ERG exploratory analyses

Model scenario ERG revision	**Inc. Cost**	**Inc. QALYs**	**ICER £/QALY**	**ICER Change**
A. Company's base-case	**+ £50,995**	**+ 1.188**	**£42,923**	**-**
R1) ERG Drug costs	+ £51,109	+ 1.188	£43,019	**+ £96**
R2) ERG Admin costs	+ £51,095	+ 1.188	£43,007	**+ £84**
R3) Dacarbazine <=6 cycles	+ £51,100	+ 1.188	£43,012	**+ £89**
R4) Life Table recalculation	+ £50,995	+ 1.189	£42,898	**- £25**
R5) European utility data	+ £50,995	+ 1.110	£45,960	**+ £3037**
R6) ERG PFS estimates	+ £42,796	+ 1.188	£36,022	**- £6901**
R7) Time on treatment costs	+ £42,463	+ 1.188	£35,742	**- £7181**
R8) Remove no mortality period	+ £50,784	+ 1.023	£49,663	**+ £6740**
R9) Remove HR advantage after 10 years	+ £50,958	+ 1.136	£44,863	**+ £1940**
R10) ERG OS model	+ £50,900	+ 0.992	£51,314	**+ £8391**
R11) Temozolomide dose & costing formula errors	+ £50,961	+ 1.188	£42,895	**- £28**
R12) Apply both utility methods together	+ £50,995	+ 1.065	£47,888	**+ £4965**
B. Base-case +R1-R9, R11, R12	**+ £41,468**	**+ 0.894**	**£46,409**	**+ £3486**
C. Base-case +R1-R12	**+ £41,508**	**+ 0.890**	**£46,662**	**+ £3739**

Abbreviations: Inc., incremental, ICER, incremental cost-effectiveness ratio, Admin., administration; PFS, progression-free survival; HR, hazard ratio; OS, overall survival
Source: adapted from ERG report, table 39

Innovation

5.22 Justifications for considering pembrolizumab to be innovative:

- The company considered pembrolizumab to be a step-change in the management of advanced melanoma because it is the first PD-L1 therapy considered by NICE, it will increase the range of treatment options and is expected to provide durable response.

- The company noted that pembrolizumab was recognised as a Breakthrough Therapy Designation for advanced melanoma by the Food and Drug Administration in the US that granted its accelerated approval; and was approved under the early access to medicines scheme by the Medicines and Healthcare products Regulatory Agency in the UK. The company noted that the approval under the early access to medicines scheme recognised that pembrolizumab treats a life threatening and seriously debilitating condition, it meets a high unmet need and provides a significant advantage over other treatments used in the UK. It stated that this designation validated that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits.

6 End-of-life considerations

6.1 Table 13 summarises the end-of-life criteria in relation to pembrolizumab in unresectable or metastatic melanoma after progression with ipilimumab.

Table 13 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company noted that people with metastatic melanoma have a median survival of up to 9 months (based on data from Balch et al. [2001], Korn et al. [2008] and Thirlwell and Nathan [2008]). The company's estimate of median overall survival in the chemotherapy group in KEYNOTE-002 adjusted for treatment switching with the 2-stage method was 7.9 months. The ERG noted that the undiscounted mean life expectancy of eligible patients in the company's base case analysis was 20.9 months, and 17.2 months in the ERG's preferred scenario.

Criterion	Data available
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 company noted that pembrolizumab offers a difference in median survival of 3.5 months (based on the 2-stage treatment switching adjustment approach) and a mean extension to life of 1.59 years (projected from cost-effectiveness model) compared with BSC. The ERG noted that the undiscounted estimate of mean survival gain per patient attributable to pembrolizumab compared with BSC was 26.1 months in the company base case analysis, and 20.1 months in the ERG's preferred scenario.
The treatment is licensed or otherwise indicated for small patient populations	The company noted that the estimated number of people eligible for pembrolizumab is expected to be approximately 628 in 2015, and approximately 300 annually thereafter (based on data from Office of National Statistics, NICE costing template on vemurafenib, company's submission for NICE technology appraisal guidance on ipilimumab for previously untreated advanced melanoma, Long et al [2011] and company's internal forecasting).
Source: company's submission table 56, clarification response page 68 and ERG report page 96	

7 Equality issues

7.1 No equality issues were identified during the scoping process.

7.2 No potential equality issues have been identified in the evidence submitted.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

The European public assessment report for pembrolizumab was published on 30 July 2015 and is available from:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003820/WC500190992.pdf