STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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LIST OF ABBREVIATIONS

AE	adverse event
AEOSI	adverse event of special interest
APaT	All Patients as Treated
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BSC	best supportive care
CEAC	cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CS	company's submission
CSR	clinical study report
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
HRQoL	health-related quality of life
IA1	first interim analysis
IA2	second interim analysis
ICER	incremental cost effectiveness ratio
INV	local investigator assessment
IPCW	inverse probability censored weighting
IRO	integrated radiology and oncology analysis (independent central assessment)
ITT	intention-to-treat
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
MEK	mitogen-activated protein kinase
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein
PD-L1	programmed cell death 1 ligand
PFS	progression-free survival
PPS	post-progression survival
PSA	probabilistic sensitivity analysis
PSS	personal social services
Q2W	every 2 weeks
Q3W	every 3 weeks
QALY	quality adjusted life year
RCT	randomised controlled trial
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SAEOSI	serious adverse event of special interest
SAP	statistical analysis plan

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Merck Sharp & Dohme in support of the use of pembrolizumab (Keytruda) for the treatment of advanced (unresectable stage III or stage IV) melanoma in patients whose disease has progressed after previous treatment with ipilimumab. A European licence for pembrolizumab is expected in July 2015. It is anticipated that the licence will be for the treatment of patients with unresectable or metastatic melanoma.

1.1 Critique of the decision problem in the company's submission

The population described in the NICE scope is patients with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab. In the company's decision problem, patients with BRAF mutation-positive melanoma must also have been previously treated with a B-Raf proto-oncogene, serine/threonine kinase (BRAF) or mitogen-activated protein kinase (MEK) inhibitor; in this respect, the population referenced in the company's decision problem is a more specific population than that specified in the NICE scope.

The intervention specified in the NICE scope is pembrolizumab, an anti-programmed cell death (anti-PD-1) agent. A dose is not stipulated. However, the company's submission (CS) focuses on pembrolizumab 2mg/kg Q3W, which is the anticipated licensed dose.

Comparators listed in the NICE scope are dacarbazine, vemurafenib, dabrafenib and BSC. Dacarbazine is one of a number of investigator choice chemotherapies used in the chemotherapy arm of the KEYNOTE-002 clinical trial, which is the primary source of evidence in the CS. Chemotherapy in this trial is considered by the company (and the ERG) to be an appropriate proxy for best supportive care (BSC). Vemurafenib and dabrafenib are BRAF inhibitors and their use is recommended only for patients with BRAF mutation-positive melanoma. Patients with BRAF mutation-positive melanoma enrolled in the KEYNOTE-002 trial had been pre-treated with a BRAF (or MEK) inhibitor and, therefore, the ERG agrees with the company that the BRAF inhibitors are not appropriate comparators.

The outcomes and economic analyses addressed by the decision problem match those specified in the NICE scope. These are standard to NICE STAs in this disease area. For cost effectiveness, outcomes were assessed over a 30-year time horizon (equivalent to a

lifetime horizon) and costs were considered from an NHS perspective. There were no pre-specified subgroup analyses in either the NICE scope or company's decision problem. However, subgroup analyses were conducted in KEYNOTE-002, including subgroup analyses by programmed cell death 1 ligand (PD-L1) status (as noted, pembrolizumab is an anti-PD-1 agent and targeting PD-1 or its ligand PD-L1 is considered to be of promising therapeutic benefit). No issues relating to current clinical practice, equity or equality have been identified.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company carried out a systematic search of the literature and identified four relevant studies: three randomised controlled trials (RCTs) (KEYNOTE-002, KEYNOTE-001 [Part B2] and KEYNOTE-006) and a non-randomised study (KEYNOTE-001 [Part B1]). However, only KEYNOTE-002 compared pembrolizumab 2mg/kg Q3W with a relevant comparator.

The company considered, but did not perform, meta-analyses using data for patients refractory to ipilimumab from the KEYNOTE-002 and KEYNOTE-001 (Part B2) trials as the progression-free survival (PFS) and overall survival (OS) outcomes for both studies were too dissimilar This was attributed to heterogeneous patient populations, in particular in terms of the poorer Eastern Cooperative Oncology Group (ECOG) performance status and more severe metastases in patients in KEYNOTE-002. The company considers that patients in KEYNOTE-002 have more advanced disease and a worse prognosis than patients expected to be seen in clinical practice in England.

After 6 months follow-up in KEYNOTE-002, PFS assessed by independent, centrally assessed, integrated radiology and oncology analysis (IRO) showed a statistically significant difference between pembrolizumab 2mg/kg Q3W and chemotherapy (hazard ratio [HR]=0.57; 95% confidence interval [CI] 0.45 to 0.73, p<0.0001). This was despite little apparent difference in terms of median PFS (2.9 and 2.7 months respectively). Median PFS is skewed by the first radiological assessment occurring after 12 weeks. From week 12 onwards, the PFS rates begin to show separation, and dramatically separate thereafter. Indeed, at 6 months the PFS rate was 34.3% for pembrolizumab vs 15.6% for the chemotherapy arm. Notable differences in median PFS assessed by local investigator (INV) were, however, reported favouring pembrolizumab 2mg/kg over chemotherapy (3.7 vs 2.6 months respectively). Differences were again statistically significant (HR=0.49; 95% CI 0.38 to 0.62; p<0.0001) with wide differences in PFS rate at 6 months (38.9% vs 15.2%), similar to PFS determined by IRO.

No difference in terms of median OS was found in KEYNOTE-002 (11.4 and 11.6 months in the pembrolizumab 2mg/kg Q3W and chemotherapy arms, respectively). The lack of a difference in median OS is attributed to immature data (the KEYNOTE-002 trial is still ongoing and to date only the results of interim analyses are available) and high rates of treatment crossover. The company assessed the suitability of various methods to adjust for crossover, and selected the two-stage approach with a full list of potential covariates included in the model to be the most appropriate. Median OS for chemotherapy was estimated to be 7.9 months (95% CI 5.4 months to 9.7 months), suggesting an improvement in median OS for pembrolizumab 2mg/kg Q3W of 3.5 months; the crossover adjusted HR was 0.63 (95% CI 0.45 to 0.88; p=0.007).

Results of subgroup analyses suggest that, in comparison to chemotherapy, the efficacy of pembrolizumab 2mg/kg Q3W may be slightly greater in PD-L1 positive patients than in PD-L1 negative patients. However, the company cautions that the number of patients in the PD-L1 negative subgroup was small (n=47 in pembrolizumab 2mg/kg arm and n=37 in chemotherapy arm) and baseline BRAF status and lactate dehydrogenase levels differed across treatment arms thus potentially confounding results. Efficacy (measured by PFS as determined by IRO) was found to be consistent across all other subgroups.

In terms of adverse events (AEs) and drug-related AEs (of any Grade, Grade ≥3 and AEs leading to discontinuation of treatment), results from the KEYNOTE-002 trial show that treatment with pembrolizumab (2mg/kg Q3W or 10mg/kg Q3W) compares favourably to chemotherapy. Immune related AEs were reported by 16.3% of patients in the pembrolizumab 2mg/kg Q3W arm. These were mostly Grade ≤2 in severity and reversible with treatment discontinuation and the use of corticosteroids. In addition, health-related quality of life (HRQoL) data, as measured by the EORTC QLQ-C30 questionnaire, suggest that when treated with pembrolizumab, patients experience less of a decrease from baseline in global health status/quality of life than when treated with chemotherapy.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers. The ERG concurs with the company that it was inappropriate to carry out a meta-analysis due to important differences in the patient populations of KEYNOTE-002 and KEYNOTE-001 (Part B2). Given that patients with BRAF mutation-positive melanoma had been pre-treated with a BRAF inhibitor prior to enrolment in the KEYNOTE-002 clinical trial, the ERG considers that an indirect comparison between pembrolizumab and either of the BRAF inhibitors would be

inappropriate. The ERG also agrees that a meaningful indirect comparison of pembrolizumab to chemotherapy is not possible due to a lack of studies of reporting results for patients receiving chemotherapy who have been previously treated with ipilimumab.

During the clarification process, the ERG requested a detailed explanation as to why the 2mg/kg Q3W dose of pembrolizumab was preferred over the 10mg/kg Q3W dose for patients who had previously progressed on ipilimumab. The company provided data from the KEYNOTE-002 and KEYNOTE-001 (Part B2) clinical trials which does not suggest any difference in efficacy between the two doses of pembrolizumab. While the ERG concurs, it also notes that in both trials, the number of patients at risk of an event (PFS or OS) becomes very small in a relatively short space of time. Therefore, it is difficult to conclusively determine that the two doses are of equal efficacy.

The ERG considers KEYNOTE-002 to be a well-conducted trial. However, KEYNOTE-002 is a Phase II trial and no evidence from a Phase III in a relevant patient population is available. Furthermore, this trial is ongoing and as the data are immature they lack reliability. A final OS analysis is planned when 370 deaths have occurred; at the last interim analysis there were 245 deaths. Treatment crossover was permitted relatively early in the trial (after 12 weeks) and a high proportion of patients crossed over to either pembrolizumab 2mg/kg (26%) or pembrolizumab 10mg/kg (22%). Of the methods considered for adjusting for treatment crossover, the ERG agrees with the company that the two-stage model was the most appropriate.

Although patients may be considered to have more advanced disease in KEYNOTE-002 than KEYNOTE-001 (Part B2) or than patients currently seen in clinical practice, the ERG considers that the findings from KEYNOTE-002 can be generalised to clinical practice in England.

1.4 Summary of submitted cost effectiveness evidence

To compare the cost effectiveness of pembrolizumab 2mg/kg with chemotherapy/BSC, the company developed a de novo partitioned survival Markov model. The Markov model comprised three health states: pre-progression, post-progression and death. All patients entered the model in the pre-progression state. Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs. The model has been developed in Microsoft Excel using a 1 week cycle length and the time horizon is set at 30 years. As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years

(QALYs). The model perspective was that of the UK NHS. Survival was estimated based on KEYNOTE-002 data (data from the chemotherapy arm were used as a proxy for chemotherapy/BSC) and published sources. Utility values were calculated from data collected during KEYNOTE-002. Resource use and costs were estimated based on information from the KEYNOTE-002 trial, published sources and clinical experts.

For the comparison of pembrolizumab 2mg/kg Q3W vs chemotherapy/BSC, the company's incremental cost effectiveness ratio (ICER) per QALY gained is £42,923. The company carried out a wide range of deterministic sensitivity analyses. Three of the four most influential parameters relate to the Gompertz PFS model. The greatest variation in the ICER occurred when the scale parameter of the Gompertz model was varied, with the lower and upper parameter adjustments generating ICERs of £28,593 and £125,879 per QALY gained respectively.

The probabilistic sensitivity analysis (PSA) results show that, compared with chemotherapy/BSC, the probability of pembrolizumab 2mg/kg Q3W being cost effective at a threshold of £50,000 per QALY gained is approximately 50%. The probabilistic ICER for pembrolizumab 2mg/kg Q3W vs chemotherapy/BSC is £67,615 per QALY gained, which is £24,692 (over 57.5%) more than the corresponding deterministic ICER. The company explains that this is due to the uncertainty in the PFS estimate and that, in some of the PSA iterations, patients are in the PFS state for 20 years or more, meaning that those in the pembrolizumab 2mg/kg Q3W arm will be treated for 20 years or more. When treatment with pembrolizumab 2mg/kg Q3W is restricted to 2 years, the deterministic and probabilistic ICERs for the comparison of pembrolizumab 2mg/kg Q3W with chemotherapy/BSC are £31,764 and £33,841 per QALY gained respectively.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers.

The decision model submitted by the company is structured appropriately, and generally implemented correctly. However, the assessment of the cost effectiveness of pembrolizumab vs chemotherapy/BSC in this appraisal depends on data from a single Phase II clinical trial (KEYNOTE-002) with only 12 months follow-up which is confounded by crossover between treatments. These limited data, supported by some data from published sources, have been used as the basis for projecting survival for an additional 29 years.

Health gain

An analysis of the company's base case results show that 72% of the estimated health gain (in terms of additional survival) attributed to treatment with pembrolizumab occurs after disease progression (and after treatment with pembrolizumab has ceased), mainly in the extended projection period (years 2 to 30). This means that the method used to predict survival is extremely influential. The ERG does not support the extrapolation method employed by the company and notes the following issues:

- Progression-free survival in the pembrolizumab arm is over-estimated as the company assumes that PFS continues indefinitely due to extrapolation, whereas all patients in the chemotherapy/BSC arm are assumed to have died or progressed at 62 weeks (the time point up to which follow-up data are available).
- The company's approach to modelling OS introduces several aspects that are not clinically supportable or explained by the KEYNOTE-002 trial protocol, including a mortality rate of zero from year 6 to year 10 as well as a large, instantaneous, leap in mortality rate at year 10
- In the base case the company used out of date and questionable external data to extrapolate survival beyond the trial period of 12 months
- The company assumed that the survival benefit continued to accrue for pembrolizumab patients well beyond the treatment period, even if the treatment had been discontinued some 20 years earlier.

Costs

Nearly all (99.1%) of the overall incremental cost is attributable to differences in direct treatment costs (drug acquisition and administration). This means that only variations in the assumed NHS price of pembrolizumab can have any meaningful effect on the estimated incremental cost per patient.

Utility

In the company's base case there is no utility penalty associated with progressive disease and hence, from the perspective of generating cost effectiveness results using the company's model, early progression is advantageous as it simply results in a reduction in treatment costs. From a real life perspective this is unrealistic.

1.6 Summary of company's case for end of life criteria being met

The company considers that pembrolizumab meets the NICE end of life criteria because: (1) patients with metastatic melanoma have a median survival of up to 9 months (2) the patient population is small (approximately 628 in 2015 and approximately 300 annually thereafter) (3) results from KEYNOTE-002 show that treatment with pembrolizumab offers both a mean

and median extension to life is greater than 3 months (utilising the two-stage [all covariates] model to adjust for median OS) compared to treatment with chemotherapy/BSC.

1.7 ERG commentary on end of life criteria

The ERG considers that pembrolizumab treatment in this population meets the NICE criteria for consideration as an 'end of life' technology as: (1) The median OS for patients with unresectable metastatic melanoma is less than 24 months. In the company's base case analysis the undiscounted mean life expectancy of eligible patients is projected to be 20.9 months, and 17.2 months in the ERG's preferred scenario (2) The number of patients who would be eligible for the treatment is small (<1,000 per annum) (3) The undiscounted estimate of mean survival gain per patient attributable to treatment with pembrolizumab compared with chemotherapy/BSC is 26.1 months in the company base case analysis, and 20.1 months in the ERG's preferred scenario.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The KEYNOTE-002 trial is considered to be at low risk of bias and measures efficacy in terms of OS, AEs and HRQoL, all of which are important outcomes to clinicians and patients.

Cost effectiveness evidence

- Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs
- The decision model submitted by the company is structured appropriately, and generally implemented correctly.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- In relation to whether the two doses of pembrolizumab can be considered to be of equal efficacy, the ERG cautions that the number of patients in each arm in KEYNOTE-002 is small and the time period for which the data are available is relatively short, making it difficult to conclusively determine that the two doses are of equal efficacy
- Since KEYNOTE-002 is still ongoing and the OS data are immature, these data (both unadjusted and adjusted) should be treated with caution
- It is unclear from the subgroup analyses whether pembrolizumab is better tailored to patients who are PD-L1 positive than patients who are PD-L1 negative

- There is currently no available RCT evidence for patients with BRAF positive melanoma not previously treated with a BRAF inhibitor.

Cost effectiveness evidence

- The company's approach to modelling OS introduces several aspects that are not clinically supportable or explained by trial protocol, such as a mortality rate of zero from year 6 to year 10 and a large, instantaneous leap in mortality rate at year 10
- External data to extrapolate survival beyond the trial period of 12 months by the company is considered by the ERG to be questionable or superseded by more recent data
- A survival benefit is assumed to continue to accrue for pembrolizumab patients well beyond the treatment period, even if the treatment was discontinued some 20 years previously. The ERG considers this to be unrealistic
- Progression-free survival in the pembrolizumab arm is assumed to continue indefinitely due to extrapolation, whereas all patients in the chemotherapy/BSC arm are assumed to have died or progressed at the end of the trial data. The ERG considers this approach to overestimate the gain in PFS for patients receiving pembrolizumab 2mg/kg 3QW
- A number of other issues have been identified that relate to input values in the model, namely: estimation of dosing costs; administration cost of systemic treatments; duration of dacarbazine treatment; and duration of pembrolizumab treatment.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented 12 corrections/modifications to the company's model. Five of these related to the survival estimates employed in the model and the remainder related to drug costs, utilities and life table mortality rates. Applying all the ERG's drug cost, utility and life table amendments results in an ICER of £46,409 per QALY gained. Including all of these changes and the ERG's preferred method of projecting survival results in an ICER of £46,662 per QALY gained.

The net result of applying the full set of ERG model amendments has a limited effect on the overall assessment of cost effectiveness. However, the apparently stable estimated ICERs per QALY gained should not be taken to indicate an absence of uncertainty. The robustness of the assumptions that are required to anticipate 29 years of future survival experience should not be over-estimated, nor the scope for substantial error that can arise from post-hoc manipulation of trial data compromised by crossover.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3.1 of the company's submission (CS) presents a brief overview of the disease/condition (unresectable or metastatic melanoma) for which the technology (pembrolizumab) is being used and section 3.2 of the CS describes the effects of the disease/condition on patients, carers and society. Information about the life expectancy of people with the disease or condition in England is presented in section 3.4 of the CS. Key points from these sections of the CS are reproduced (as bulleted items) by the Evidence Review Group (ERG) in Box 1. The ERG considers that these key points appropriately summarise the underlying health problems.

Box 1 Company's overview of unresectable or metastatic melanoma

- Melanoma is a heterogeneous disease reflected by its complex pathobiology … [and] disproportionately affects a younger population than other cancers, resulting in a significant impact for patients, family and wider society
    - Approximately 27% of cases diagnosed with melanoma in the UK between 2009 and 2011 were in patients aged less than 50 years, while 24% of cases affected patients aged 75 and over
    - This compares with 11% and 36%, respectively, when considering all cancers combined (excluding non-melanoma skin cancer)[1]
- Several classifications have been developed to describe how deeply a melanoma has grown into the skin and whether it has spread to regional lymph nodes or distant (metastatic) sites at the time of initial diagnosis[2,3] … The Tumour, Node, and Metastases (TNM) staging represents the cornerstone for the management of melanoma:
    - In stage III melanoma, the melanoma has spread to the lymph nodes or lymphatic channels and it may or may not be ulcerated
    - In stage IV melanoma, the cancer has spread elsewhere in the body, with the brain, lung, liver, the distant lymph nodes and other areas of the skin being the most common places of metastasis[4]
- Given its life-threatening nature, a diagnosis of metastatic melanoma strongly impacts patients' life expectancy and … emotional impact can be long lasting and profound, with the most common reactions being anxiety, depression, vulnerability and a deterioration in patients' quality of life[5-9]
- The purpose of treatment for patients with unresectable or metastatic melanoma is to enable patients to resume everyday tasks and activities (by slowing down the progression of disease)
- Although some progress has been made in the treatment of metastatic melanoma over recent years, it still has a dismal prognosis, with a 5-year OS rate of between 20% and 34% for stage IIIc patients, and between 5% and 22% for patients with stage IV disease[10]
- At a societal level, metastatic melanoma imposes a substantial financial cost to both the health care system and the wider economy

Source: CS, sections 3.1, 3.2 and 3.4

2.2 Critique of company's overview of current service provision

Sections 3.3 to 3.6 of the CS present a brief overview of current service provision with section 2 of the CS presenting an overview of the technology (pembrolizumab) under consideration in this STA for the disease/condition (unresectable or metastatic melanoma). Pembrolizumab is not currently licensed for the treatment of patients with unresectable or metastatic melanoma in the UK. The estimated date of Marketing Authorisation is July 2015; the company received a positive opinion from the European Medicines Agency Committee for Medicinal Products (CHMP)[11] in May 2015. Pembrolizumab is expected to be indicated for the treatment of unresectable or metastatic melanoma in adults with no stipulation about whether patients must have been previously treated. This single technology appraisal (STA) is focused however on patients previously treated with ipilimumab (and a B-Raf proto-oncogene, serine/threonine kinase [BRAF] or mitogen-activated protein kinase [MEK] inhibitor if BRAF mutation-positive) and so the treatment algorithm, with the company's proposed positioning for pembrolizumab, is summarised in Figure 1. The ERG notes that MEK inhibitors are not currently recommended by the National Institute for Health and Care Excellence (NICE).

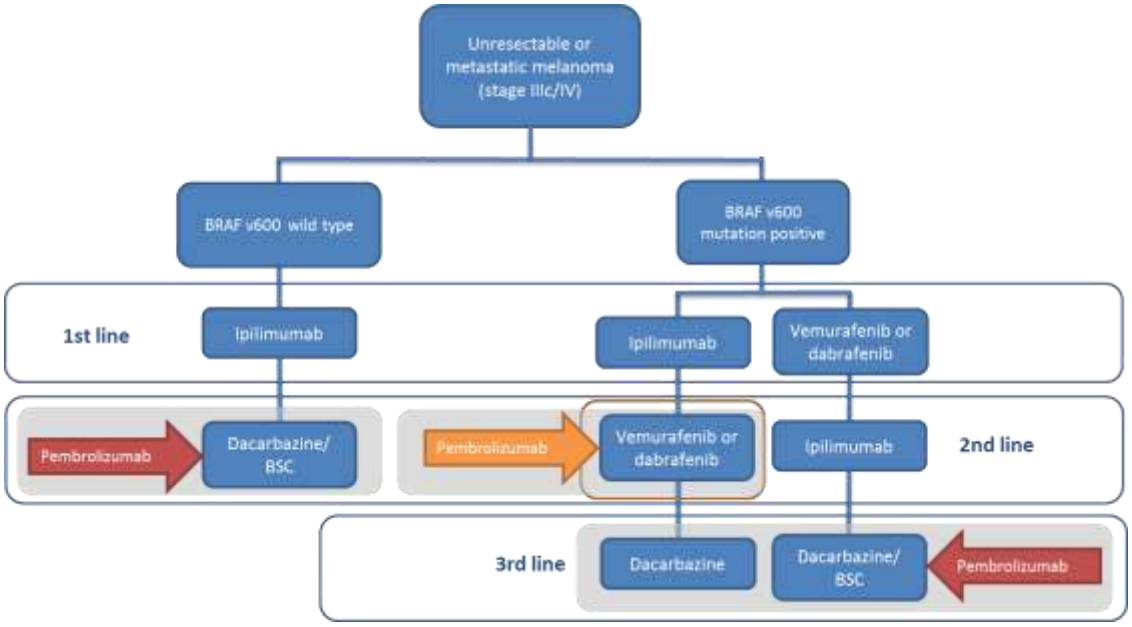

Figure 1 Treatment algorithm for unresectable or metastatic melanoma with proposed positioning for pembrolizumab presented by the company

Source: Company's response to the ERG clarification request (figure 15), modified by company from CS (figure 3)

The ERG agrees with the company (section 2.5.1 of CS) that "The treatment pathway for melanoma has evolved over the last 3 years, given the positive NICE guidance issued for ipilimumab,[12,13] vemurafenib[12] and dabrafenib".[14] The ERG also concurs that the algorithm

presented by the company does largely reflect current treatment options as recommended by current NICE guidance[12-14] and certainly for patients with negative BRAF status (BRAF wild-type) where the ERG notes that treatment options are currently more limited than for patients with BRAF mutation-positive melanoma.

Regardless of whether ipilimumab or a BRAF inhibitor (vemurafenib or dabrafenib) is used first for patients with BRAF mutation-positive melanoma, the company states that there is no evidence that the effectiveness of either agent is diminished, no matter where along the treatment pathway it is used.[15] The duration of response to BRAF inhibitors does not tend to be as long-lasting as with ipilimumab, in part due to the ability of melanoma tumours to develop resistance resulting in disease progression after 6 to 7 months of treatment.[16] However, it can take weeks or even months to build a complete immune response against a tumour with ipilimumab.[17] Hence, in terms of the choice between ipilimumab and BRAF inhibitors, BRAF inhibitors tend to be preferred if a rapid response is required and ipilimumab tends to be preferred otherwise.

Regarding other systemic therapies, the company notes that dacarbazine is approved for the treatment of advanced melanoma, although its use is declining rapidly in the UK. Today dacarbazine tends to be limited to use when immunotherapy (such as ipilimumab) or targeted therapies (such as BRAF inhibitors or pembrolizumab) are not suitable. This, the company notes, is because dacarbazine is associated with a low level of clinical activity even in treatment-naïve patients. The company cites response rates for dacarbazine (as used in the control arm of nine trials[16,18-25]) to be between 6.0% and 12.1% with a median duration of response between 6.9 months and 11.2 months. British Association of Dermatologist guidelines for the management of cutaneous melanoma produced in 2010[26] (prior to the use of ipilimumab or BRAF inhibitors) also note that no systemic therapy has been shown to extend survival significantly. These guidelines[26] recommend the use of dacarbazine as palliative chemotherapy.

Best supportive care (BSC) implies that no active systemic anti-cancer treatment is given to patients. The ERG agrees that BSC is likely to be the last line of treatment for patients.

Given pembrolizumab is expected to provide a durable response for a significant proportion of patients treated, it is described by the company as offering “a step-change in the management of patients with advanced melanoma” (section 2.5 of CS). Clinical advice received by the ERG supports the view that pembrolizumab would be a valuable additional treatment option in view of the poor prognosis for patients with unresectable or metastatic melanoma, particularly for those patients with no durable response to ipilimumab. Additional

support for the innovative nature of the drug is provided by the company in section 2.5 of the CS as follows:

- In the US, pembrolizumab was granted Breakthrough Therapy Designation for advanced melanoma by the US Food and Drug Administration (FDA) in January 2013 and granted accelerated approval in September 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF mutation-positive, a BRAF inhibitor [27]
- In the UK, pembrolizumab was the first medicine to be approved under the Medicines and Healthcare Products Regulatory Agency Early Access to Medicines Scheme (EAMS): pembrolizumab received Promising Innovative Medicines designation (EAMS Step 1) in October 2014, and in March 2015 a positive Scientific Opinion was issued (EAMS number 00025/0626)[28] for use in the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care agents (EAMS Step 2).

The company estimates that 628 patients will be eligible for treatment with pembrolizumab following treatment with ipilimumab (and a BRAF inhibitor if BRAF mutation-positive) in England in 2015 and approximately 300 annually thereafter. The ERG agrees that following previous treatment with ipilimumab (and a BRAF inhibitor if BRAF mutation-positive), the number of patients in England will be around this number.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 1 summarises the decision problem described by the company in the CS in relation to the final scope issued by NICE. Each parameter is discussed in more detail in the text following the Table (Section 3.1 to Section 3.7).

Table 1 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company's submission
Population	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 BRAF mutation-positive, a BRAF or MEK inhibitor
Intervention	Pembrolizumab	Pembrolizumab (specifically 2mg/kg in the CS)
Comparator(s)	Dacarbazine Vemurafenib* Dabrafenib* BSC	BSC (including dacarbazine)
Outcomes	The outcome measures to be considered include: • PFS • OS • ORR • AEs • HRQoL	The outcome measures to be considered include: • PFS • OS • ORR • AEs • HRQoL
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any patient access schemes for the comparator technologies should be taken into account	The cost effectiveness will be expressed in terms of an incremental cost per QALY The time horizon considered will be 30 years Costs will be considered from an NHS and PSS perspective Patient Access Scheme is proposed by the company is included in the submitted model
Subgroups to be considered	None	None
Other considerations	None	None

* For people with BRAF mutation-positive melanoma
AE=adverse event; BRAF=B-Raf proto-oncogene, serine/threonine kinase; BSC=best supportive care; CS=company's submission); MEK=mitogen-activated protein kinase; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year
Source: CS, adapted from table 1

3.1 Population

Pembrolizumab does not currently have a licence in Europe for patients with melanoma. However, in May 2015, the company received a positive opinion from the CHMP[11] and the latest draft Summary of Product Characteristics (SmPC)[29] states that pembrolizumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. It makes no reference to patients having been previously treated for melanoma. The NICE

scope does however specify that patients must have been previously treated with ipilimumab. Similar to the NICE scope, the patient population referenced in the company's decision problem must have been treated with ipilimumab. Furthermore, in the company's decision problem, patients with BRAF mutation-positive melanoma must also have been previously treated with a BRAF or mitogen-activated protein kinase (MEK) inhibitor. The ERG notes that MEK inhibitors are not currently recommended for treatment in England and so the vast majority of patients with BRAF mutation-positive melanoma currently receive BRAF inhibitors (vemurafenib or dabrafenib). Therefore, in this respect, the population referenced in the company's decision problem is a more specific population than that specified in the NICE scope (which makes no reference to previous treatment with a BRAF or MEK inhibitor). However, clinical practice in England does appear to be changing with regard to the use of BRAF inhibitors (see Section 2.2). Currently, however, the majority of patients with BRAF mutation-positive melanoma who are expected to be treated with pembrolizumab will also have received a BRAF inhibitor.

The majority of clinical evidence cited in the CS is derived from the KEYNOTE-002 randomised controlled trial (RCT).[30] In this trial, patients were refractory to ipilimumab, i.e. all patients had started treatment with ipilimumab and then progressed before completing treatment or had progressed within 24 weeks of receiving the last dose of ipilimumab. The ERG is aware that some patients seen in clinical practice complete treatment and are progression-free for longer than 24 weeks. Results from the MDX010-020[31] trial demonstrate that patients treated with ipilimumab alone had a response rate of 13.8%. Therefore the majority of patients treated with ipilimumab in clinical practice are likely to be refractory to ipilimumab and so the clinical evidence presented is consistent with the population specified in the NICE scope and referenced in the company's decision problem. It is therefore also likely to be generalisable to the patient population seen in clinical practice in England.

A summary of the different patient populations specified by the anticipated licence, NICE scope, decision problem and addressed in KEYNOTE-002 is provided in Table 2.

Table 2 Patient populations addressed by the company's submission

Population for whom pembrolizumab is expected to be licensed	Population in final scope issued by NICE*	Population specified in the company's decision problem	Population addressed by the KEYNOTE-002 trial†
Adults with advanced (unresectable or metastatic) melanoma	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 BRAF mutation-positive, a BRAF or MEK inhibitor¥	Patients with unresectable stage III or metastatic melanoma refractory to ipilimumab; patients with BRAF mutation-positive melanoma must also have been previously treated with a BRAF or MEK inhibitor¥

BRAF= B-Raf proto-oncogene, serine/threonine kinase; MEK=mitogen-activated protein kinase
* A separate STA is currently being conducted for patients treated with pembrolizumab who are ipilimumab naïve
† A supportive, non-random study, KEYNOTE-002 (Part B1)[32] includes both patients who were previously treated with ipilimumab (not necessarily refractory) and who were ipilimumab naïve
¥ The ERG notes that MEK inhibitors are not currently recommended for the treatment of patients with advanced melanoma in England; however, the majority of patients with BRAF mutation-positive melanoma in the KEYNOTE-002 trial were pre-treated with a BRAF inhibitor

3.2 Intervention

The intervention specified in the CS and in the company's decision problem statement is pembrolizumab, an anti-programmed cell death (anti-PD-1) agent, which is administered intravenously. However, it is clear from the CS that different doses of pembrolizumab have been used in previous clinical studies.[32-34] Specifically, the dose that is expected to be licensed is 2mg/kg every 3 weeks (Q3W) and the company therefore focuses its evidence on pembrolizumab 2mg/kg Q3W. The rationale for this dose is explored and critiqued by the ERG in Section 4.4.1. However, the company presented some evidence for the 10mg/kg dose of pembrolizumab (Q2W or Q3W) mostly in the appendices of the CS; where appropriate these data are included in the ERG report.

3.3 Comparators

Comparators specified in the NICE scope are dacarbazine, vemurafenib, dabrafenib (both BRAF inhibitors) and BSC. Only BSC (including dacarbazine) was considered to be a relevant comparator by the company in its statement of the decision problem. Investigator choice chemotherapy was a comparator in the KEYNOTE-002 trial where chemotherapy options included intravenous paclitaxel plus carboplatin, carboplatin alone, paclitaxel alone, dacarbazine or oral temozolomide. Chemotherapy in this trial is considered by the company to be a proxy for BSC based on previous evidence[35,36] of no benefit for chemotherapy over BSC and because dacarbazine is mostly used in a palliative setting.[37] It is noted by the ERG that in one of the trials[35] cited by the company, a statistically significant benefit in overall survival (OS) was found for chemotherapy compared with BSC. However the authors attributed this to differences in baseline characteristics in the two trial arms. Therefore the

ERG agrees with the company that as there is no consistent evidence showing that use of palliative chemotherapy is associated with an increase in OS, BSC and dacarbazine can be considered to be effectively equivalent comparators.

According to NICE guidance,[14,38] vemurafenib and dabrafenib should only be considered for patients with BRAF mutation-positive melanoma; the company did not identify any trials comparing pembrolizumab to these BRAF inhibitors. As the KEYNOTE-002 trial required all enrolled patients who were BRAF mutation-positive to have received prior treatment with a BRAF (or MEK) inhibitor (the majority of whom received a BRAF inhibitor; from the clinical study report [CSR][39] the ERG notes that [redacted] had received vemurafenib]), it would not have been possible to use evidence from this trial in an indirect comparison with vemurafenib or dabrafenib. Therefore the ERG agrees that it is not meaningful to compare pembrolizumab with either vemurafenib or dabrafenib.

3.4 Outcomes

Clinical evidence is reported in the CS for all five outcomes specified in the scope: OS, progression-free survival (PFS), tumour response rate (reported as overall response rate [ORR] and disease control rate), adverse events (AEs) of treatment and health-related quality of life (HRQoL). However, it is noted that the OS data presented for KEYNOTE-002 are immature as the specified number of events required for the final analysis have not yet occurred. The company states that the final OS analysis is expected to be available at the end of 2015. It is also noted that because patients were allowed to cross over from the comparator arm to pembrolizumab on disease progression in the KEYNOTE-002 trial, the company also conducted OS analyses adjusting for crossover using different methods. The ERG considers that a lack of mature OS data combined with high rates of treatment crossover increases the difficulty of analysing and interpreting OS data.

3.5 Economic analysis

As specified in the final NICE scope, the cost effectiveness of treatments was expressed in terms of the incremental cost per QALY gained. Outcomes were assessed over a 30-year time horizon (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

No subgroups were specified in the final NICE scope. However, as noted in Section 3.1, evidence from the KEYNOTE-002 trial was only available for patients refractory to ipilimumab and, if BRAF mutation-positive, previously treated with a BRAF or MEK inhibitor.

Although not specified as a subgroup in its decision problem, the company also performed subgroup analyses for the biomarker positive subgroup defined by programmed cell death 1 ligand (PD-L1) expression level for the outcomes OS, PFS and ORR in KEYNOTE-002. Subgroup analyses of PFS were also performed based on clinically relevant baseline patient or tumour characteristics. The following factors were included for analysis: sex (female vs male); age category (≤65 vs >65 years); race (white vs non-white); region (US vs ex-US); Eastern Cooperative Oncology Group (ECOG) status (0 vs 1); baseline lactate dehydrogenase (LDH) level (normal vs elevated); BRAF mutation status (mutant vs wild type); baseline tumour size measured by independent review committee (< median in overall population vs ≥ median in overall population); investigator's choice of chemotherapy recorded via interactive voice response system prior to randomisation (types with >10% patients in the chemotherapy arm).

3.7 Other considerations

As noted in section 3.8 of the CS, the company is not aware of any issues relating to current clinical practice or any equity or equality issues.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS adequately describes the search strategies used to identify relevant studies relating to the use of pembrolizumab for metastatic melanoma, the searches were not specific to treatment after ipilimumab or ipilimumab naïve melanoma. The company conducted two systematic searches for the clinical evidence: (1) a search for direct evidence and (2) a search for indirect evidence and adverse reactions. Full details of the strategies used to derive clinical evidence were reported in section 4.1 and appendices 2, 8 and 12 of the CS. The ERG's brief description and critique of the searches is reported in Appendix 1 of this report. In summary, the ERG concluded that searching was carried out to an adequate standard and accurately reflected the population and indication. The ERG is confident that the company did not miss any relevant references.

4.1.2 Eligibility criteria

Appropriately, the citations identified were independently assessed for inclusion through two stages by two reviewers using the criteria shown in Table 3. First, the reviewers independently scanned all abstracts and proceedings. Second, full text articles were then obtained and the same two reviewers independently reviewed these. Disagreements about whether to include a study or not were resolved by reaching consensus with the help of a third reviewer.

Table 3 Eligibility criteria used for company's systematic review

Parameter	Included	Excluded
Population	Patients with unresectable stage III or IV melanoma previously treated with ipilimumab	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Interventions	Pembrolizumab	Any other intervention
Comparators	Dacarbazine BSC*	Any other comparison
Outcomes	At least one of the following outcomes: ORR, PFS, OS	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	RCTs	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language	English	Any other language

*This intervention may be assessed in either ipilimumab-naïve or ipilimumab experienced populations
BSC=best supportive care; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial
Source: CS, table 6

4.1.3 Risk of bias

A descriptive critical appraisal of KEYNOTE-002 and KEYNOTE-001 (Part B2)[33] was conducted by the company. The company conducted the assessment using the criteria recommended by NICE for company's submissions.[40]

4.1.4 Evidence synthesis

Since only one study (KEYNOTE-002) directly compared pembrolizumab with an appropriate comparator (chemotherapy), findings were appropriately presented in a narrative. No indirect treatment comparison or mixed treatment comparison was carried out to compare pembrolizumab to other specified comparators by the company. Given patients with BRAF mutation-positive melanoma had already been pre-treated with BRAF inhibitors in the KEYNOTE-002 trial, both the company and the ERG considered that an indirect comparison of pembrolizumab with BRAF inhibitors would be inappropriate.

Since, the company's literature search did not identify any studies comparing pembrolizumab to BSC, an indirect comparison of pembrolizumab to BSC may have been considered appropriate. However, the company's literature search did not identify any studies comparing chemotherapy to BSC in patients previously treated with ipilimumab. Therefore, the company stated it was not possible to conduct an indirect comparison in order to obtain an estimate of the efficacy of pembrolizumab relative to BSC in this patient population. The ERG concurs with the company.

The company did consider conducting a meta-analysis comparing pembrolizumab 2kg/mg Q3W with pembrolizumab 10mg/kg Q3W. However from examining the PFS and OS outcomes in the two relevant trials (KEYNOTE-002 and KEYNOTE-001 [Part B2]), the company concluded that the two trials were heterogeneous; the company attributed this heterogeneity to differences in the patient characteristics across the two trials (see Section 4.2). Had it been possible to conduct such a meta-analysis, the results may have been informative in order to support the decision to focus on the 2mg/kg Q3W dose of pembrolizumab. However, the ERG agrees with the company that a meta-analysis was inappropriate due to the patient populations being too dissimilar.

4.2 Identified studies

Four studies were identified by the company: three RCTs (KEYNOTE-002, supportive KEYNOTE-001 [Part B2] and KEYNOTE-006[34]) and the non-random KEYNOTE-001 (Part B1) study.[32] The company states: "The second interim-analysis (IA2) of KEYNOTE-002 … provides the main evidence base for this submission" (section 1.3 of CS). The ERG agrees that this is the only study that is directly relevant to the decision problem. The ERG provides an assessment of each study's relevance to the decision problem in Table 4.

Table 4 Identified studies and relevance to the decision problem

Study	ERG's assessment of relevance to company's decision problem
KEYNOTE-002, n=540	Of primary relevance: This was the only trial that compared pembrolizumab 2mg/kg Q3W with a comparator of interest (chemotherapy) in patients refractory to ipilimumab (and also a BRAF or MEK inhibitor if the patient had BRAF mutation-positive melanoma); includes 180 patients who received pembrolizumab 2mg/kg Q3W and 179 patients who received chemotherapy; 181 patients received pembrolizumab 10mg/kg Q3W
KEYNOTE-001 (Part B2), n=173	Supportive efficacy and safety evidence for different doses of pembrolizumab in patients refractory to ipilimumab (and also a BRAF or MEK inhibitor if the patient had BRAF mutation-positive melanoma); includes 89 patients who received pembrolizumab 2mg/kg Q3W; 84 patients received pembrolizumab 10mg/kg Q3W This is the only supportive study presenting evidence from a random sample of the patient population relevant to the NICE scope and company's decision problem
KEYNOTE-002 (Part B1), n=135	Supportive safety and efficacy evidence for different doses of pembrolizumab in patients previously treated with ipilimumab and patients who were ipilimumab naïve; none of the 22 patients who received pembrolizumab 2mg/kg Q3W had been previously treated with ipilimumab; 56 patients received pembrolizumab10mg/kg Q2W (16 of whom had received prior ipilimumab) and 56 patients received pembrolizumab 10mg/kg Q3W (32 of whom had received prior ipilimumab)
KEYNOTE-006, n=831	Supportive efficacy and safety evidence for pembrolizumab compared to ipilimumab in an ipilimumab naïve patient population and used to support some assumptions made to derive evidence for cost effectiveness; no patient received pembrolizumab 2mg/kg Q3W; 279 patients received pembrolizumab 10mg/kg Q2W, 277 patients received pembrolizumab 10mg/kg Q3W and 278 patients received ipilimumab

In summary, the ERG considers the primary contribution to the evidence base of each of the identified studies is as follows:

- KEYNOTE-002 is of primary relevance to the decision problem, being the only study that presents evidence for pembrolizumab 2mg/kg Q3W compared with chemotherapy in a relevant patient population
- KEYNOTE-001 (Part B2) provides evidence for the relative effectiveness of pembrolizumab 2mg/kg Q3W with pembrolizumab 10mg/kg Q3W in a relevant patient population
- KEYNOTE-001 (Part B1) provides some evidence from a non-randomised population of patients treated with pembrolizumab 10mg/kg Q3W; however none of the evidence for pembrolizumab 2mg/kg Q3W is relevant since all these patients were ipilimumab naïve
- KEYNOTE-006 presents evidence only for ipilimumab naïve patients treated with pembrolizumab 10mg/kg Q3W (and Q2W) and is therefore largely irrelevant to the company's decision problem.

Table 5 Baseline characteristics of patients in KEYNOTE-002 and KEYNOTE-001 (Part B2)

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%
No. of lines of previous therapies							
0	<1%[c]	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%

APaT=all patients as treated; BRAF=B-Raf proto-oncogene, serine/threonine kinase; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; ITT=intention-to-treat; ULN=upper limit of normal

*For KEYNOTE-002, the ERG notes that data for M-stage differ between table 15 and table 39 of the CS. The ERG presents data from table 15 of the CS for this characteristic, which correspond with the data presented in table 10-9 of the CSR for KEYNOTE-002

† For KEYNOTE-001 (Part B2), the characteristics of age, BRAF status, LDH level and M-stage differ between table 16 and table 39 of the CS. The ERG presents data presented in these tables which also correspond with those presented in table 10-21 of the CSR for KEYNOTE-001 (Part B2)

Source: CS, adapted from tables 15, 16 and 39

4.3 Critique of trials of interest including trial methodology and quality

Given that only KEYNOTE-002 is considered by the ERG to be directly relevant to the decision problem, only a description and critique of this trial is presented. Information on the trial characteristics of the supportive trials that include patients previously treated with ipilimumab (i.e. KEYNOTE-001 [Parts B1 and B2] but not KEYNOTE-006) are presented in Appendix 2 of this report.

4.3.1 Trial characteristics

The key characteristics of the KEYNOTE-002 trial are summarised in Table 6. KEYNOTE-002 was conducted internationally and randomised 540 patients in a 1:1:1 ratio to pembrolizumab 2mg/kg Q3W or pembrolizumab 10mg/kg Q3W or to investigator choice chemotherapy. Randomisation was stratified by ECOG performance status (0 vs 1), LDH levels (normal vs elevated) and BRAF mutational status. The ERG is of the opinion that the KEYNOTE-002 trial was well-designed and conducted. However a number of caveats must be considered:

- The ERG notes that patients in KEYNOTE-002 were refractory to ipilimumab, whereas the patient population specified in the decision problem (and NICE scope) is, less specifically, patients pre-treated with ipilimumab; however as noted in Section 3.1, the majority of patients treated with ipilimumab in clinical practice are also likely to be refractory to ipilimumab. While none of the participating treatment centres were located in the UK, the ERG does however believe the study population is likely to be generalisable to patients refractory to ipilimumab in the UK
- The ERG further notes that KEYNOTE-002 is a Phase II trial and not a Phase III trial, evidence from Phase III trials is usually submitted when obtaining a marketing authorisation. To date, the only evidence available for pembrolizumab from a Phase III trial is for patients who are ipilimumab naïve (KEYNOTE-006)
- It should also be recognised that KEYNOTE-002 is still ongoing. To date, there have only been two interim analyses (see also Section 4.3, Table 7). It is stated in the CS that the company anticipates that data from the final analysis will be available by the end of 2015 when 370 deaths will have occurred.

Table 6 Trial characteristics of KEYNOTE-002

Characteristics of KEYNOTE-002	
Location	Global study conducted in 12 countries (Argentina, Australia, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and United States)
Design	Phase II, multi-centre, randomised controlled trial
Population	Histologically or cytologically confirmed diagnosis of unresectable stage III or metastatic melanoma not amenable to local therapy Participants must be refractory to ipilimumab Participants with BRAF gene mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF gene and/or MEK protein inhibitor
Intervention and comparator	Pembrolizumab 2mg/kg Q3W (n=180) Pembrolizumab 10mg/kg Q3W (n=181) Investigator choice chemotherapy (carboplatin + paclitaxel, carboplatin alone, paclitaxel alone, dacarbazine, or temozolomide) (n=179)
Primary outcomes	PFS OS
Secondary outcomes	ORR Response duration OS, PFS, and ORR in the biomarker positive subgroup defined by PD-L1 expression level (cut-off point to be estimated from external data) receiving either pembrolizumab or chemotherapy Safety, tolerability and AE profile of single agent pembrolizumab 2mg/kg Q3W and 10mg/kg Q3W; the pharmacokinetics profile of single agent pembrolizumab at 2mg/kg Q3W and 10mg/kg Q3W
Duration of study	The study is ongoing. The study commenced in October 2012, and completed enrolment in November 2013. The data-cut-off date for IA2 was May 12, 2014 based on the trigger event of 210 deaths. The final analysis will be performed after 370 deaths have occurred; [redacted]

AE=adverse event; BRAF=B-Raf proto-oncogene, serine/threonine kinase; IA2=second interim analysis; MEK=mitogen-activated protein kinase; OS=overall survival; ORR=overall response rate; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival
Source: CS, adapted from table 9 and CSR, section 11.1

4.3.2 Participant characteristics

Participant characteristics for KEYNOTE-002 have been previously summarised in Section 4.2, Table 5. In KEYNOTE-002, the company comments that patient characteristics are generally balanced between the three arms of the KEYNOTE-002 trial; the ERG agrees with this assessment.

However, the company states in section 5.11.3 of the CS that the population in the KEYNOTE-002 trial has more advanced disease and a worse prognosis than patients expected to be seen in clinical practice in England. In section 4.13.2 of the CS, the company states two main reasons for this:

- Patients in the trial had previously received more lines of treatment, in particular prior chemotherapy which the company anticipates would now be preferred as a treatment option after pembrolizumab; 48% of all patients had received prior chemotherapy
- In the trial, disease progression had to have occurred within 24 weeks of their last of 2 doses of ipilimumab.

The ERG concurs with the company that patients in KEYNOTE-002 appear to have relatively advanced disease for the following two reasons:

- All patients were refractory to ipilimumab and nearly three-quarters (73%) of all patients had received at least two previous lines of therapy
- A high proportion (83%) of patients had visceral metastases (stage M1c).

The ERG believes it is however uncertain whether this information necessarily translates into a patient population with a worse prognosis than would be seen in clinical practice. Conversely, it could be argued that patients included in KEYNOTE-002 may have a better prognosis than patients who are routinely seen in clinical practice. Patients in the trial must have been considered fit enough (ECOG performance status 0 to 1) for further immunotherapy with pembrolizumab following treatment with ipilimumab; currently patients progressing after ipilimumab often only receive BSC (i.e. no chemotherapy) due to rapidly escalating symptoms.

4.3.3 Statistical approach adopted

Given that only KEYNOTE-002 is considered by the ERG to be directly relevant to the decision problem, only a description and critique of this trial is presented in this Section. Additional information for KEYNOTE-001 (Part B2) RCT and for the KEYNOTE-001 (Part B1) non-randomised study is presented in Appendix 2. Information relevant to the statistical approach taken by the company to analyse data from KEYNOTE-002 is taken from the CSR (including the statistical analysis plan [SAP]), the trial protocol, and the CS.

Trial population

For the analysis of the primary outcomes, PFS and OS, the intention-to-treat (ITT) population was used. All patients were analysed according to the treatment arm to which they were initially randomised, regardless of which treatment they actually received. Analyses of the secondary outcomes were performed using the full analysis set (FAS), consisting of all randomised patients with measurable disease at baseline based on independent central review. During the clarification process, the company explained that following regulatory agency feedback, the protocol was amended and an analysis of ORR using the ITT population was also performed.

Outline of analyses

An outline of the planned analyses and their purpose is provided in Table 7. The company states that KEYNOTE-002 is ongoing but is no longer recruiting patients. Recruitment continued throughout the interim analyses.

Table 7 KEYNOTE-002: Summary of interim analysis strategy

Interim analysis number	Key endpoints for interim analysis	Anticipated approximate timing of interim analysis (from study start)	Sample size included for the analysis (three arms)	Purpose of analysis
Interim analysis 1 (IA1)	ORR	10 months	120	Discontinue one inferior pembrolizumab arm
Interim analysis 2 (IA2)	PFS/OS	15 months	510	Demonstrate superiority of pembrolizumab in PFS Stop for futility based on OS
Final analysis	OS	24 months	510	Demonstrate superiority of pembrolizumab in OS

ORR=overall response rate; OS=overall survival; PFS=progression-free survival
Source: CS, table 10

Efficacy outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes of the KEYNOTE-002 study are listed in Table 8.

Table 8 Analysis strategy for key efficacy endpoints

Endpoint	Definition	Statistical method
Primary outcomes		
PFS	Defined as time from randomisation to the first documented disease progression (based on assessment from a central imaging vendor using RECIST 1.1) or death due to any cause, whichever occurred first	Stratified Log-rank test Cox model with Efrons's tie handling method for estimation was used to assess the treatment difference in PFS (i.e., hazard ratio and its 95%CI) K-M method for PFS curve estimation in each treatment arm
OS	Defined as the time from randomisation to death due to any cause	Stratified Log-rank test Cox model with Efrons's tie handling method for estimation. K-M method for OS curve estimation in each treatment arm
Secondary outcomes		
ORR	Defined as the proportion of the patients in the analysis population who had either a CR or PR. Responses were based on confirmed assessments from a central imaging vendor using RECIST 1.1.74	Stratified Miettinen & Nurminen method
Response duration	For patients who demonstrated confirmed CR or PR, response duration was defined as the time from first documented evidence of CR or PR until disease progression or death	Summary statistics using K-M method

CR=complete response; K-M=Kaplan-Meier; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; CI=confidence interval
Source: CS, adapted from table 11

The stratified Log-rank test and stratified Cox model used randomisation stratification factors: ECOG performance status (0 vs 1), LDH levels (normal vs elevated) and BRAF mutational status.

The company explains that as progressive disease (PD) could occur at any point between assessments, the date of PD was approximated as the date of the first assessment at which PD was observed, regardless of study drug discontinuation.

The ERG is satisfied that all outcomes were pre-specified in the trial SAP and that all outcomes were fully reported in the CSR.

Censoring methods

For the primary analysis, patients without documented death at the time of the final analysis were censored at the date of the last follow-up. Response duration for patients who had not progressed or died at the time of analysis was censored at the date of their last tumour assessment.

Two sensitivity analyses were performed in order to investigate the robustness of the PFS endpoint, using alternative censoring rules. The company provides a summary of the censoring rules for primary and sensitivity analyses, as shown in Table 9.

Table 9 Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary analysis	Sensitivity analysis 1	Sensitivity analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥2 missed disease assessment	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 missed disease assessment	Progressed at date of documented PD or death

PD=progressive disease
Source: CS, table 13

A supportive analysis for OS that censored patients at crossover was also performed.

Subgroup analyses

The company performed subgroup analyses for the biomarker positive subgroup defined by PD-L1 expression level for the outcomes OS, PFS and ORR. The cut-off point for PD-L1 expression was predetermined using data from KEYNOTE-001 patients. Subgroup analyses were also performed for a range of baseline and tumour characteristics for PFS (see Table 10 for a list of performed subgroup analyses).

Crossover adjustment methods

Patients in the chemotherapy arm were allowed to crossover to pembrolizumab 2mg/kg Q3W or 10mg/kg Q3W after 12 weeks and once the progressive disease was confirmed by independent central assessment by the integrated radiology and oncology analysis (IRO). It was pre-specified that rank-preserving structural failure time (RPSFT) methods would be

used to adjust estimates of OS for crossover. The company explains that trial based information was required to assess the clinical validity of the crossover adjustment method and that these assessments should be made *a posteriori.* Following on from the recent crossover adjustment guidelines issued by the NICE Decision Support Unit (DSU),[41] the company decided that additional crossover adjustments, namely inverse probability censored weighting (IPCW) and two-stage methods, would also be used to estimate OS in the chemotherapy arm. A detailed discussion of the company's approach to crossover adjustment is provided in Section 4.4.4.

ERG assessment of statistical approach

A summary of the checks made by the ERG in relation to the statistical approach adopted in the KEYNOTE-002 trial is provided in Table 10.

Table 10 ERG assessment of statistical approach used to analyse KEYNOTE-002 trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (section 4.4.1)	The ERG is satisfied that the methods used to calculate the sample size are correct; however the ERG has not been able to reproduce the sample size calculation due to lack of information
Protocol amendments	Provided in the CSR (section 9.7.1)	The ERG notes that the changes detailed in the protocol amendments were unlikely to have been driven by the results of the trial and are therefore not a cause for concern
Missing data approach	The company reports that a model-based approach was used to handle missing data for both OS and PFS. For ORR, patients with missing data were considered to be non-responders; for response duration, non-responders were excluded from analyses	The ERG is satisfied that the company took a suitable approach to handling missing data
Subgroup analyses for the primary outcome	Pre-specified subgroup analyses in the CS: • Age category (≤65 vs >65 years) • Sex (female, male) • Race (white, non-white) • ECOG status (0 vs 1) • Baseline LDH level (normal vs elevated LDH) • BRAF mutation status • Region (US, Ex-US) • Chemotherapy (types with greater than 10% patients in the chemotherapy arm) • PD-L1 expression (high vs low) (depending on assay availability) • Initial response to ipilimumab (complete or partial response, stable disease for at least three months vs progressive disease in three months) A post-hoc subgroup analysis of baseline tumour size was performed, as KEYNOTE-001 indicated that baseline tumour size was an important predictive factor for efficacy	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR
Sensitivity analyses for the primary outcome	Pre-specified sensitivity analyses in the SAP: • PFS based on investigator assessment • PFS using two different sets of censoring rules • OS where patients were censored at crossover Post-hoc analyses of OS using different crossover adjustment methods were also performed	The ERG is satisfied that the results of all sensitivity analyses are provided in the CSR

BRAF=B-Raf proto-oncogene, serine/threonine kinase; CS=company's submission; CSR=clinical study report; ECOG=Eastern Cooperative Oncology Group; ERG=Evidence Review Group; LDH=lactate dehydrogenase; ORR=overall response rate; OS=overall survival; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival; SAP=statistical analysis plan; US=United States

Risk of bias

The risk of bias assessment for KEYNOTE-002 is presented in Table 11 and that for KEYNOTE-001 (Part B2) in Table 41 of Appendix 2. The ERG is satisfied with the assessments presented in the CS, and is therefore of the opinion that KEYNOTE-002 has an overall low risk of bias.

Table 11 Assessment of risk of bias for KEYNOTE-002

Risk of bias criteria	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Source: CS, adapted from table 17

4.4 Critique of trial results and interpretation

Given that only KEYNOTE-002 is considered by the ERG to be directly relevant to the decision problem, in the remainder of this Section, only a description and critique of this trial is presented except where the findings from the other trials are considered by the ERG to be of relevance for interpreting the evidence. A brief summary of evidence and interpretation for the KEYNOTE-001 (Part B2) RCT and KEYNOTE-001 (Part B1) non-randomised study is presented in Appendix 2.

Only evidence for PFS and OS for KEYNOTE-002 are reported in this Section since these findings are the efficacy findings of most importance for estimating the cost effectiveness of pembrolizumab. A summary of the evidence for ORR in KEYNOTE-002 is however presented by the ERG in Appendix 3.

The company only presented results for the pembrolizumab 2mg/kg Q3W and chemotherapy arms from KEYNOTE-002 in the main body of the CS; findings for the 10mg/kg Q3W arm were however provided in its appendices (appendix 6 of the CS). For completeness, the ERG has included data in tables for 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab and, where available (from the CSR), for the two doses combined. However, following the company's rationale for using 2mg/kg Q3W (Section 4.4.1), the ERG has only commented on the pembrolizumab 2mg/kg Q3W dose in the text.

4.4.1 Rationale for pembrolizumab 2mg/kg dose

Compared to chemotherapy, KEYNOTE-002 considers the efficacy of two doses of pembrolizumab: 2mg/kg Q3W and 10mg/kg Q3W. As the anticipated licensed dose of pembrolizumab is 2mg/kg Q3W, the company focussed primarily on the efficacy results for pembrolizumab 2mg/kg Q3W compared with chemotherapy from KEYNOTE-002 in the CS. However, during the clarification process, the ERG requested more context as to why the 2mg/kg Q3W dose was preferred over the 10mg/kg Q3W dose. In response, the company stated:

- The positive CHMP opinion indicates that pembrolizumab 2mg/kg will be the licensed dose
- In the CS, no clinically or statistically significant difference in efficacy or safety were observed between the two pembrolizumab Q3W doses (2mg/kg and 10mg/kg)
- The latest draft version of the European SmPC recommends that pembrolizumab 2mg/kg is "administered intravenously over 30 minutes every 3 weeks" (page 63 of company's response to ERG clarification letter).

An additional summary of evidence was also presented in the clarification response utilising evidence from KEYNOTE-002 and KEYNOTE-001 (Part B2) only. The data for KEYNOTE-002 had been previously presented in appendix 6 of the CS. However, the company now also provided findings from a more recent data-cut for KEYNOTE-001 (Part B2). The results of the company's data analyses show no statistically significant or clinically meaningful differences in efficacy between the two doses of pembrolizumab. In KEYNOTE-002, for independent, centrally assessed PFS by IRO, the company demonstrates overlapping Kaplan-Meier (K-M) curves when comparing pembrolizumab doses (hazard ratio [HR]=0.91; 95% confidence intervals [CI] 0.71 to 1.16; p=0.43898). For OS data, the company suggests that all data should be interpreted with caution because the data are immature. The results of KEYNOTE-001 (Part B2) also suggest equal efficacy for pembrolizumab doses in relation to PFS (HR=0.84; 95% CI 0.57 to 1.23) and OS (HR=1.09; 95% CI 0.68 to 1.75). Thus the company argues in its clarification response that the evidence "strongly support the regulators agreement that the 2mg/kg Q3W dose is the appropriate one."

The ERG notes that in both trials, the number of patients at risk of an event (PFS or OS) becomes very small in a relatively short space of time. For example, Figure 2 shows the K-M curves for PFS in KEYNOTE-002. In the 2mg/kg and 10mg/kg Q3W arms the numbers of patients at risk (i.e. patients who have not progressed or been censored) are 180 and 181 respectively at the start of the trial. The ERG notes that, after only 3 months, the numbers have halved in both arms and by 12 months, only four and five patients respectively are at

risk. This results in wide confidence intervals around the PFS rate at each point in time (3, 6, 9 and 12 months) in each of the pembrolizumab arms, which overlap as shown in Table 12. Although the data are not presented in this ERG report, a similar pattern is observed for PFS in KEYNOTE-001 Part B2.

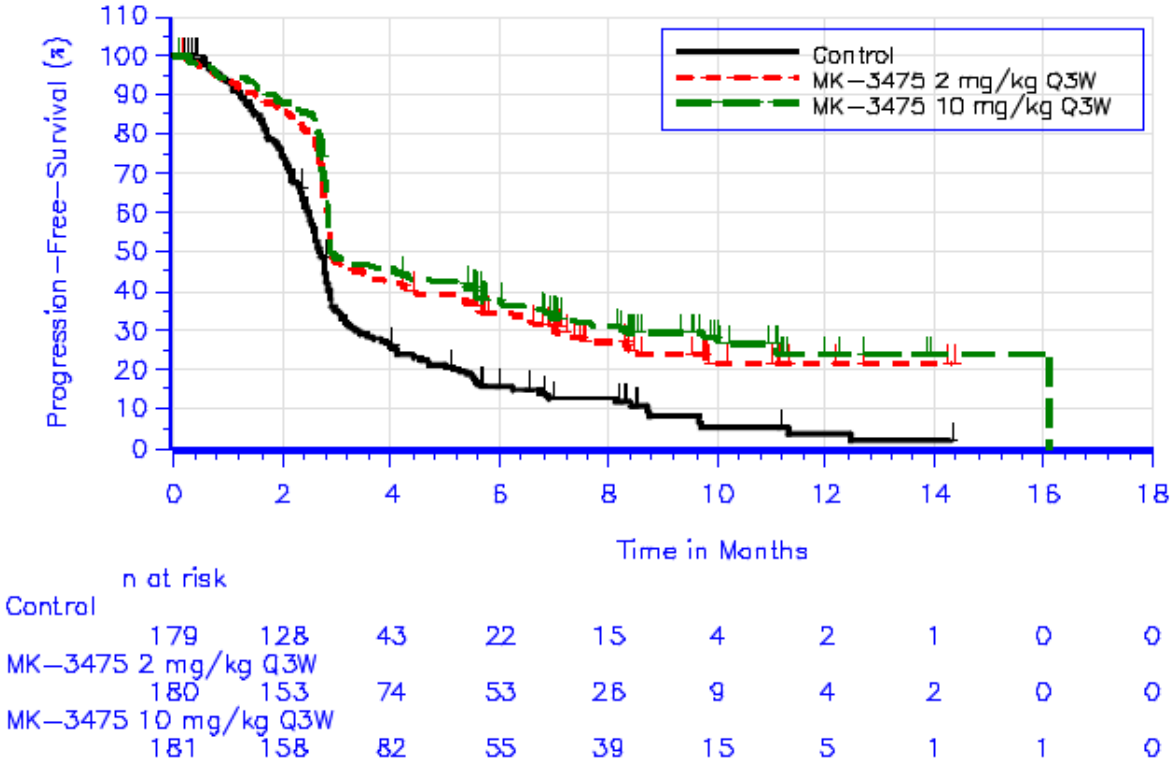

Figure 2 Kaplan-Meier curve for progression-free survival based on central assessment (IRO) in KEYNOTE-002

Source: Figure 1 in appendix 6 of the CS (reproduced as figure 16 of company's response to ERG clarification letter)

Table 12 Progression-free survival rate at fixed time-points based on central assessment (IRO) in the two pembrolizumab arms in KEYNOTE-002

Pembrolizumab dose	PFS rate at month 3 in %† (95% CI)	PFS rate at month 6 in %† (95% CI)	PFS rate at month 9 in %† (95% CI)	PFS rate at month 12 in %† (95% CI)
2mg/kg Q3W	47.5 (40.0 to 54.7)	34.3 (27.4 to 41.3)	23.7 (17.0 to 31.1)	21.6 (14.5 to 29.6)
10mg/kg Q3W	48.7 (41.2 to 55.8)	37.7 (30.6 to 44.8)	29.4 (22.5 to 36.6)	24.1 (16.4 to 32.5)

CI=confidence interval; IRO=integrated radiology and oncology analysis; ITT=intention-to-treat; PFS=progression-free survival
† From product-limit (K-M) method for censored data
Source: CS, adapted from table 21 and appendix 6 (table 4)

It can be clearly observed that the K-M OS curves for both doses of pembrolizumab also overlap in both trials; the overlap occurs at numerous time points in KEYNOTE-002 and at

around 10 months in KEYNOTE-001 (Part B2). The ERG notes that, compared to PFS, the decrease over time in the number of patients at risk of an OS event is less rapid; nevertheless there are still around 90% fewer patients at risk at 12 months in KEYNOTE-002 and 53% to 56% fewer in KEYNOTE-001 (Party B2). The ERG shares the company's concern about the immaturity, and therefore the reliability, of the OS data in KEYNOTE-002.

In summary, the ERG concurs with the company that the clinical trial evidence currently available and presented does not suggest any difference in efficacy when comparing the two doses of pembrolizumab. The ERG however cautions that the number of patients in each arm is small and the time period for which the majority of the data are available is relatively short, making it difficult to conclusively determine that the two doses are of equal efficacy.

4.4.2 Progression-free survival findings in KEYNOTE-002

Progression-free survival based on central assessment (IRO)

The company provides a K-M plot of the PFS analysis in figure 8 of the CS. The results of the PFS analyses based on independent central assessment (IRO) are provided in Table 13.

Pembrolizumab 2mg/kg Q3W was shown to have a statistically significant effect on PFS in comparison to chemotherapy (HR=0.57; 95% CI 0.45 to 0.73; p<0.0001). However, the difference in median PFS between treatment arms does not suggest a large treatment effect; median PFS was 2.9 months in the pembrolizumab 2mg/kg Q3W arm and 2.7 months in the chemotherapy arm. The company attributes the small difference in median PFS to the timing of the first scheduled response assessment (Week 12), claiming that the median PFS is likely to underestimate the treatment effect of pembrolizumab 2mg/kg Q3W in comparison to chemotherapy. The company highlights that after Week 12, PFS rates for the two treatment arms separate, as demonstrated by the PFS rates at 6, 9, and 12 months summarised in Table 14. The ERG concurs with the company's interpretation of the data.

Table 13 Analysis of progression-free survival based on independent central assessment (IRO) in KEYNOTE-002

Treatment arm	No. of events (%)	Person-months	Event rate/100 person-months (%)	Median PFS† (months) (95% CI)	PFS rate at 6 months (%)† (95% CI)	Treatment vs chemotherapy HR (95% CI)‡ p-value§
Pembrolizumab 2mg/kg Q3W n=180	129 (71.1)	804.6	16.0	2.9 (2.8 to 3.8)	34.3 (27.4 to 41.3)	0.57 (0.45 to 0.73) p<0.0001
Pembrolizumab 10mg/kg Q3W n=181	126 (69.6)	881.1	14.3	2.9 (2.8 to 4.7)	37.7 (30.6 to 44.8)	0.50 (0.39 to 0.64) p<0.0001
Pembrolizumab (both doses) n=361	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy n=179	155 (86.6)	584.3	26.5	2.7 (2.5 to 2.8)	15.6 (10.5 to 21.5)	

CI=confidence interval; HR=hazard ratio; IRO=integrated radiology and oncology analysis; ITT=intention-to-treat; PFS=progression-free survival
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs 1), LDH level (normal vs elevated) and mutation (mutant vs wild type)
§ One-sided p-value based on stratified log-rank test
Sources: CS, adapted from table 20 and appendix 6 (table 3); CSR, table 11-4

Table 14 Progression-free survival rate at fixed time-points based on independent central assessment (IRO) in KEYNOTE-002

Treatment arm	PFS rate at month 3 in %† (95% CI)	PFS rate at month 6 in %† (95% CI)	PFS rate at month 9 in %† (95% CI)	PFS rate at month 12 in %† (95% CI)
Pembrolizumab 2mg/kg Q3W	47.5 (40.0 to 54.7)	34.3 (27.4 to 41.3)	23.7 (17.0 to 31.1)	21.6 (14.5 to 29.6)
Pembrolizumab 10mg/kg Q3W	48.7 (41.2 to 55.8)	37.7 (30.6 to 44.8)	29.4 (22.5 to 36.6)	24.1 (16.4 to 32.5)
Pembrolizumab (both doses) n=361	[redacted]	[redacted]	Not reported	Not reported
Chemotherapy n=179	35.0 (27.9 to 42.2)	15.6 (10.5 to 21.5)	8.0 (4.0 to 13.9)	3.6 (0.9 to 9.5)

CI=confidence interval; IRO=integrated radiology and oncology analysis; ITT=intention-to-treat; PFS=progression-free survival
† From product-limit (K-M) method for censored data
Sources: CS, adapted from table 21 and appendix 6 (table 4); CSR, table 11-4

Progression-free survival based on local investigator assessment (INV)

The company provides a K-M plot of the PFS determined by INV in figure 9 of the CS. The results of PFS determined by INV are presented in Table 15.

A statistically significant improvement in PFS was observed for pembrolizumab 2mg/kg Q3W in comparison to chemotherapy (HR=0.49; 95% CI 0.38 to 0.62; p<0.0001), in accordance with the results from the PFS determined by IRO. The difference in median PFS between treatment arms suggested a greater treatment benefit when the results of PFS determined by INV are used; median PFS was 3.7 months for the pembrolizumab 2mg/kg Q3W arm and 2.6 months for the chemotherapy arm. The company highlights that substantial treatment benefit is demonstrated even at 3 months, and that PFS rates continue to separate thereafter, as demonstrated by the PFS rates at 6, 9, and 12 months (Table 16).

Table 15 Analysis of progression-free survival based on local investigator assessment (INV) in KEYNOTE-002

Treatment arm	No. of events (%)	Person-months	Event rate/100 person-months (%)	Median PFS† (months) (95% CI)	PFS rate at 6 months (%)† (95% CI)	Treatment vs chemotherapy HR (95% CI)‡ p-value§
Pembrolizumab 2mg/kg Q3W n=180	122 (67.8)	864.7	14.1	3.7 (2.9 to 5.4)	38.9 (31.6 to 46.1)	0.49 (0.38 to 0.62) p<0.0001
Pembrolizumab 10mg/kg Q3W n=181	112 (61.9)	979.2	11.4	5.4 (3.8 to 6.8)	44.9 (37.3 to 52.1)	0.41 (0.32 to 0.52) p<0.001
Pembrolizumab (both doses) n=361	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Chemotherapy n=179	157 (87.7)	594.1	26 .4	2.6 (2.4 to 2.8)	15.2 (10.2 to 21.0)	

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; PFS=progression-free survival
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs 1), LDH level (normal vs elevated) and BRAF mutation (mutant vs wild type)
§ One-sided p-value based on stratified log-rank test
Source: CS, adapted from table 22 and appendix 6 (table 5)

Table 16 Progression-free survival rate at fixed time-points based on local investigator assessment (INV) in KEYNOTE-002

Treatment arm	PFS rate at month 3 in %† (95% CI)	PFS rate at month 6 in %† (95% CI)	PFS rate at month 9 in %† (95% CI)	PFS rate at month 12 in %† (95% CI)
Pembrolizumab 2mg/kg Q3W	54.7 (47.1 to 61.7)	38.9 (31.6 to 46.1)	32.2 (24.8 to 39.7)	18.0 (9.7 to 28.3)
Pembrolizumab 10mg/kg Q3W	60.3 (52.7 to 67.0)	44.9 (37.3 to 52.1)	36.3 (28.8 to 43.8)	30.9 (23.0 to 39.1)
Pembrolizumab (both doses) n=361	Not reported	Not reported	Not reported	Not reported
Chemotherapy	32.9 (25.9 to 39.9)	15.2 (10.2 to 21.0)	9.5 (5.5 to 14.8)	4.2 (1.1 to 10.7)

CI=confidence interval; ITT=intention-to-treat; PFS=progression-free survival
† From product-limit (K-M) method for censored data.
Source: CS, adapted from table 23 and appendix 6 (table 6)

Progression-free survival sensitivity analyses

The company reports that results from the PFS sensitivity analyses using two alternative censoring approaches (as detailed in Table 9) were consistent with those from the primary PFS analysis. The ERG agrees with the company's conclusion.

Progression-free survival subgroup analyses

Table 10 of this ERG report lists all subgroup analyses performed by the company. Results of all performed subgroup analyses are provided in appendix 7 of the CS. The results summarised in Table 17 suggest that, in comparison to chemotherapy, the efficacy of pembrolizumab 2mg/kg Q3W was greater in PD-L1 positive patients (marked difference between the arms) than in PD-L1 negative patients (median PFS and PFS rates similar between arms at 6 months). This, the company notes, is consistent with the mechanism of action of an anti-PD-1 agent such as pembrolizumab; they also note that the PD-L1 negative subgroup is small with imbalances in BRAF mutation status and LDH levels between treatment arms, which may have confounded the results. Interestingly, PFS rates appear to be markedly higher between the pembrolizumab 10mg/kg Q3W arm and chemotherapy arm in both PD-L1 positive and PD-L1 negative subgroups. The ERG requested p-values for interaction for all performed subgroup analyses in order to investigate the statistical significance of subgroup effects, which the company provided in their clarification response. The subgroup effect for PD-L1 status was not found to be statistically significant for pembrolizumab 2mg/kg vs chemotherapy (p=0.11), or indeed for pembrolizumab 10mg/kg vs chemotherapy (p=0.58).

Efficacy was found to be consistent across all other subgroups. No statistically significant p-values for interaction were observed (from data again provided by the company during the clarification process) from the other subgroups analyses.

Table 17 Progression-free survival based on independent central assessment (IRO) by PD-L1 status in KEYNOTE-002*

Treatment arm	Median PFS (Months) (95% CI)	PFS Rate at Month 6 in % (95% CI)	Treatment vs chemotherapy HR (95% CI)
PD-L1 positive			
Pembrolizumab 2mg/kg Q3W n=98	3.5 (2.9 to 5.6)	38.1 (28.5 to 47.6)	0.54 (0.39 to 0.75)
Pembrolizumab 10mg/kg Q3W n=95	4.0 (2.8 to 6.0)	41.5 (31.3 to 51.3)	0.49 (0.35 to 0.69)
Pembrolizumab (both doses) n=193	[redacted]	[redacted]	[redacted]
Chemotherapy n=98	2.8 (2.6 to 2.9)	12.8 (7.0 to 20.5)	
PD-L1 negative			
Pembrolizumab 2mg/kg Q3W n=47	2.8 (2.7 to 2.8)	19.3 (9.4 to 31.9)	0.89 (0.53 to 1.50)
Pembrolizumab 10mg/kg Q3W n=46	2.8 (2.8 to 5.6)	32.6 (19.7 to 46.1)	0.41 (0.23 to 0.72)
Pembrolizumab (both doses) n=98	[redacted]	[redacted]	[redacted]
Chemotherapy n=37	2.7 (2.0 to 3.0)	21.6 (10.2 to 35.8)	

* PD-L1 status was unknown for 119 patients
CI=confidence intervals; HR=hazard ratio; IRO=integrated radiology and oncology analysis (independent central assessment); ITT=intention-to-treat; NR=not reached; OS=overall survival
Sources: CS, adapted from appendix 7 (table 2); CSR, table 11-32 and table 11-33

4.4.3 Overall survival findings in KEYNOTE-002

The results of the OS analysis from the ITT population (unadjusted for treatment crossover) are provided in Table 18. The results of the interim analysis suggest that there is no statistically significant difference between pembrolizumab 2mg/kg Q3W and chemotherapy in terms of OS (HR=0.88; 95% CI: 0.64 to 1.22; p=0.2294). However, this estimate of treatment benefit does not take into consideration that patients in the chemotherapy arm were allowed to crossover to the pembrolizumab 2mg/kg Q3W arm following disease progression.

The company provides a K-M plot of the unadjusted OS analysis in figure 10 of the CS. It advises that due to the large amount of censoring and small number of patients at risk beyond 6 months, median OS should be interpreted cautiously. The OS data will be mature at the final OS analysis, to be performed when 370 deaths have occurred; as of the most recent interim analysis (IA2), 245 people had died in KEYNOTE-002.

Table 18 Analysis of overall survival in KEYNOTE-002

Treatment	No. of events (%)	Person-months	Event rate/ 100 person-months (%)	Median OS† (months) (95% CI)	OS rate at month 3 (%)† (95% CI)	Treatment vs chemotherapy HR‡ (95% CI)‡ p-value§
Pembrolizumab 2mg/kg Q3W n=180	73 (40.6)	1289.6	5.7	11.4 (10.2 to NR)	85.5 (79.4 to 89.9)	0.88 (0.64 to 1.22) p=0.2294
Pembrolizumab 10mg/kg Q3W n=181	69 (38.1)	1348.3	5.1	12.5 (9.7 to NR)	86.7 (80.9 to 90.9)	0.78 (0.56 to 1.08) p=0.0644
Pembrolizumab (both doses) n=361	[redacted]	Not reported	Not reported	[redacted]	[redacted]	[redacted]
Chemotherapy n=179	78 (43.6)	1247. 2	6.3	11.6 (9.0 to 16.3)	85.3 (79.2 to 89.8)	

HR=hazard ratio; ITT=intention-to-treat; NR=not reached; OS=overall survival
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs 1), LDH level (normal vs elevated) and BRAF mutation (mutant vs wild type)
§ One-sided p-value based on stratified log-rank test
Sources: CS, adapted from table 24 and appendix 6 (table 7); CSR, table 11-13

Overall survival subgroup analysis

The only subgroup analysis for OS was an analysis of PD-L1 status. The K-M curve is provided in the CS (figure 2, appendix 7) and the company states that this demonstrates no substantial difference in OS according to PD-L1 status. However, it could also be interpreted that the results suggest that the efficacy of pembrolizumab 2mg/kg Q3W was slightly greater in PD-L1 positive patients than in PD-L1 negative patients. The ERG requested p-values for interaction for all performed subgroup analyses in order to investigate the statistical significance of subgroup effects, which the company provided in their clarification response. From data provided by the company during the clarification process, the subgroup effect for PD-L1 status was not found to be statistically significant for pembrolizumab 2mg/kg vs chemotherapy (p=0.58), or indeed for pembrolizumab 10mg/kg vs chemotherapy (p=0.64).

4.4.4 Overall survival: crossover adjustment analyses in KEYNOTE-002

A considerable proportion (48%) of patients in the chemotherapy arm crossed over to either pembrolizumab 2mg/kg 3QW (n=46 of 179 patients, 26%) or pembrolizumab 10mg/kg 3QW (n=40 of 179 patients, 22%). It is unclear from the CS and/or the CSR how patients were assigned to treatment.

It was pre-specified in the trial protocol[42] that the rank-preserving structural failure time (RPSFT) method would be used to adjust for the effects of treatment switching from the chemotherapy arm to the pembrolizumab 2mg/kg Q3W or pembrolizumab 10mg/kg Q3W arm. Additional post-hoc analyses were also conducted using different methods: inverse

probability censored weighting (IPCW) and two-stage correction (using two different models). The company explains that they employed these methods in line with NICE DSU guidelines[41] for the adjustment of treatment crossover. These guidelines recommend that key trial based information should be assessed in order to choose the most clinically valid adjustment approach.

The company states that having considered the switching mechanism (which in this instance was typically related to disease progression and therefore non-random), key trial characteristics, the proportion of patients switching and the clinical validity of the outputs obtained, the two-stage method was considered to be the most suitable crossover adjustment method. The company states that results from the two-stage full covariate adjustment model were used as its estimate for OS as these were more conservative than as used by the simple adjustment model.

Findings from crossover methods

The estimates for crossover adjusted OS using each of these methods are provided in Table 19 alongside the unadjusted OS for the chemotherapy arm. The results from the RPSFT analysis are consistent with those from the unadjusted analysis. A slightly greater treatment effect between arms is observed in the RPSFT adjusted analysis compared with the unadjusted analysis; however, this difference in OS is not statistically significant. In contrast, the findings from the IPCW and two-stage methods suggest a statistically significant difference between pembrolizumab 2mg/kg and chemotherapy. These methods estimated a survival advantage for pembrolizumab 2mg/kg of between 3.5 and 3.9 months, depending on the method utilised.

However, the ERG concludes that it is difficult to directly compare results from the different adjustment methods as the methods have been conducted using different patient populations in terms of which arms were adjusted for at treatment crossover. In the company's response to ERG clarification questions, the company states that the RPSFT method adjusted for crossover to both pembrolizumab 2mg/kg Q3W and pembrolizumab 10mg/kg Q3W in the survival analyses. The IPCW and two-stage and methods only adjusted for patients who crossed over to pembrolizumab 2mg/kg Q3W, i.e. patients who crossed over to the 10mg/kg Q3W treatment arm were excluded from the analysis. The company explained that the reason that only patients who crossed over to pembrolizumab 2mg/kg Q3W were adjusted for in the survival analyses was because this dose was the one that was anticipated to be the licensed dose. The company did not explain why the RPSFT analysis did not exclude patients who crossed over to pembrolizumab 10mg/kg Q3W. The ERG

hypothesises that, as the RPSFT was the method pre-specified in the trial protocol, and the other methods were conducted post-hoc, at the time of the RPSFT analysis, the company did not know which dose would be put forward as the licensed dose.

Table 19 Analysis of median overall survival in KEYNOTE-002

Treatment	Median OS (Months) (95% CI)	Hazard ratio (95% CI), p-value
Pembrolizumab 2mg/kg Q3W	11.4 (10.2 to NR)	
Chemotherapy (unadjusted, no crossover correction)	11.6 (9.0 to 16.3)	0.88 (0.64 to 1.22) p=0.229
Chemotherapy (RPSFT correction)*	11.1 (9.7 to NR)	0.81 (0.50 to 1.23) p=0.229
Chemotherapy (IPCW correction)	7.5†	0.68 (0.48 to 0.96) p=0.028
Chemotherapy (Two-stage correction - simple model)	7.8 (5.3 to 9.7)	0.63 (0.45 to 0.88) p=0.006
Chemotherapy (Two-stage correction - all covariates)	7.9 (5.4 to 9.7)	0.63 (0.45 to 0.88) p=0.007

* The RPSFT method was the only method to adjust for crossover to pembrolizumab 2mg/kg Q3W and pembrolizumab 10mg/kg Q3W whereas all other methods only adjusted for patients who crossed over to pembrolizumab 2mg/kg Q3W; the RPSFT method was the method pre-specified by the company to adjust for treatment crossover, all other analyses were conducted post-hoc
†The IPCW approach does not produce a median (and its confidence interval) as one of the model outputs
CI=confidence interval; HR=hazard ratio; IPCW=inverse probability censored weighting; NR=not reached; OS=overall survival; RPSFT=rank-preserving structural failure time
Source: CS, adapted from tables 24 to 26

Having considered the limitations of the RPSFT and IPCW methods for adjusting OS in KEYNOTE-002 and considering the company's justification for the two-stage adjustment method, the ERG concurs that the use of the two-stage method is suitable for adjusting for crossover. The suitability of each method is explored below.

Suitability of RPSFT method

In the CS, the company proposes that the RPSFT method is unsuitable due to the fact that the RPSFT analysis results imply that pembrolizumab 2mg/kg patients die more quickly post-progression than chemotherapy patients, stating that there is no clinical explanation for such an effect. The company refers to figure 30 of the CS which shows (adjusted) post-progression survival (PPS) after implementing RPSFT. To demonstrate that this effect could not be possible, the company refers to figure 31 of the CS which shows unadjusted PPS for patients treated with pembrolizumab 2mg/kg Q3W, patients treated with chemotherapy who crossed over to pembrolizumab 2mg/kg Q3W and chemotherapy patients who did not crossover. The company states that patients receiving chemotherapy who did not crossover to pembrolizumab 2mg/kg Q3W experienced shorter PPS than those receiving

pembrolizumab 2mg/kg Q3W or crossing over to pembrolizumab 2mg/kg Q3W (as shown in figure 31 of the CS). These findings indicate that the results of the RPSFT analysis cannot be valid as the RPSFT results suggest that patients treated with pembrolizumab 2mg/kg Q3W die more quickly post-progression than patients treated with chemotherapy. However, the company's argument is seriously flawed since data presented in figure 31 of the CS is entirely observed, with no adjustments for key characteristics that may differ between patient groups. For example, chemotherapy patients who are shown to die more quickly in figure 31 of the CS may have been ineligible for crossover and therefore may have been sicker and had a generally poorer prognosis that the patients who did crossover.

As the ERG considered the company's justification for the rejection of the RPSFT methods to be flawed, the ERG asked for further clarification from the company. In the company's response to the ERG clarification questions, more details were provided as to why the company believed the RPSFT method to be unsuitable. In particular, the company provided evidence that the assumption of a "common treatment effect", which is necessary to utilise RPSFT methods, does not hold. The company demonstrates that patients who switch to the pembrolizumab 2mg/kg Q3W arm experience a different treatment effect when they progress than that experienced by patients initially allocated to pembrolizumab 2mg/kg Q3W. They do this by comparing the treatment effect (pembrolizumab 2mg/kg vs chemotherapy) for patients initially allocated to pembrolizumab 2mg/kg at 8, 12 and 20 weeks after baseline vs the treatment effect at 8, 12 and 20 weeks post-progression for patients who crossed over to pembrolizumab 2mg/kg 3QW vs chemotherapy. In order to generate hazard ratios (using Cox proportional hazards methods) for these two patient groups, the comparable non-crossover patients (matching all crossover criteria as listed on page 67 of the CS, and having survived the "washout" period of 28 days which a crossover patient would have to survive before receiving pembrolizumab) were used as the chemotherapy arm for all analyses. The hazard ratios are provided in Table 20.

The results suggest that patients initially treated with pembrolizumab 2mg/kg Q3W experience a different treatment effect to patients who crossover to pembrolizumab 2mg/kg on disease progression. Therefore, the assumption of a "common treatment effect" does not hold. The ERG is of the opinion that this argument for the rejection of the RPSFT method is valid, under the assumption that the crossover criteria have adequately captured the prognostic differences between those who do and do not switch treatment on disease progression.

Table 20 Hazard ratios for overall survival for pembrolizumab vs chemotherapy (from start of trial) and for patients who crossed over to pembrolizumab vs chemotherapy (post-progression) in KEYNOTE-002

Comparison	Hazard ratio at different time points from start of trial (top row) or post-progression (bottom row)		
	8 weeks (95%CI)	12 weeks (95%CI)	20 weeks (95%CI)
From start of trial: Pembrolizumab 2mg/kg Q3W vs chemotherapy patients who did not crossover	0.919 (0.668 to 1.264)	0.904 (0.657 to 1.244)	0.916 (0.666 to 1.260)
Post-progression: Patients initially treated with chemotherapy who crossed over to pembrolizumab 2mg/kg Q3W vs chemotherapy patients who did not crossover	0.312 (0.150 to 0.649)	0.313 (0.151 to 0.650)	0.275 (0.132 to 0.573)

Source: Company's response to ERG clarification letter, adapted from table 1

Suitability of the IPCW method

The company explains that IPCW is an unsuitable method due to the relatively small number of patients in KEYNOTE-002 and the high proportion of patient crossover. The ERG agrees that these are important limitations of the IPCW method; both the RPSFT and the two-stage methods are more appropriate for adjusting data affected by treatment switching when the sample size is small and when there is a relatively large proportion of patient crossover.

Suitability of the two-stage method

Given the weaknesses of the RPSFT and IPCW methods, the company also considered the use of the two-stage method to adjust for crossover. Two models were run for the two-stage crossover adjustment analysis: a simple model accounting for ECOG performance status and a model accounting for all potentially relevant prognostic markers that could differ between patients in the pembrolizumab 2mg/kg Q3W arm and patients who crossed over to pembrolizumab 2mg/kg Q3W from chemotherapy (i.e. ECOG performance status, tumour size, LDH, BRAF status, melanoma stage and age). The latter model was the method that the company argued was most appropriate as it was considered to provide a more conservative estimate of OS than the simple model. There are two main arguments for this:

- The two-stage method is valid when switching occurs after a specific disease-related time-point (i.e. disease progression) if relevant confounders are measured until this point; the ERG agrees with the company that this is an appropriate approach for KEYNOTE-002 (assuming that the confounders accurately capture all prognostic markers that differ between patients who do and who do not crossover on disease progression)
- Adjusted OS obtained for the chemotherapy arm can be validated using an external data source, in this instance, the Korn algorithm.[43] This procedure generates an OS

curve that reflects the characteristics of patients in the chemotherapy arm of the KEYNOTE-002 trial, which can be compared to the two-stage adjusted OS data. The high degree of similarity (as shown in figure 32 of the CS) between the two curves suggests that the two-stage approach is a suitable method to use for these data. The ERG considers that comparing the adjusted OS data to data generated using the Korn algorithm[43] is an appropriate method for assessing the validity of the adjusted OS.

4.5 Critique of the adverse event data

As per information regarding clinical efficacy results, the safety results provided in the main body of the CS focused on the anticipated licensed dose of pembrolizumab 2mg/kg Q3W. For completeness, the company also presented data for the 10mg/kg Q3W dose in appendix 13 of the CS. The majority of AE evidence is derived from the KEYNOTE-002 trial.

4.5.1 Adverse event data collected

For KEYNOTE-002, data were presented for the following broad types of AEs (see table 47 of CS):

- Patients with one or more AE, Grade ≥3 AE or serious AE (SAE)
- Drug-related (i.e. considered "possibly," "probably," or "definitely" related to study medication by the local investigator) AEs: any Grade, Grade ≥3 AEs and SAEs
- AEs, drug-related AEs, SAEs and serious drug-related AEs leading to treatment discontinuation
- Death.

In addition, the company reported specific AE data in relation to the following:

- Common AEs (i.e. incidence ≥15% in either treatment arm, text of CS)
- Any Grade AEs (incidence ≥10 % in either treatment arm in appendix 11 [table 1] of CS)
- Grade ≥3 AEs (incidence ≥1% in either treatment arm, text and table 48 of CS)
- Drug-related AEs with incidence ≥10 % in either treatment arm (text of CS)
- Drug-related Grade ≥3 AEs with incidence ≥10 % in either treatment arm (text and table 49 of CS)
- Adverse events of special interest (AEOSI) including potentially immune-related AEs (text and tables 50 and 51 of CS)
- Selected pre-specified AEs of potential immune aetiology (table 52 of CS).

The 'All Patients as Treated' (APaT) population was used for the analysis of safety data in KEYNOTE-002. Additional AE data are provided in the CS from the supportive KEYNOTE-001 (Part B2) RCT and non-random KEYNOTE-001 (Part B1) study. The main body of the CS also includes a brief descriptive paragraph comparing treatment-related AEs experienced by patients in KEYNOTE-006 treated with pembrolizumab (10mg/kg Q2W and 10mg/kg Q3W) and ipilimumab. Since the ERG considers data from KEYNOTE-002 are

most relevant to the decision problem these findings are summarised by the ERG in Appendix 4.

4.5.2 Adverse event data reported in KEYNOTE-002

From the data summarised in Table 21, the ERG notes that the following types of AEs were all notably fewer in the pembrolizumab 2mg/kg Q3W arm than in the chemotherapy arm: Grade ≥3 AEs, any Grade drug-related AEs, drug-related Grade ≥3 AEs and drug-related AEs leading to discontinuation of treatment. Only serious AEs (SAEs) and death were notably more common in the pembrolizumab 2mg/kg 2QW arm than in the chemotherapy arm. However, drug-related SAEs were marginally fewer in the 2mg/kg Q3W pembrolizumab arm than in the chemotherapy arm. Despite deaths from AEs being reported by around 5% to 6% of all participants, only one death (in the pembrolizumab 2mg/kg Q3W arm) was considered to be drug-related.

Table 21 Broad types of adverse events reported in KEYNOTE-002

Type of adverse event	Pembrolizumab 2mg/kg Q3W n=178	Pembrolizumab 10mg/kg Q3W n=179	Chemotherapy n=171
Patients with one or more AEs (any Grade)	172 (96.6%)	178 (99.4%)	167 (97.7%)
Grade ≥3 AE	83 (46.6%)	79 (44.1%)	88 (51.5%)
Any grade drug-related AE	121 (68.0%)	133 (74.3%)	138 (80.7%)
Drug-related Grade ≥3 AE	20 (11.2%)	25 (14.0%)	45 (26.3%)
SAE	79 (44.4%)	66 (36.9%)	57 (33.3%)
Serious drug-related AE	14 (7.9%)	20 (11.2%)	17 (9.9%)
Death from SAE	11 (6.2%)	8 (4.5%)	8 (4.7%)
Drug-related AE leading to death	1 (0.6%)	0 (0.0%)	0 (0.0%)
AE leading to discontinuation	18 (10.1%)	26 (14.5%)	20 (11.7%)
Drug-related AE leading to discontinuation	5 (2.8%)	12 (6.7%)	10 (5.8%)
SAE leading to discontinuation	15 (8.4%)	20 (11.2%)	14 (8.2%)
Serious drug-related AE leading to discontinuation	5 (2.8%)	8 (4.5%)	4 (2.3%)

AE=adverse event; SAE=serious adverse event
Source: CS, adapted from appendix 13 (table 1)

Anaemia and fatigue were the most common Grade ≥3 AEs in the pembrolizumab 2mg/kg Q3W arm and in the chemotherapy arm in KEYNOTE-002. The most common drug-related Grade ≥3 AEs occurring in at least 1% of patients in the pembrolizumab 2mg/kg Q3W arm also included fatigue (1.1%) as well as generalised oedema (1.1%) and myalgia (1.1%). Common Grade ≥3 AEs occurring in at least 3% of participants in the chemotherapy arm, included anaemia (5.3%), fatigue (4.7%), leukopenia (3.5%) and neutropenia (3.5%) with many other Grade ≥3 AEs occurring in at least 1% of the population. The company notes that Grade ≥3 AEs were more common in the chemotherapy arm of KEYNOTE-002 than

previously reported in single-agent chemotherapy studies. This is attributed to the fact that patients were more heavily pre-treated in this trial than in previously reported studies.

4.5.3 Adverse events and immune-related adverse events by pembrolizumab dose in KEYNOTE-002

Although the company states the safety profile was not notably different between patients by dose, the ERG observes from Table 21 that most AEs other than SAEs, death from SAEs and drug-related AEs leading to death occurred with lower frequency in the 2mg/kg Q3W arm compared with 10mg/kg arm. All AEOSIs occurred at a lower frequency in the 2mg/kg Q3W arm compared with 10mg/kg arm (Table 22). The ERG considers that this finding may suggest that a higher dose of pembrolizumab results in a greater likelihood of AEs and/or that it simply reflects the longer exposure to the drug in the 10mg/kg Q3W arm in the trial (Table 23). Alternatively, differences may be occurring simply by chance, which may explain the notably higher proportion of SAEs and deaths in the 2mg/kg Q3W arm compared with the 10mg/kg Q3W arm.

Table 22 Broad types of adverse events of special interest reported in KEYNOTE-002

Type of adverse event	Pembrolizumab 2mg/kg Q3W n=178	Pembrolizumab 10mg/kg Q3W n=179	Chemotherapy n=171
Patients with one or more AEOSIs (any Grade)*	29 (16.3%)	35 (19.6%)	3 (1.8%)
Grade ≥3 AEOSI	5 (2.8%)	13 (7.3%)	1 (0.6%)
Any grade drug-related AEOSI	23 (12.9%)	30 (16.8%)	0 (0.0%)
Drug-related Grade ≥3 AEOSI	4 (2.2%)	12 (6.7%)	0 (0.0%)
Serious AEOSI	8 (4.5%)	10 (5.6%)	2 (1.2%)
Serious drug-related AEOSI	6 (3.4%)	9 (5.0%)	0 (0.0%)
Death from AEOSI	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug-related AEOSI leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEOSI leading to discontinuation	2 (1.1%)	9 (5.0%)	1 (0.6%)
Drug-related AEOSI leading to discontinuation	2 (1.1%)	9 (5.0%)	0 (0.0%)
Serious AEOSI leading to discontinuation	2 (1.1%)	7 (3.9%)	1 (0.6%)
Serious drug-related AEOSI leading to discontinuation	2 (1.1%)	7 (3.9%)	0 (0.0%)

AEOSI=adverse event of special interest
Source: CS, adapted from appendix 13 (table 6)
*These are also cited as immune-related AEs in the CS (section 14.3.1)

Table 23 Exposure to treatment reported in KEYNOTE-002

Exposure, days	Pembrolizumab 2mg/kg Q3W n=178	Pembrolizumab 10mg/kg Q3W n=179	Chemotherapy n=171
Median (range)	112.5 (1 to 499)	145 (1 to 505)	61 (1 to 335)
Mean (SD)	144.2 (107.7)	157.0 (115.1)	75.5 (66.4)

Source: CS, adapted from appendix 13 (table 1)

Specific types of immune-related AEs specified in the CHMP (with incidences of these AEs in KEYNOTE-002) include:

- Pneumonitis 1.7% in both pembrolizumab arms
- Colitis: 1.1% in the pembrolizumab 2mg/kg 3QW arm and 1.7% in the pembrolizumab 10mg/kg 3QW arm
- Endocrinopathies including hyperthyroidism, hypophysitis and hypothyroidism: 3.9%, 0.6% and 6.2% respectively in the pembrolizumab 2mg/kg 3QW arm and 1.1%, 0.6% and 8.4%respectively in the pembrolizumab 10mg/kg 3QW arm
- Hepatitis: 1.1% in both arms of pembrolizumab
- Nephritis: 0.6% in both arms of pembrolizumab;
- Uveitis: 0.6% in the pembrolizumab 10mg/kg 3QW arm only
- Pancreatitis: 0.6% in the pembrolizumab 2mg/kg 3QW arm only
- Severe skin reactions: 1.1% in both pembrolizumab arms
- Myositis: 0.0% in both arms.

The company reports that immune-related AEs were typically Grade ≤2 in severity. They were also reported to be generally reversible with treatment discontinuation and use of corticosteroids. As shown in Table 22, AEOSIs leading to discontinuation (including serious AEOSIs, drug-related AEOSIs and serious drug-related AEOSIs) constituted a small proportion of all patients with AEOSIs in the pembrolizumab 2mg/kg Q3W arm.

As the company explains in the CS, the primary method of assessing immune-related AEs in KEYNOTE-002 was the analysis of AEOSIs. The list of terms is updated periodically based on emerging pembrolizumab safety data. Immune-related AEs pre-specified prior to the start of KEYNOTE-002 (and the incidence of these AEs in pembrolizumab 2mg/kg, pembrolizumab 10mg/kg and chemotherapy arms respectively) were as follows:

- Grade ≥3 diarrhoea and Grade ≥2 colitis (1.7%, 2.8%, 0.0%)
- Grade ≥3 hyperthyroidism, hypophysitis and hypothyroidism (0.6%, 0, 0)
- Grade ≥2 pneumonitis (0.0%, 1.7%, 0.0%)
- Grade ≥3 rash (no events in any arm).

For these AEs, p-values and 95% confidence intervals for between-treatment differences in the percentage of patients with Tier-1 events was calculated using the stratified Miettinen

and Nurminen method. No statistically significant differences were reported between either arm of pembrolizumab and chemotherapy.

4.5.4 Summary of adverse event data

Overall, the company concludes that the AE data suggest that the safety profile of patients treated with pembrolizumab 2mg/kg Q3W is acceptable and compares favourably to chemotherapy. The ERG concurs with the company's conclusion. The ERG has received clinical advice that the AEs experienced with chemotherapy treatment fit within well-established algorithms for cytotoxic chemotherapy in acute oncology services. In contrast, AEs with pembrolizumab are still relatively unfamiliar to those working in acute oncology services; however, some AEs have become more common as a result of treatment with ipilimumab. Managing colitis and endocrinopathies requires the involvement of specialities other than oncology.

4.6 Critique of the health related quality of life data

HRQoL data are only presented from the KEYNOTE-002 trial. Assessments were made using both the condition specific European Organisation for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire and the generic EuroQoL EQ-5D questionnaire. Patient reported outcomes were assessed at the following time points: baseline-cycle 1 (week 0), cycle 2 (week 3), cycle 3 (week 6), cycle 5 (week 12), cycle 9 (week 24); cycle 13 (week 36), end of chemotherapy/pre-crossover, discontinuation/end of treatment and once post-progression at the safety follow up (approximately 30 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever occurred first). EQ-5D data were used to inform the cost effectiveness analyses and thus not reported by the company in the clinical section of the CS.

Score changes from baseline and the proportions of improvement/deterioration at week 12, as measured by the EORTC QLQ-C30 global health status/quality of life score, are described as an "exploratory endpoint" and presented as evidence for clinical effectiveness in section 4.7 and in appendix 27 of the CS.

At week 12, statistically significant improvements in the global health status/quality of life scale of the EORTC QLQ-C30, as observed by a lower reduction in the least squares mean change from baseline, were reported for pembrolizumab 2mg/kg Q3W compared to chemotherapy. The difference in least squares mean change from baseline at week 12 in HRQoL assessed with EORTC QLQ-C30 was 6.5 (95% CI 1.53 to 11.53, p=0.011) for pembrolizumab 2mg/kg Q3W vs chemotherapy. A similar finding was reported for pembrolizumab 10mg/kg Q3W compared with chemotherapy (6.6; 95% CI 1.65 to 11.50), p=0.009). There were no statistically significant differences between the pembrolizumab arms: 0 (95% CI -4.75 to 4.83, p=0.986).

The CS does not report response rates for the EORTC QLQ-C30 questionnaire. However, in the CSR it is reported: "[redacted]" (page 126 of CSR) For this reason "[redacted]" (page 130 of CSR).

The company concludes that, overall, the EORTC QLQ-C30 results suggest that there is less of a decrease from baseline in a patient's global health status/quality of life when treated with pembrolizumab 2mg/kg 3QW compared with chemotherapy. However, the company does also state that a score change of 10 points is considered clinically meaningful.[44] Hence the ERG notes that no clinically meaningful difference in HRQoL as measured by the EORTC QLQ-C30 was observed.

4.7 Conclusions of the clinical effectiveness section

The majority of the evidence submitted by the company that is relevant to the NICE scope and the company's decision problem is from the KEYNOTE-002 trial. The CS is focussed on the clinical evidence supporting the use of pembrolizumab 2mg/kg Q3W since this is the anticipated licensed dose. Analysis of data currently available from KEYNOTE-002 and KEYNOTE-001 (Part B2) suggest that pembrolizumab 2mg/kg Q3W is no more or less efficacious than pembrolizumab 10mg/kg Q3W. However, the ERG cautions that the number of patients in each arm of the KEYNOTE-002 trial is relatively small and the time period for which the majority of the data are available is relatively short, making it difficult to conclusively determine that the two doses of pembrolizumab are of equal efficacy.

In KEYNOTE-002, pembrolizumab 2mg/kg Q3W was superior to chemotherapy measured by PFS rates at 6 months (IRO: 34.3% vs 15.6%; INV: 38.9% vs 15.2%). Statistically significant differences in median OS between pembrolizumab 2mg/kg Q3W and chemotherapy were only reported after adjusting OS data for treatment crossover. An improvement in median OS for pembrolizumab 2mg/kg Q3W of 3.5 months using the two-stage method (all covariates) was demonstrated. This method of adjustment is the preferred approach of the company and the ERG. Although pembrolizumab is an anti-PD-1 agent, a treatment effect was observable in patients treated with pembrolizumab 2mg/kg regardless of PD-L1 status and the subgroup effect for PD-L1 status was not found to be statistically significant for either PFS or OS for pembrolizumab 2mg/kg vs chemotherapy. Pembrolizumab 2mg/kg Q3W compares favourably to chemotherapy in terms of its safety profile with fewer AEs and drug-related AEs (of any Grade, Grade ≥3 and leading to discontinuation of treatment). Immune-related AEs were reported by 16.3% of patients in the pembrolizumab 2mg/kg arm, most of which were reported to be generally reversible with treatment discontinuation and the use of corticosteroids.

While none of the participating treatment centres in KEYNOTE-002 were located in the UK and despite a trial population with relatively advanced melanoma, the ERG considers that the patient population, and therefore the trial findings, are likely to be generalisable to patients who are refractory to ipilimumab in England. While both the company and the ERG have assessed the trial to have an overall low risk of bias, it should be noted that KEYNOTE-002 is an ongoing Phase II trial lacking mature OS data with a relatively high proportion of treatment crossover from chemotherapy to pembrolizumab (48% to either dose). Thus the ERG urges caution in interpreting these OS findings and considers that only when more mature OS data become available will the true effect between treatments be estimated.

5 ECONOMIC EVALUATION

5.1 Introduction

This Section provides a structured critique of the economic evidence submitted by Merck Sharp & Dohme in support of the use of pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab and, if BRAF mutation-positive, a BRAF or MKE inhibitor. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic copy of their economic model that was developed in Microsoft Excel.

5.2 The company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company undertook a search to identify studies reporting the cost effectiveness of pembrolizumab, compared with other therapies, for the treatment of patients with advanced melanoma who have progressed following treatment with ipilimumab. Details of the search strategies employed by the company are included in appendix 15 of the CS. The databases and the initial time horizon for each search are summarised in Table 24. In all cases the searches were updated in March 2015.

Table 24 Database search details

Database searched	Initial time horizon*
Medline (via OVID SP)	1946 to 21 July 2014
Medline In-process (via OVID SP)	
EMBASE	1975 to 24 September 2014
The Cochrane Library (including the NHS EED and HTA databases)	Searches to 17 July 2014
Econ-Lit	1866 to June 2014

* An updated search of all databases was undertaken in March 2015
EED=economic evaluation database; HTA=health technology assessment

Hand searches were also performed from several databases: the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and International Society For Pharmacoeconomics and Outcomes Research (ISPOR) conferences. These searches were constrained to the most recent 2 years (from July 2014) and updated searches were carried out in March 2015. In addition, the NICE website[45] was searched to identify relevant information from previous company submissions.

5.2.2 Eligibility criteria used in the study selection

The company's inclusion/exclusion criteria used in the study selection are presented in Table 25. The ERG is satisfied that these criteria are relevant to the decision problem.

Table 25 Economic evaluation search inclusion/exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Patients with advanced melanoma previously treated with ipilimumab	None
Interventions	Any medical treatment of advanced melanoma, or best supportive care, no treatment or placebo	Non-pharmacological interventions
Outcomes	Studies including a comparison of costs between the intervention and comparator arms. Results should also include either incremental QALYs (or another measure of health outcome/clinical effectiveness), or be structured with a cost minimisation argument	Cost-only outcomes (without a cost-minimisation argument, e.g. burden of illness studies)
Study type	Full economic evaluations, comparing at least two interventions in terms of cost consequence, cost minimisation, cost effectiveness, cost utility or cost benefit	Reviews (systematic or otherwise), letters and comment articles
Publication type	Economic evaluations	Burden of illness studies
Language restrictions	Studies for which a full text version is available in English	Not available in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated. Studies that fail to present extractable results

Source: CS, adapted from table 57

5.2.3 Included and excluded studies

No relevant studies were identified by the company.

5.2.4 Conclusions of the cost effectiveness review

The company suggests that the lack of relevant studies can be explained by the fact that a positive NICE recommendation for the use of ipilimumab for previously untreated unresectable melanoma (TA319[13]) was published in July 2014, less than a year before the CS for this appraisal was sent to NICE.

5.3 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers.

The ERG acknowledges that the company reports the methods and results for searches carried out to identify HRQoL associated with advanced melanoma as well as resource requirements and costs associated with the treatment of advanced melanoma. The ERG considers these details to be very helpful.

5.4 Overview of manufacturer's economic modelling

5.4.1 NICE reference case checklist

Table 26 NICE Reference case checklist completed by ERG

Attribute	Reference case[46]	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	The company's model focuses on pembrolizumab 2mg/kg Q3W, which is the anticipated licensed dose
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Cost effectiveness analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 30 year time horizon
Synthesis of evidence on health effects	Based on systematic review	No – data have primarily been taken from a single clinical trial
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs and the EQ-5D instrument has been used to collect HRQoL data
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes - HRQoL data were collected as part of the KEYNOTE-002 trial. Mixed international trial population may show heterogeneity of response
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model
Discounting	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate

HRQoL=health related quality of life; QALY=quality adjusted life year

5.4.2 Drummond checklist

Table 27 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	Interim analysis of trial OS data after only 12 months follow-up, and allowing crossover between treatment arms, prevents a direct comparison of survival without crossover adjustment, and reduces discriminatory power
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Yes	-
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	-
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

5.4.3 Description of company's economic model

The company has developed a de novo economic model to allow the comparison of two treatment regimens, pembrolizumab 2mg/kg Q3W and chemotherapy/best supportive care (BSC). A schematic of the company's submitted economic model is provided in the CS and is reproduced in Figure 3. It is a partitioned survival model which comprises three mutually exclusive health states: pre-progression (progression-free survival [PFS]), post-progression and death. All patients enter the model in the pre-progression state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state, i.e. patients in the pre-progression state can move to either the post-progression health state or death health state, whilst patients in the post-progression state can only move to the death health state. Estimates of OS and PFS are based on survival data from the KEYNOTE-002 clinical trial. The proportion of patients in the post-progression state is estimated as the difference between OS and PFS.

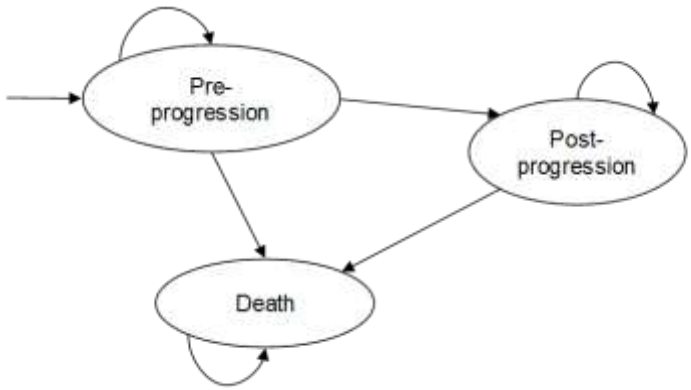

Figure 3 Schematic of company's model
Source: CS, figure 25

Patients receive either pembrolizumab 2mg/kg Q3W or chemotherapy/BSC until progression. The chemotherapy/BSC arm is modelled based on chemotherapy of investigators' choice as observed in the KEYNOTE-002 clinical trial. Treatment switches to subsequent therapies are not modelled. The pre-progression and post-progression health states are associated with specific treatment, resource utilisation and AE costs. Time-to-death sub-states are used to capture patients' HRQoL as a function of length of time until death (<30 days, 30-89 days, 90-179 days and ≥180 days to death).

The model has been developed in Microsoft Excel and employs a cycle length of 1 week (no half-cycle correction). The time horizon is 30 years and health effects are measured in

QALYs. The perspective is that of the NHS and cost and outcomes are discounted at an annual rate of 3.5%.

Variants of the company's model structure have been used in the modelling of metastatic oncology for numerous STAs, including three recent NICE STAs which considered advanced melanoma (TA268,[12] TA269[38] and TA321[14]).

5.4.4 Population

The model parameters used to define baseline patient characteristics have been estimated using a weighted average of values from the control and the pembrolizumab 2mg/kg Q3W arms of the KEYNOTE-002 trial. At baseline, the average patient age is 60 years, 60.7% are male and 44.5% have an ECOG score of 1. Just over 93% of patients have stage IV cancer and, for 82.2% of the patients, cancer has been categorised as being metastatic stage M1c.

5.4.5 Intervention and comparator technology

Pembrolizumab was implemented in the model in line with the anticipated licence and dose, i.e. 2mg/kg Q3W as an IV infusion over 30 minutes.

In the KEYNOTE-002 trial the comparator arm was chemotherapy of investigator's choice which, in the CS, is referred to as BSC. The chemotherapy/BSC components, dose and dosing schedule used in the model are shown in Table 28.

Table 28 Comparator components, dose and dosing schedule

Chemotherapy (dose)	Proportion of patients (%) (KEYNOTE-002)	Administrations*			
		Days between	Period (days)	Length of breaks (days)	Frequency (cycles)
Dacarbazine (1000mg/m2)	26.3	21	Indefinite	-	Q3W
Paclitaxel (175mg/m2)	16.4	7	42	14	Q1W
Paclitaxel (in combination with carboplatin) (175mg/m2)	24.6	7	42	14	Q1W
Carboplatin (AUC=5)	7.6	21	Indefinite	-	Q3W
Temozolomide (1000mg/m2)	25.1	28	Indefinite	-	Q4W

AUC=area under the curve; Q1W=every week; Q3W=every three weeks; Q4W=every for weeks
*TA268[12]
Source: CS, adapted from tables 73, 74 and 75

5.4.6 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. The time horizon is set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[46] both costs and outcomes are discounted at 3.5%.

5.4.7 Treatment effectiveness

It is stated in the CS that the company's modelling approach relies on data from the KEYNOTE-002 trial and, as a consequence, the effect of 'tumour flare', which will lead to longer post-progression survival, has not been incorporated. The company states that this means that their approach to modelling is conservative.

The description contained within the CS as to how trial data have been incorporated into the model is considered by the ERG to be unclear. This summary, therefore, is based on an examination of the company's model.

Progression-free survival

Progression-free survival for patients receiving pembrolizumab 2mg/kg Q3W was modelled using data from the KEYNOTE-002 clinical trial up to 13 weeks, after which PFS was modelled by fitting a Gompertz model. In the chemotherapy/BSC arm KEYNOTE-002 K-M data were used without modification up to 62 weeks, after which all patients were assumed to have died.

Overall survival

For pembrolizumab 2mg/kg Q3W, KEYNOTE-002 trial data were used directly for the first year. The period encompassing year 2 until year 10 was modelled using long-term ipilimumab survival data (reported by Schadendorf et al 2015).[47] For the remainder of the model period (years 11 to 30) Balch et al 2001[48] registry analysis data were used to represent melanoma survival, and background mortality data from the UK Office for National Statistics Life Tables[49] were also applied.

For the chemotherapy/BSC arm, 'uncrossed' KEYNOTE-002 trial data were used for the first year. Thereafter OS was modelled by applying the hazard ratio (0.63) obtained by comparing the simple two-stage (all covariates) crossover adjusted comparator arm data with pembrolizumab 2mg/kg Q3W data over the first year of the trial to the pembrolizumab 2mg/kg Q3W OS projection.

Modelled time-on-treatment for all treatments

Patients are only assumed to receive treatment during the PFS period. Dose adjustments were made to account for those patients who stop taking therapy early due to toxicity. Information presented in the company's model (sheet entitled 'Dosing', cells D74 and D75) shows that it has been assumed that 87.5% of patients in the pembrolizumab 2mg/kg Q3W arm, and 70.8% of patients in the chemotherapy/BSC arm, receive the expected dose. The remaining patients receive no therapy.

5.4.8 Health related quality of life

Health related quality of life data, using the EQ-5D instrument, were collected as part of the KEYNOTE-002 trial at nine time points: baseline (week 0), week 3, week 6, week 12, week 24, week 36, end of chemotherapy/pre-crossover, discontinuation/end of treatment, and safety follow-up (approximately 30 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever came first). Data from the FAS population (second interim analysis data set [May 2014]) were analysed. The proportion of missing EQ-5D data was less than 10%. None of the sites involved in the KEYNOTE-002 trial were based in the UK (48.9% of patients in the pembrolizumab 2mg/kg Q3W group and 54.2% in the control group were treated in US centres). However, the UK time trade off value set[50] was used to calculate utility values.

Analyses showed that there was no statistically significant difference in baseline utilities across the three treatment arms (pembrolizumab 2mg/kg Q3W, pembrolizumab 10mg/kg Q3W and the chemotherapy group). HRQoL was age-adjusted using the utility decrement of

0.0038 that has been calculated by Kind et al.[51] Based on the baseline age of patients included in the KEYNOTE-002 trial, this decrement was applied annually from the age of 60 to 75 to reflect the natural decrease in utility associated with increasing age.

The utility values used in the model are based on time to death rather than disease status (i.e. progression-free or progressed). The company notes that analysis shows that, in terms of mean utility, there is very little difference between the score associated with PFS and that associated with progressed disease (0.74 and 0.68 respectively). The company considered that utility values based on disease status could not adequately capture the decline in HRQoL experienced by patients with advanced melanoma in the final months of life.

Time to death is categorised into the following groups:

- 180 or more days to death
- 90 to 179 days to death
- 30 to 89 days to death
- under 30 days to death.

Patient EQ-5D scores collected during each time category are used to estimate the mean utility associated with that category. In the base case, the analyses for the intervals relating to time to death less than 180 days employed data that were associated with a known death date. However, for the category of 180 or more days to death all patients, including censored patients, were included in the analysis.

Table 29 Mean EQ-5D utility scores by time to death

Time to death (days)	Number of patients	Number of records	Mean EQ-5D score	Standard error	95% CI
	Non-missing EQ-5D index score				
≥180*	225	773	0.78	0.01	0.76 to 0.79
90-179	65	116	0.62	0.03	0.57 to 0.67
30-89	64	84	0.52	0.03	0.45 to 0.58
<30	25	26	0.42	0.07	0.28 to 0.56

*This group also includes patients who did not die within the trial, who may have reported EQ-5D at any time
Source: CS, appendix 20 (table 4)

The company carried out a systematic review to identify studies reporting HRQoL for patients with advanced melanoma. Eleven studies[16,52-61] were identified. The company points out that the published sources seem to report higher values than those estimated using KEYNOTE-002 data and suggests that this may be due to the poorer prognosis of patients included in their trial.

Disutility associated with adverse events

Although detail is not included in the CS, figures in the company's model show that, in the base case, one-off utility decrements have been applied in the first cycle of treatment. The figures have been calculated from the proportion of the cohort in the KEYNOTE-002 trial experiencing an AE and the utility decrement associated with that AE (Beusterien et al[58]). The decrement associated with pembrolizumab 2mg/kg Q3W treatment is -0.00123 and the decrement associated with chemotherapy/BSC is -0.00065.

5.4.9 Resources and costs

Therapy costs

The list price for pembrolizumab 2mg/kg Q3W, pending confirmation from the Department of Health, is £1,315 per 50mg vial. However, the company is offering a patient access scheme (PAS) discount of [redacted] which reduces the cost per 50mg vial to £[redacted]

The drug costs associated with chemotherapy/BSC were based on the level of chemotherapy usage in the comparator arm of the KEYNOTE-002 clinical trial, namely the proportion of patients assumed to be receiving different active therapies and the average dose administered per active treatment. These data were combined with published drug costs (Table 30). The company's base case analysis has assumed no vial sharing.

Table 30: Chemotherapy/BSC drug costs

Treatment	Drug cost (no vial sharing)
Dacarbazine	£58.04
Paclitaxel	£29.24
Carboplatin	£116.21
Paclitaxel (in combination with carboplatin)	£29.24
Interferon alfa-2b	£41.55
Vindesine	£156.60
Temozolomide	£187.98

Source: CS, Table 77

Administration costs

Administration costs have been sourced from NHS Reference Costs 2013/14[62] and are shown in Table 31.

Table 31 Drug administration costs

Treatment	Type of administration (NHS reference costs 2013/2014)[62]	Daycase or outpatient?	Cost
Pembrolizumab 2mg/kg Q3W	Simple chemotherapy (SB12Z)	Daycase	£245.17
Dacarbazine	Complex chemotherapy (SB13Z)	Daycase	£316.95
Paclitaxel	Complex chemotherapy (SB13Z)	Daycase	£325.95*
Paclitaxel (in combination with carboplatin)	Complex chemotherapy (SB13Z)	Daycase	£325.95*
Carboplatin	Complex chemotherapy (SB13Z)	Daycase	£316.95
Temozolomide	Oral chemotherapy	Outpatient (first visit only)	£136.48

*Weighted average to reflect the cost associated with subsequent elements of the chemotherapy cycle of systemic therapies requiring more than one administration per cycle
Source: CS, table 79

Health state unit costs and resource use

Resource use data collected as part of the MELODY study[63] have been used by the company to estimate health state costs. These data have previously been used in a model developed as part of the STA considering the use of ipilimumab for patients with previously treated advanced (unresectable or metastatic) melanoma (TA268).[12] The company notes that although these data are probably out of date they are the most appropriate as no alternative information sources were identified during the search for economic literature. Depending on the health state that patients were in, resource use and frequency were related to outpatient and inpatient care, home care, radiologic exams and terminal care. Full details are presented in appendix 25 of the CS.

Adverse event costs

The company's model includes grade 3 or 4 AEs experienced by more than 3% of patients and those AEs that were considered to be expensive to manage. Incidence data were taken from the KEYNOTE-002 trial. The cost of treating thrombocytopenia was taken from NHS Reference Costs 2013/14[62] and all other costs were values used in the TA319[13] model inflated to 2014 prices (the company did not provide the inflation method used).

Table 32 Adverse event costs

Adverse event	Average cost/patient	Source
Fatigue	£200.79	TA319[13] (inflated to 2014 costs)
Diarrhoea	£491.25	
Nausea and vomiting	£213.49	
Anaemia	£376.61	
Endocrine disorders	£487.17	
Neutropenia	£629.42	
Leukopenia	£0.00	Assumption
Thrombocytopenia	£316.00	NHS Reference Costs 2013/14[62] (Thrombocytopenia daycase SA12K)
Hyponatremia	£0.00	Assumption
Platelet count decreased	£0.00	Assumption

Source: CS, table 80

5.4.10 Model validation

Clinical benefit

The company compared outcomes from the KEYNOTE-002 trial with outcomes generated by their model and found that the percentage of patients who had not progressed at 6 months was similar, albeit slightly higher. The ERG notes that the model employs PFS and OS trial evidence directly for the first 13 weeks and 12 months respectively.

The company points out that their QALY and survival estimates for patients receiving BSC are higher than those generated by the company's model used in the TA268[12] submission (ipilimumab for previously treated [unresectable or metastatic] melanoma).

Expert validation

The company reports that the model approach and inputs have been validated by an external health economist who is a leading expert in health economic practice and methodology development in the UK as well as a member of a NICE ERG. In addition, the accuracy of the implementation and programming of the model was verified via the company's internal quality control processes using an internal quality control checklist.

5.4.11 Results included in company's submission

Predicted (per patient) resource use costs included in the company's model are presented in Table 33.

Table 33 Summary of predicted resource use by category of cost

Cost category	Pembrolizumab 2mg/kg Q3W	BSC	Incremental	Absolute increment	% absolute increment
Treatment	£49,891	£475	£49,417	£49,417	95.86%
Administration	£2,913	£1,795	£1,119	£1,119	2.17%
Pre progression	£1,891	£1,256	£636	£636	1.23%
Post progression	£8,036	£7,934	£102	£102	0.20%
Adverse events	£89	£99	-£10	£10	0.02%
Terminal care	£4,134	£4,403	-£269	£269	0.52%
Total	£66,955	£15,960	£50,995	£51,553	100.00%

BSC=best supportive care
Source: CS, table 87

The incremental cost effectiveness ratio (ICER) generated by the company's economic model is presented in Table 34. The model results show that, when compared to chemotherapy/BSC, use of pembrolizumab 2mg/kg Q3W leads to a lifetime increase in cost to the UK NHS of £50,995 per patient. However, its use offers an additional 1.188 QALYs per patient. The resultant ICER for this comparison is £42,923 per QALY gained.

Table 34 Company base case cost effectiveness results (including PAS)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs baseline (QALYs)
BSC	£15,960	1.07	-	-	-
Pembrolizumab 2mg/kg Q3W	£66,955	2.26	£50,995	1.188	£42,923

ICER=incremental cost effectiveness ratio; LYG= life years gained; PAS=patient access scheme; QALYs=quality adjusted life years
Source: CS, table 82

5.4.12 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out a wide range of deterministic sensitivity analyses. ICERs per QALY gained were generated using the 5% and 95% confidence interval values for the variables (except where indicated otherwise). The ICERs per QALY gained for the ten most influential parameters are shown in Table 35. Three of the four most influential parameters relate to the way in which the Gompertz model is used to estimate PFS. It can also be seen that adjusting the hazard ratio from the two-stage (all covariates) crossover model has a major impact on the size of the ICER per QALY gained.

Table 35 Results from changing the ten most influential parameters

Parameter	Parameter adjustment		Difference in estimate
	Lower	Upper	
PFS Pembrolizumab 2mg/kg Q3W (13weeks+): Gompertz: scale	£125,879.35	£28,592.99	£97,286.36
HR from 2 stage crossover analysis	£31,864.78	£128,080.27	£96,215.49
PFS Pembrolizumab 2mg/kg Q3W (13weeks+): Gompertz: treatment effect	£66,341.31	£30,599.51	£35,741.8
PFS Pembrolizumab 2mg/kg Q3W (13weeks+): Gompertz: shape	£44,277.79	£41,637.43	£2,640.36
Cost: deliver simple parenteral chemotherapy at first (day case)	£41,961.77	£43,884.36	£1,922.59
Time to death utilities: pembrolizumab 2mg/kg Q3W pooled (>180 days)	£44,102.47	£42,356.70	£1,745.77
Pembrolizumab 2mg/kg Q3W: proportion of patients receiving expected dose	£42,089.82	£43,712.43	£1,622.61
Cost: after end of intensive follow-up	£42,357.68	£43,488.45	£1,130.77
Cost: deliver subsequent elements of a chemotherapy cycle (day case)	£43,267.21	£42,578.92	£688.29
Average length of intensive follow-up	£43,201.93	£43,867.29	£665.36

HR=hazard ratio; PFS=progression-free survival
Source: Company's model

Scenario analyses

A wide range of scenario analyses were undertaken to assess the structural and methodological assumptions implemented in the model. The scenarios that had the most influence on the ICER per QALY gained (±>£5,000) are shown in Table 36. Thirteen scenarios are shown in this table and ten of them relate to alterations in the way in which either PFS or OS is modelled.

Table 36 Scenario analyses that change the ICER per QALY gained by at least £5,000

Parameter	Base case	Sensitivity analysis	ICER per QALY gained	Difference from base case
Base case	N/A	N/A	£42,923	N/A
Scenarios that increase the base case ICER per QALY gained by >£5,000				
Time horizon	30 years	10 years	£58,086	+£15,163
Source of utility estimates	Time to death utilities from KEYNOTE-002	Utilities based on pre and post progression KEYNOTE-002 data pooled over 2 arms	£48,056	+£5,133
Crossover adjustment	Two stage approach with full covariate adjustment	IPCW approach	£47,991	+£5,068
Overall survival	Three part curve fit (K-M during 1st year, years 2 to 10 use Schadendorf et al 2015[47] data, then Balch et al 2001[48] registry data	Assuming same relative rate of survival as ipilimumab using MDX010-020 data from TA268[12]	£55,813	+£12,890
		Using HR from KEYNOTE-002 two-stage on external data using gp100 data from TA268[12]	£61,664	+£18,741
		Using HR from KEYNOTE-002 two-stage on external data using Korn[43] data	£67,713	+£24,790
PFS curve fit	Gompertz	Curve fit to K-M data – Lognormal	£61,492	+£18,569
		Curve fit to K-M data – Log-logistic	£68,078	+£25,155
Scenarios that decrease the base case ICER per QALY gained by >£5,000				
Vial sharing allowed	No	Yes	£37,208	-£5,715
Data set used for comparator arm	Chemotherapy arm from KEYNOTE-002 clinical trial	Korn[43] dataset	£33,681	-£9,242
		Gp100 data from TA268[12]	£33,424	-£9,449
PFS curve fit	Gompertz	Curve fit to K-M data Exponential	£33,357	-£9,566
		Curve fit to K-M data Weibull	£35,667	-£7,256

HR=hazard ratio; ICER=incremental cost effectiveness ratio; ICPW=inverse probability of censoring weighted; K-M=Kaplan Meier data; N/A=not applicable; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, table 90

Probabilistic sensitivity analyses

The company undertook probabilistic sensitivity analysis (PSA) to derive the mean ICERs per QALY gained for pembrolizumab 2mg/kg Q3W vs BSC. PSA was carried out using 1000 iterations of the cost effectiveness model.

The cost effectiveness plane and cost effectiveness acceptability curve (CEAC) for this comparison are shown in Figure 4 and Figure 5 respectively.

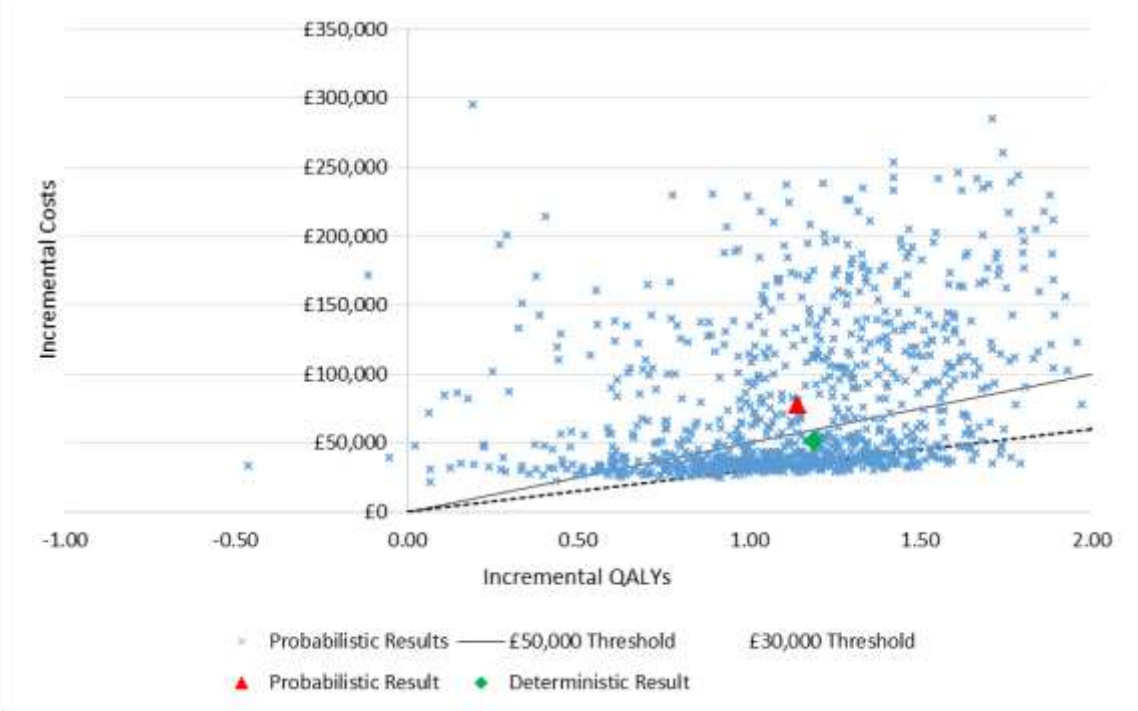

Figure 4 Scatterplot of PSA results (1000 simulations, with PAS)

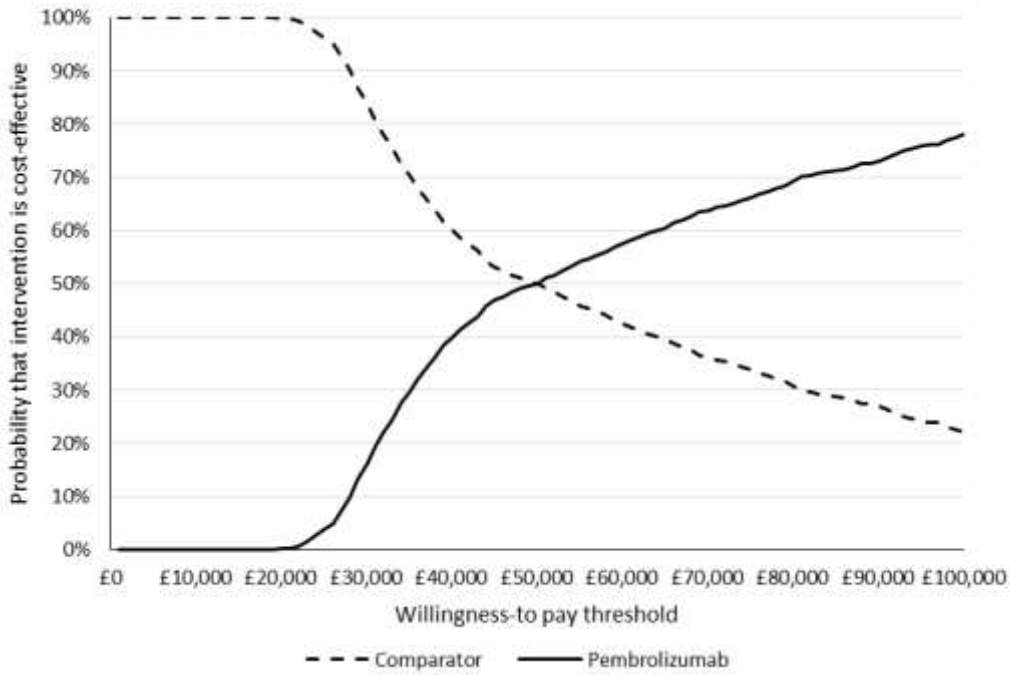

Figure 5 Cost effectiveness acceptability curve

The PSA results show that, compared with BSC, the probability of pembrolizumab 2mg/kg Q3W being cost effective is approximately 50% at a threshold of £50,000 per QALY gained. The probabilistic ICER for pembrolizumab 2mg/kg Q3W vs BSC is £67,615 per QALY gained, which is £24,692 more than the corresponding deterministic ICER (£42,923 per QALY gained). The company explains that this is due to the uncertainty in the relatively

short-term PFS data from the KEYNOTE-002 clinical trial which means that in some samples a substantial proportion of patients are being treated for 20 years or more. The company considers such a scenario to be unrealistic and notes that the KEYNOTE-006[34] trial protocol states that patients should be treated until they have completed 24 months of treatment with pembrolizumab. On the basis of this protocol, revised cost effectiveness estimates were generated assuming that patients in the PFS state would stop treatment after 2 years. This results in deterministic and probabilistic cost effectiveness estimates that are similar, with the deterministic ICER per QALY gained for the comparison of pembrolizumab 2mg/kg Q3W and BSC being approximately £10,000 less than the base case estimate (see Table 37).

Table 37 Cost effectiveness results assuming patients in the progression-free state stop treatment with pembrolizumab 2mg/kg Q3W after 2 years

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs baseline (QALYs)
Deterministic results					
Chemotherapy/BSC	£15,960	1.07			
Pembrolizumab 2mg/kg Q3W	£53,698	2.26	£37,738	1.188	£31,764
Probabilistic results					
Chemotherapy/BSC	£15,497	1.14			
Pembrolizumab 2mg/kg Q3W	£54,020	2.28	£38,523	1.138	£33,841

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, table 89

The results from the PSA analysis that assumes that patients in the PFS state stop treatment with pembrolizumab 2mg/kg Q3W after 2 years show that the probability of pembrolizumab 2mg/kg Q3W being cost effective is 87% at a threshold of £50,000 per QALY gained.

5.5 Detailed critique of the company's economic model

5.5.1 Overview

In order to explore the strengths and weaknesses of the decision model submitted by the company, it is helpful to consider which aspects of the model contribute most to the estimate of cost effectiveness (as measured by the ICER) of pembrolizumab 2mg/kg Q3W therapy compared to chemotherapy/BSC.

An analysis of the base case model results reported in the CS shows that 99.1% of the overall incremental cost is attributable to differences in direct treatment costs (drug acquisition and administration). This means that only variations in the assumed NHS price of

pembrolizumab 2mg/kg Q3W can have any meaningful effect on the estimated incremental cost per patient. The effective NHS price of a new product is determined by the company, either by its list price or through a PAS agreed with the Department of Health. The remit of the ERG only extends to checking that the dosing costs have been accurately calculated. In this appraisal all other cost elements included in the model have no real effect on the size of the ICER per QALY gained.

Therefore, the major aspect of the model to be considered relates to the patient benefit claimed by the company as a result of treating patients with pembrolizumab 2mg/kg Q3W rather than conventional therapies utilised in the control (chemotherapy/BSC) arm, expressed in terms of additional survival time (OS) and QALYs. In the company's base case analysis 72% of this estimated health gain occurs after confirmed disease progression, mainly in the extended projection period (years 2 to 30), beyond the currently available follow-up data from the KEYNOTE-002 clinical trial. Thus, the most important element of the company's model is the long-term projection of interim clinical trial survival results to obtain an expected remaining lifetime for the trial population. Since 28% of the estimated health gain is attributed to the pre-progression phase of the KEYNOTE-002 trial, the analysis of these data constitutes the second key element of the submitted model worthy of close attention.

5.5.2 Progression-free survival

Figure 6 shows the KEYNOTE-002 PFS data used to populate the company's model. In the pembrolizumab 2mg/kg Q3W arm, K-M trial data are used directly until week 13 (91 days), and thereafter a Gompertz model is applied to project PFS indefinitely. In the chemotherapy/BSC arm, the trial K-M data are used directly until the final date when any patient was observed to be still progression-free (62 weeks), at which point all remaining patients are presumed to die or to suffer disease progression immediately.

The ERG has tested the use of simple exponential projective models from 90 days in both arms and obtained good results. In particular, the more parsimonious exponential approach (one less model parameter) achieves a slightly better fit to the pembrolizumab 2mg/kg Q3W data than the Gompertz function. Furthermore, the mean and maximum residuals are also smaller. The Gompertz model tends to over-estimate PFS in the long-term, whereas truncating the chemotherapy/BSC arm without any projection under-estimates PFS in the chemotherapy/BSC arm. Therefore, the incremental gain in PFS attributable to pembrolizumab 2mg/kg Q3W when projected in the long-term is exaggerated by about 30%.

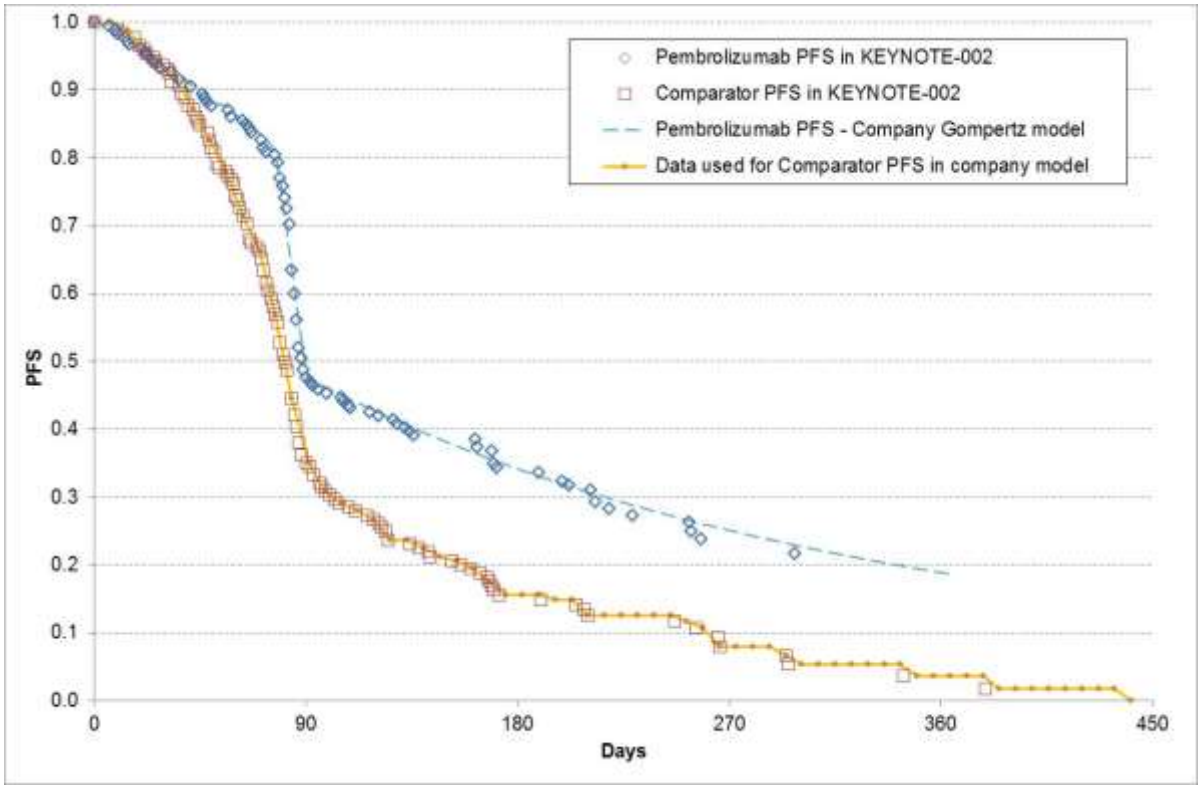

Figure 6 Progression-free survival data used in company's model, and K-M data from KEYNOTE-002 trial

The ERG requested detailed K-M PFS results from the KEYNOTE-002 trial based on assessment by INV (which is more representative of clinical practice than independent assessment by IRO) and using an alternative non-informative right-censoring rule to avoid biasing PFS estimates. Exponential projective models were fitted successfully to both arms (Figure 7), and indicate that the risk of disease progression is reduced substantially in the long-term in the pembrolizumab 2mg/kg Q3W arm ([redacted]).

Over the remaining lifetime of patients, the ERG estimates a net extended PFS benefit of 127 days (4.18 months) attributable to pembrolizumab 2mg/kg Q3W compared to 5.35 months in the company base case.

[redacted]

Figure 7 Progression-free survival data (investigator assessment) using revised censoring, with exponential projection functions fitted to both KEYNOTE-002 trial arms for estimating PFS beyond 90 days

5.5.3 Overall survival

The company's model estimates OS in three time phases, based on three separate data sources (Figure 8 and Figure 9). The assumptions underlying each segment require justification, and the methods used in their implementation require careful consideration.

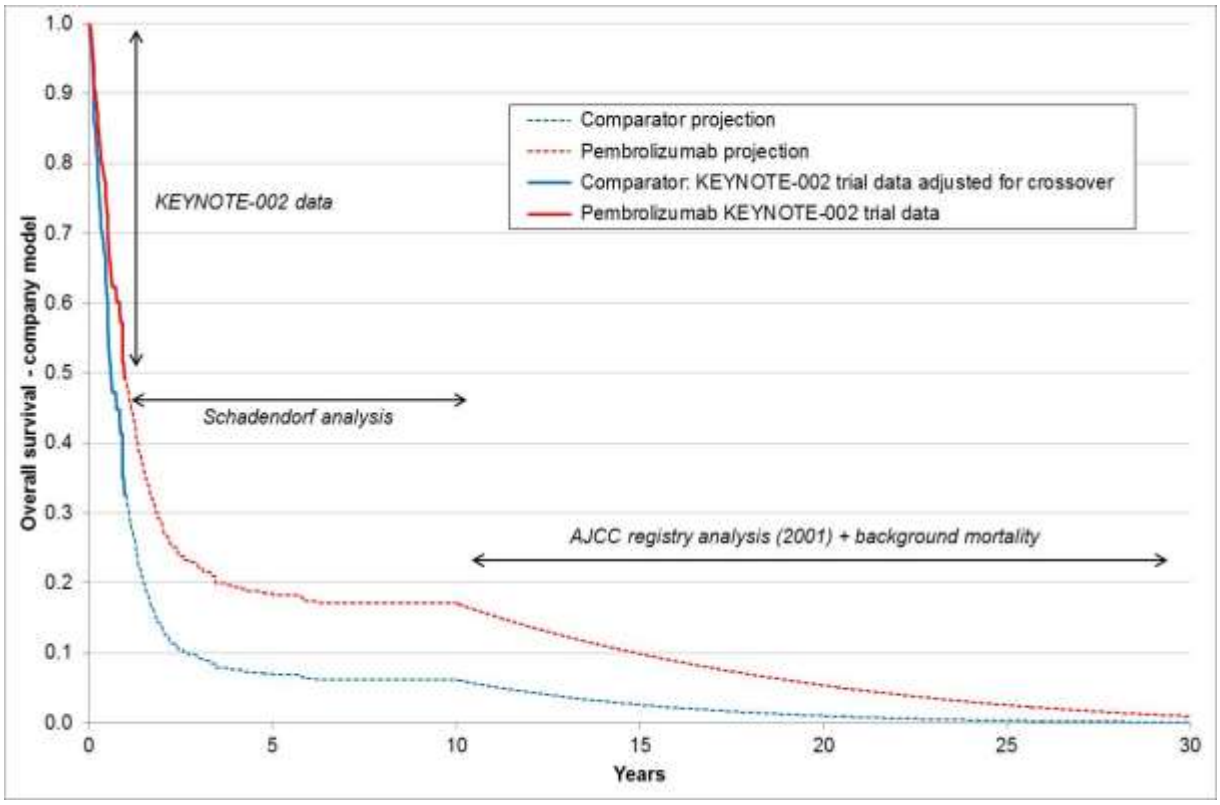

Figure 8 Overall survival data in company's model base case, based on three time phases from three separate data sources

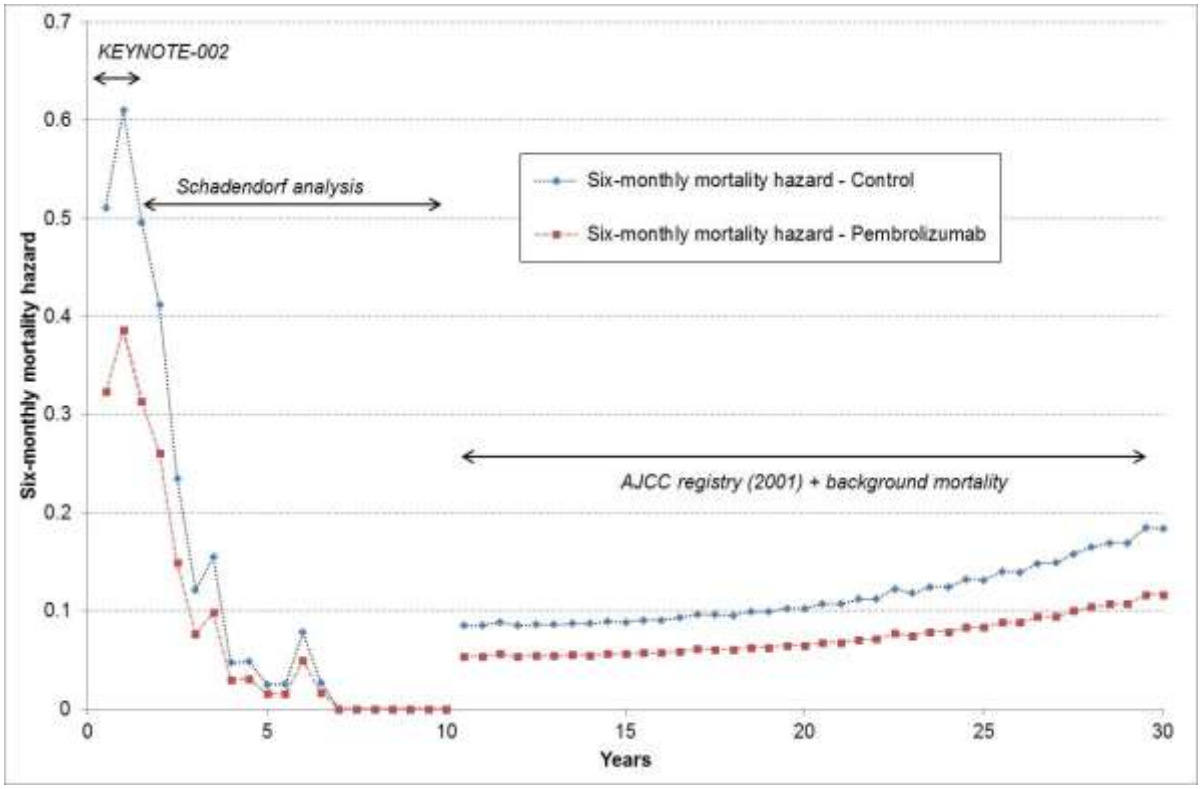

Figure 9 Six-monthly mortality in the company's model base case

Trial period: KEYNOTE-002 Interim analysis (0 to 12 months)

In the company's model, KEYNOTE-002 OS K-M data are used at weekly time points to populate the pembrolizumab 2mg/kg Q3W arm, indicating an estimated mean survival within the first year of 8.83 months (compared with 8.88 months for the more accurate daily K-M data).

In the base case analysis, the comparator KEYNOTE-002 K-M data are used for the first 12 months after adjustment of the trial chemotherapy/BSC arm by the 2-stage full covariates method for crossover correction. This has the effect of producing an important separation between the two trial arms in favour of pembrolizumab 2mg/kg Q3W. The health gain associated with crossover adjustment in the first year of the model is modest. However, the differential in OS established by the end of the first year is propagated through the rest of the model, accumulating a much larger estimated survival gain over 30 years.

The ERG carried out a simple comparison of the mortality risk profiles of patients in the pembrolizumab 2mg/kg Q3W arm of the KEYNOTE-002 trial with those receiving pembrolizumab after crossover from the chemotherapy/BSC arm. This suggested that a similar beneficial effect from use of pembrolizumab occurs in both patient groups, indicating that correction for crossover is probably justified.

Mid-term projection: (12 months to 10 years)

The company's model depends crucially on a single pooled analysis of selected arms from ten phase II and phase III clinical trials together with two retrospective observational studies reported by Schadendorf et al 2015,[47] relating to a variety of treatment protocols which all include the use of ipilimumab. Data were derived by digitisation of the 'previously treated' OS curve in figure 2 of that paper, extending for nearly 10 years. The use made of these data within the company's model involves strong assumptions:

1. The Schadendorf et al 2015[47] mortality trend is used directly in the model to create an OS profile for the pembrolizumab 2mg/kg Q3W treated arm. The chemotherapy/BSC arm is then generated by applying a hazard ratio to the corresponding pembrolizumab 2mg/kg Q3W arm values. This method is used for the whole period from 12 months to 30 years. This is the **strongest possible assumption** of persistent survival benefit since no account is taken of the diminishing number of patients remaining progression-free, and the reduction in the number of patients who may benefit from pembrolizumab 2mg/kg Q3W as increasing numbers discontinue treatment. The ERG estimates that after 4 years all patients will have died or progressed, and none will remain on treatment, yet it is assumed that all surviving patients continue to receive additional benefit every subsequent year from the same reduction in mortality risk relative to patients in the chemotherapy/BSC arm as was seen in the first year of the clinical trial.

2. Examination of the OS trends over 30 years in the company's base case scenario (Figure 10 and Figure 11) indicates that in both arms there is a period from 6 to 10 years when no deaths occur at all from any cause. This would be remarkable in a fully healthy cohort but is completely implausible in patients whose metastatic disease has progressed after multiple phases of treatment.

   This anomaly has arisen from a flawed interpretation of the Schadendorf et al 2015[47] data. As in all right-censored K-M analyses, the number of patients still at risk falls rapidly in the tail of the analysis so that deaths recorded become increasingly rare, resulting in an extended period when no events are observed at all. This 'plateau' does not indicate that the risk of further events no longer exists, but only that the diminished remnant of the population still under observation is too small to allow detection of events even though a real risk of death still exists.

Figure 10 and Figure 11 indicate clearly that a steady long-term mortality trend exists for 3 years prior to the last recorded event (at 77 months) and is consistent with a continuing simple fixed mortality rate of 5.4% per year (i.e. an exponential risk function). This is an instance of the adage that “absence of evidence is not evidence of absence”.

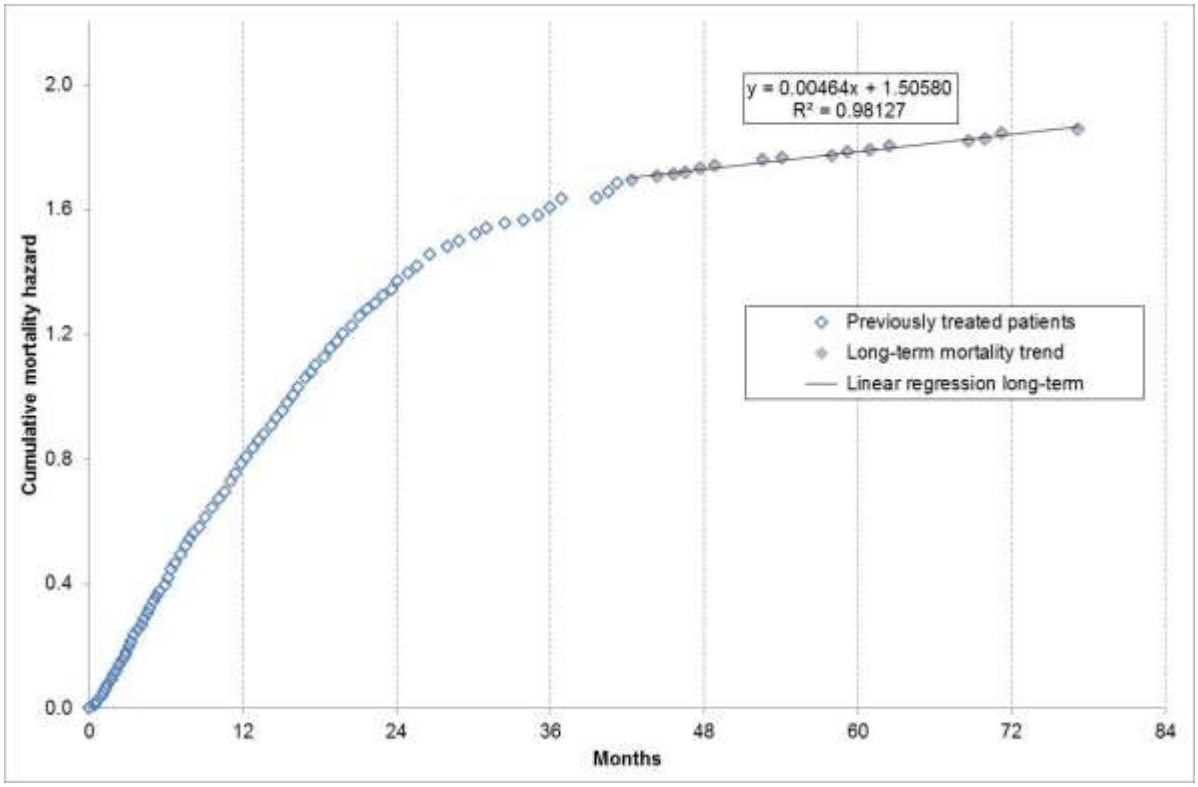

Figure 10 Cumulative mortality hazard from Schadendorf et al 2015 pooled analysis of 10 ipilimumab clinical trials and 2 retrospective observational studies

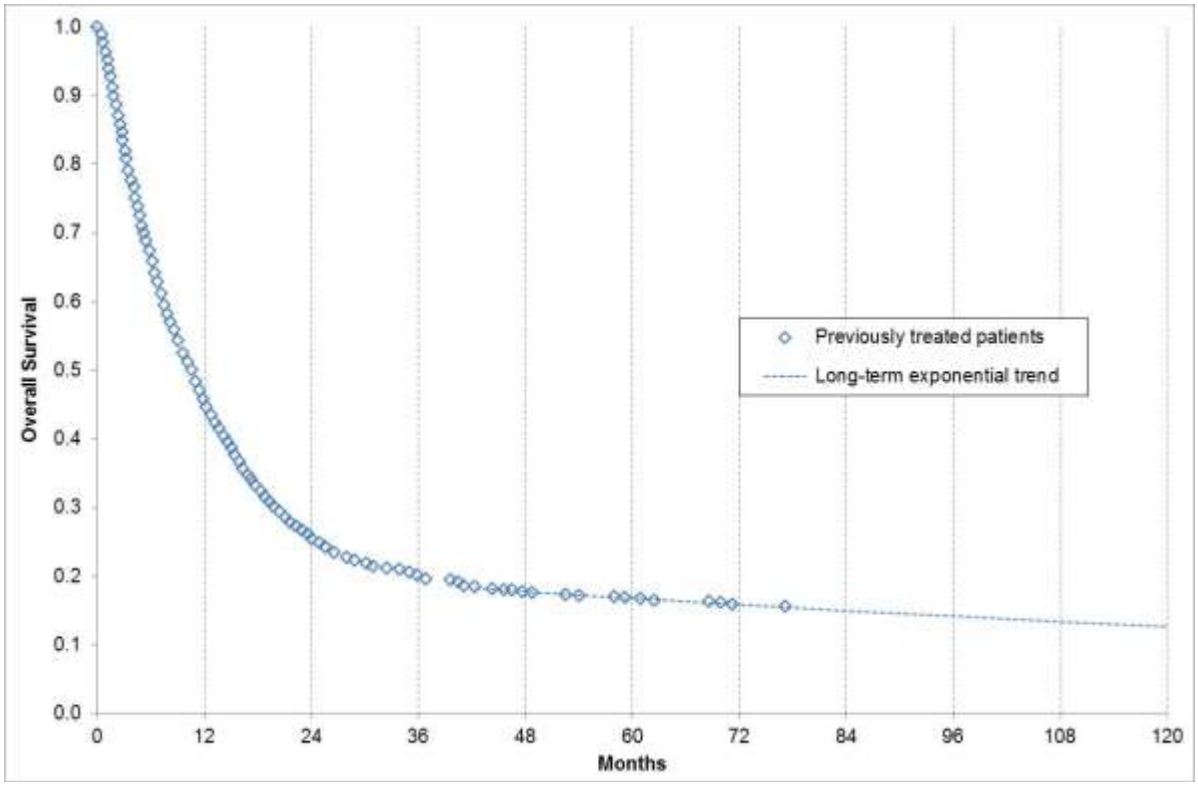

Figure 11 OS from Schadendorf et al 2015 pooled analysis of 10 ipilimumab clinical trials and 2 retrospective observational studies, with exponential long-term projection

3. The use made by the company of the results from the Schadendorf et al 2015[47] analysis assumes that the multiple heterogeneity evident in the pooled studies (different ipilimumab dosing, various co-medications, use of retreatment and/or maintenance therapy, trial or retrospective observation) has no influence on long-term survival. Examination of the cited references in the Schadendorf et al 2015[47] paper reveals that for the subgroup of patients used to populate the company's model ('previously treated') the reported follow-up is generally 3 years or less, and the maximum follow-up time is 4 years and 7 months (one study). It therefore appears that additional follow-up information must have been obtained from some of these studies. The figure 2 in the Schadendorf et al 2015 paper[47] (used to calibrate the company's model) shows 15 patients still alive after 8 years and the last patient is reported as censored at 10 years. Clearly there is a large risk of uncontrolled selection bias in the conduct of this study which would disproportionately affect estimation of long-term survival.

Long-term projection: (10 to 30 years)

In the company's model the same melanoma-specific mortality rates are applied to surviving patients in both the pembrolizumab 2mg/kg Q3W and chemotherapy/BSC arms. These rates are derived from a paper (Balch et al 2001[48]) describing an analysis undertaken on a large

US database of melanoma patients which formed the basis for melanoma staging in the sixth edition of the AJCC Cancer Staging Manual.[64] However, this exercise was subsequently updated and new findings were published in 2009[4] as the basis for an improved classification of melanoma staging in the seventh edition of the AJCC Cancer Staging Manual.[65] The new analysis is based on more than twice as many patients (38,898 compared with 17,600 previously), and included data for 7972 patients with stage IV disease compared to only 1158 in the previous exercise, so that for the first time 10-year survival curves could be estimated separately for the stage IV subgroups (M1a, M1b, M1c).

There are several problems with the use made of the Balch et al[47] 2001 analysis used in the company's model:

- The average life expectancy of a cohort of patients diagnosed with metastatic melanoma is now known to be significantly influenced by the subgroup casemix, which is only captured by the new analysis (Balch et al 2009[4])
- Both analyses are based on patients diagnosed and treated prior to the first approval by NICE of ipilimumab in 2011,[11] and therefore relate solely to the era of therapies which are widely considered to have little effect on survival. By contrast, all patients in the KEYNOTE-002 trial had been previously treated with ipilimumab and found to be refractory. Therefore, the Balch et al 2001[47] analyses apply to a distinctly different population from that recruited to either arm of the KEYNOTE-002 trial.

The registry data analysed in the two Balch et al studies[4,47] measure survival from the time of diagnosis, whereas patients in the KEYNOTE-002 trial had all been pre-treated with various drugs, including some receiving more than five prior types of treatment. Since it is well understood that a large proportion of newly diagnosed metastatic melanoma patients die within a few months of diagnosis, those who survived to enter the KEYNOTE-002 trial are likely to be drawn from a minority of 'good survivors' compared with others diagnosed at the same time point. Even if this problem could be overcome by selecting a later point on the Balch et al 2001[47] survival curve to introduce the Balch et al 2001[47] trends for survival projection, this would still depend upon being able to characterise the time since diagnosis for all patients in the KEYNOTE-002 trial.

Projection implausibility

Examination of the company's base case projected OS profile (Figure 8) and the corresponding changes in 6-monthly hazard rates (Figure 9) highlights two major implementation problems identified by the ERG:

- The mid-term projection phase involves a long period in which no patients die

- Between the end of phase 2 and the beginning of phase 3 the mortality increases instantly from zero to higher (and increasing) non-zero levels (Figure 9).

On both counts this method of projecting survival is implausible. In the real world hazard functions for a cohort of patients change slowly over time unless there is a clear clinical reason for a sudden alteration affecting all patients at the same time (usually required by the trial protocol). In this instance the 10 year time point for a sudden change has no valid clinical explanation attributable to either of the two secondary sources.[4,47] Moreover the extended zero-risk period between 6 and 10 years has the effect of artificially extending the survival advantage for pembrolizumab 2mg/kg Q3W established after 6 years, thus reducing the estimated ICER per QALY gained.

The ERG carried out a sensitivity analysis in which the zero-risk feature was removed by advancing the time point at which the long-term trend is introduced (i.e. at 6.2 rather than 10 years). This has the effect of reducing the estimated incremental discounted QALYs gained associated with use of pembrolizumab 2mg/kg Q3W by 13.9% and increasing the base case ICER to over £50,000 per QALY gained. However, this does not resolve a more fundamental question – whether the three data sources (KEYNOTE-002, Schadendorf et al 2015[47] analysis and the Balch et al 2001[47] analysis) are compatible, and can provide a reliable basis for estimating life-time survival.

Indefinite mortality advantage

The long-term mortality hazard trends in Figure 9 indicate that mortality risk increases in both arms of the model indefinitely in a simple ratio. This is anomalous on two counts:

- It implies that a long-term survival benefit continues to accrue for pembrolizumab 2mg/kg Q3W treated patients despite the reduction over time in the proportion of surviving patients still estimated to be receiving treatment
- It is also applied to mortality from other causes, which should be independent of cancer therapy and increase at the same rate in both arms in accord with increasing mortality in the general population with age.

This exposes a fundamental flaw in the model design. A long-term time trend for OS is estimated for the pembrolizumab 2mg/kg Q3W arm based on the first 12 months of trial data, extended by the Schadendorf et al 2015[47] trend to 10 years, and finally the Balch et al 2001[47] 10 year trend is used to extend survival projection by a further 20 years. Then the pembrolizumab 2mg/kg Q3W OS estimate is revalued and used to represent the chemotherapy/BSC arm. The revision is made by applying the estimated crossover-adjusted

hazard ratio from the interim analysis of KEYNOTE-002 trial data at 12 months. This revaluation continues to be applied for the whole period of the model from 12 months to 30 years without any recognition that the proportion of surviving patients still receiving pembrolizumab 2mg/kg Q3W in the company's model falls steadily from 38.7% at 12 months to less than 4.4% at 10 years. The implication is that a limited initial OS advantage is expected to provide substantial life-long additional protection from all causes of death despite most patients discontinuing pembrolizumab 2mg/kg Q3W up to 20 years earlier. The ERG considers this to be unrealistic.

As a sensitivity analysis the ERG has modified the company's model beyond 10 years, to constrain both arms to be subject to the same mortality rates. This has the effect of reducing the estimated survival gain for pembrolizumab 2mg/kg Q3W by about 5%, and thereby increasing the deterministic ICER by £1,940 per QALY gained.

The company's alternative methods for estimating overall survival

All four methods proposed by the company for estimating OS employ the Schadendorf et al[47] analysis and/or the Balch et al 2001[47] analysis, both of which have been found by the ERG to be flawed. In table 90 of the CS, three of the four alternative scenarios considered yielded ICERs more than £10,000 per QALY gained greater than the company's base case. The fourth scenario used both Schadendorf et al[47] and Balch et al 2001[47] and reduced the base case ICER by only £2,000 per QALY gained. The ERG therefore concentrated attention on the company's base case extrapolation method, as each of the alternative scenarios are similarly compromised.

5.5.4 Costs

Acquisition cost of systemic treatment per dose

Pembrolizumab is prescribed for infusion as 2mg/kg of body weight for each dose. The distribution of body weight among patients in the KEYNOTE-002 trial is used to estimate the required doses by dividing patients into weight bands corresponding to whole numbers of vials required. This method should give an accurate result provided that the number of patients is sufficiently large that the balance between bands in the trial approximates closely to that of the general melanoma population. However, body weight can vary widely between different countries. For this reason the ERG re-estimated costs, based on UK values reported from the Health Survey for England (HSE) 2012[66] (82.5kg for males and 69.5kg for females), and using a log-normal distribution for body weight. This approach results in a small increase in the cost per dose of 0.25% when no vial sharing is assumed.

Other systemic treatments given to patients in the chemotherapy/BSC arm are prescribed relative to a patient's body surface area (BSA). In the company's model a single average BSA value is used for all patients (males and females) so that no account is taken of the variation of BSA within the population, nor is a method used to optimise the overall cost of treatment by using the least expensive combination of vial sizes available.

The ERG has re-estimated the overall average cost per dose for each available treatment (dacarbazine 850mg/m^2, dacarbazine 1000mg/m^2 paclitaxel 175mg/m^2 and temozolomide 1000mg/m^2) based on separate male and female dose banding and using a normal distribution to describe the variation in BSA. Dacarbazine is assumed in the company's model to be prescribed for infusion as 1000mg/m^2 doses. However, the ERG has examined several local NHS* treatment protocols for dacarbazine, and found approximately equal numbers of sites using two regimens (850mg/m^2 and 1000mg/m^2). In addition, the KEYNOTE-002 trial protocol specifies temozolomide dosing as 200mg/m^2. Table 38 summarises the ERG estimated acquisition costs, compared with those used in the company's model.

Table 38 Estimated cost per dose of systemic therapy

Regimen	ERG estimate	Company's model	ERG estimate	Company's model
	No vial sharing	No vial sharing	Full vial sharing	Full vial sharing
Dacarbazine 850mg/ m^2	£40.90	-	£40.36	-
Dacarbazine 1000mg/ m^2	£47.76	£58.04	£47.22	£40.93
Paclitaxel 175mg/m^2	£34.14	£29.24	£33.46	£24.44
Temozolomide 1000mg/ m^2 (optimum)	£141.62	£187.98	N/A#	N/A#
Temozolomide 1000mg/ m^2 (realistic)	£143.18	£187.98	N/A#	N/A#
Temozolomide 200mg/ m^2	£39.09	N/A#	N/A#	N/A#

N/A not applicable (oral medication)
company's model assumes 1000mg/m^2 dose but KEYNOTE-002 uses 200mg/m^2 dose

Applying the various ERG revised dosing cost only affects the cost of treatment in the chemotherapy/BSC arm and the effects are very modest.

It should also be noted that there are multiple coding errors in the company's model which relate to scenarios in which chemotherapy/BSC is chosen as the treatment option for

* East Midlands Cancer Network (Oct 2014); Lancashire & South Cumbria Cancer Network (Nov 2012); Royal Surrey County Hospital (Oct 2014); Thames Valley Cancer Network (Mar 2015); Derby-Burton Local Cancer Network (Mar 2015); Clatterbridge Cancer centre (May 2015); South East London Cancer Network (July 2009); Betsi Cadwaladr University Health Board (June 2013)

comparator patients, and also for the use of a 1000mg/m^2 dose for temozolomide, rather than the 200mg/m^2 used in the KEYNOTE-002 trial.

Administration cost of systemic treatment per dose

In the company's model the cost of administration of systemic treatment is classified according to Healthcare Resource Group (HRG) categories. The ERG has taken advice on the correct costing category for each treatment, and found that in four cases the company's model incorrectly assigns a more expensive HRG (complex chemotherapy) where a cheaper code is routinely used (simple chemotherapy) in practice. When the ERG revised these codes the cost of treatment in the chemotherapy/BSC arm reduced slightly, and the estimated ICER increased by £84 per QALY gained.

Duration of dacarbazine treatment

In the company's model dacarbazine treatment is assumed to continue until disease progression occurs. However, clinical advice indicates that in UK practice a maximum of six cycles of treatment is normally applied. Modifying the company's model to apply this limit decreases the cost of care in the chemotherapy/BSC arm and thereby increases the estimated ICER by £89 per QALY gained.

Duration of pembrolizumab treatment

The company's model uses estimated PFS as the basis for costing drug treatment in both arms. However, in practice this is normally an over-estimate as patients frequently withdraw from treatment as a result of emergent AEs before any disease progression is identified. The company's model applies single average proportional adjustments for this effect. The ERG asked the company to provide results from a K-M analysis of time to treatment discontinuation in the pembrolizumab 2mg/kg Q3W arm of the KEYNOTE-002 trial. Figure 12 indicates the differences between PFS and time on treatment during the trial, and shows an exponential trend fitted to the treatment data.

[redacted]

Figure 12 Time to pembrolizumab treatment discontinuation in KEYNOTE-002 with fitted exponential projection model compared with pembrolizumab PFS

The ERG modified the company's model to use the pembrolizumab 2mg/kg Q3W 'on treatment' data directly in the first year followed by projected estimates thereafter. For the chemotherapy/BSC arm, the pembrolizumab 2mg/kg Q3W values were used after adjustment by the ratio of PFS in the chemotherapy/BSC arm to PFS in the intervention arm

in the KEYNOTE-002 trial at each time point. This alteration has been applied as an alternative to the simple averages used in the submitted model.

This ERG model amendment has a substantial effect on treatment costs, especially for pembrolizumab 2mg/kg Q3W. Compared with the company's base case scenario, the incremental cost is reduced by more than £8,000 per patient, and the ICER is reduced by £7,181 per QALY gained.

Post-progression therapies

The company has assumed that post-progression therapies will only be used for palliative/BSC purposes (having no impact on OS), and will be balanced between the two arms of the trial. The ERG considers this to be a reasonable assumption since these patients have been heavily pre-treated with ipilimumab and various chemotherapy agents (77% of patients in the pembrolizumab 2mg/kg Q3W arm of the KEYNOTE-002 trial had two or more previous lines of therapy, and [redacted] had five or more lines of therapy). Following progression, it is very unlikely that further treatment for patients randomised to either the pembrolizumab 2mg/kg Q3W or the chemotherapy/BSC trial arms will differ.

5.5.5 Source of utility values

In the company base case the main utility parameters are drawn from EQ-5D responses in the KEYNOTE-002 trial scored according to the UK value set. However, in international trials it is often the case that patient responses to theEQ-5D questionnaire differ significantly. The ERG requested a breakdown of utility scores between US and non-US patients, which shows clearly that in the US subgroup EQ-5D responses are generally more optimistic. The company has acknowledged that this is a relevant issue and included a sensitivity analysis in their response to clarification questions. The ERG has made an appropriate amendment to the model which shows that using non-US utility data reduces incremental QALYs by 6.6% and increases the estimated ICER by £3,037 per QALY gained.

5.5.6 Life table mortality rates

The company's model uses published annual Life Table estimates[49] for England and Wales to represent other causes of death in long-term survival projections (10-30 years). Separate mortality rates for males and females are weighted for the gender balance in the KEYNOTE-002 trial for each year of age from 50 to 100. This approach is flawed because mortality is systematically lower for females than for males so that over time the gender balance shifts in favour of females. Without making allowance for this drift leads to an over-estimate of mortality in the cohort as a whole. The ERG has calculated representative mortality rates

using dynamic weighting, which when applied in the model increases the incremental survival and QALYs by less than 1%, and reduces the estimated ICER by £25/QALY.

5.5.7 Utility estimation

The company model offers two options for estimating health-related utility. The base case results are based on a method which calculates utility in relation to a set of short time periods preceding death, which capture the known decline in quality of life during the terminal phase of disease. The alternative option uses simple averages for patients classified as either progression-free or post-progression following pembrolizumab 2mg/kg Q3W treatment. However, these options are not mutually exclusive, but complementary since patients suffer from both progression-related disutility and terminal disutility. Applying the alternative progression-based method reduces the incremental QALYs by 9% and increases the base case ICER from £42,923 per QALY gained to £48,056 per QALY gained. When the ERG then includes a time-to-death disutility as well, the incremental QALYs increase slightly and the ICER is revised to £47,888 per QALY gained.

5.6 Conclusions of the cost effectiveness section

The decision model submitted by the company is structured appropriately, and generally implemented correctly. However, several important issues were identified relating to the approach taken to costing treatment for both pembrolizumab 2mg/kg Q3W and chemotherapy, and also concerning the most relevant utility values to apply to the model. These have all been resolved by the ERG through model amendments.

The main aspect of the company's model with which the ERG disagrees is the method used to project the very limited survival data available from the trial (less than one year follow-up in the KEYNOTE-002 trial). This involves grafting on a trend derived from a pooled analysis of various trials and observational studies, followed by a long-term trend derived from a registry analysis which has since been updated and extended in a later publication[4]. There are serious anomalies apparent in the results of using this approach, rendering it clearly implausible.

Using experience gained from an earlier melanoma appraisal (TA268),[12] the ERG has substituted an alternative projective model for OS (detailed below in Section 6), which resolves these problems in the submitted model. However the net result of applying the full set of model amendments has a limited effect on the overall assessment of cost effectiveness, and is probably insufficient to influence significantly any recommendations arising from this appraisal.

6 ADDITIONAL WORK UNDERTAKEN BY ERG

Details of all revisions made by the ERG to the company's model in Microsoft Excel are presented in Appendix 5.

6.1 Alternative survival paradigm

The ERG finds the company's approach to OS modelling unconvincing in several respects, but most importantly the use of the Schadendorf et al 2015[47] analysis to extend the modest survival gain seen in the first year of the KEYNOTE-002 trial for a further nine years. We also acted as the ERG in the first appraisal of ipilimumab in malignant melanoma in 2011/12 (TA268)[11]. During this appraisal the company submitted additional evidence drawn from seven of the studies later included in the Schadendorf et al 2015[47] analysis. In response, the ERG submitted an addendum[67] which concluded:

> *"The ERG does not consider the pooling of isolated treatment arms across trials to be appropriate….the broader pooling of data from all patients who received ipilimumab, regardless of dosing regimen or patient baseline characteristics, can only result in uninterpretable results of no relevance to the current decision problem."*

The Schadendorf et al 2015[47] paper is an extension of this company analysis including more studies (especially more observational data) and thereby adds further incompatibility into the evidence base. The ERG therefore considers the pooled survival analysis to be inherently compromised and unreliable. Moreover, it is contradictory to use evidence of continuing ipilimumab survival gain from a population which included many patients showing evidence of response to treatment as the basis for estimating future additional benefits in a cohort all of whom were selected as being refractory to ipilimumab treatment.

In the addendum to the TA268[11] ERG report, the ERG pursued the question of long-term melanoma survival in the light of observations from clinical advisors, and considered whether there may be two distinct sub-populations with contrasting prognoses – a large majority subject to high mortality rates and a small minority with excellent survival prospects extending for several years. The survival curves published in support of the seventh AJCC melanoma staging and classification (Balch et al 2009[4]) were used to develop and test an alternative two-group projection model, based on a mixed exponential function. This proved very effective, accurately replicating the published AJCC results[4] (Figure 13), and the results of the MDX010-020[31] trial. The ERG has subsequently validated this approach in other data sets.

In the light of these findings, the ERG has applied this method to generate expected survival profiles matched for casemix (M1a:M1b:M1c) for each arm of the KEYNOTE-002 trial. Then these curves were substituted for both projection phases of the company's model, adjusting the point on the AJCC casemix matched profile to correspond to a common mortality rate in both the KEYNOTE-002 data and the projection model (Figure 14). This avoids the serious problems previously described for the company's model, and can be justified on the grounds that beyond the observed trial period, the great majority of pembrolizumab 2mg/kg Q3W patients cease treatment rapidly due to disease progression or AEs, and future survival will be largely determined by the conventional treatment options current in the AJCC registry era.

The time adjustment required to match the mortality rates when joining the two parts of the curve amounted to about 15 months and give an approximation to the amount of survival advantage that would be expected from using this approach to survival projection. When this method of survival projection is substituted for that in the company's model, the estimated survival gain is reduced by 17%, and the estimated ICER increases by £8,391 per QALY gained.

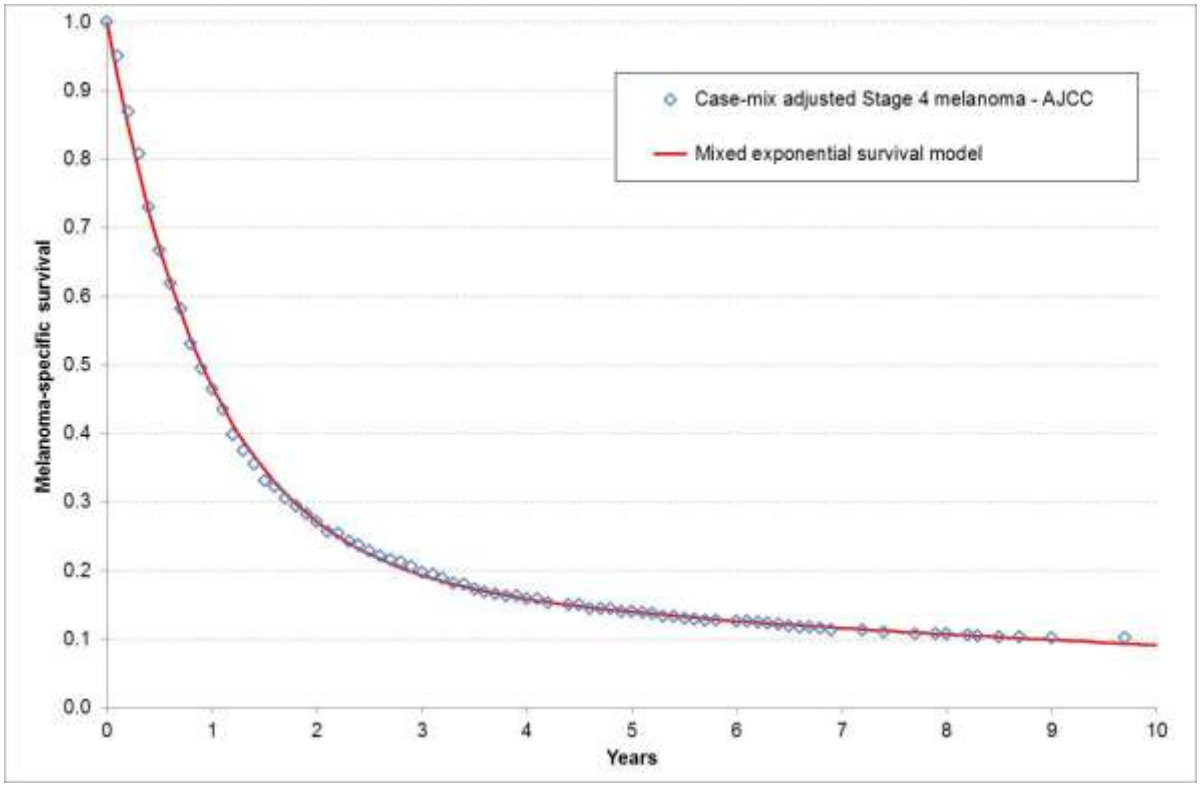

Figure 13 Ten-year survival in stage IV malignant melanoma in the AJCC registry (Balch et al 2009), modelled by mixed exponential function

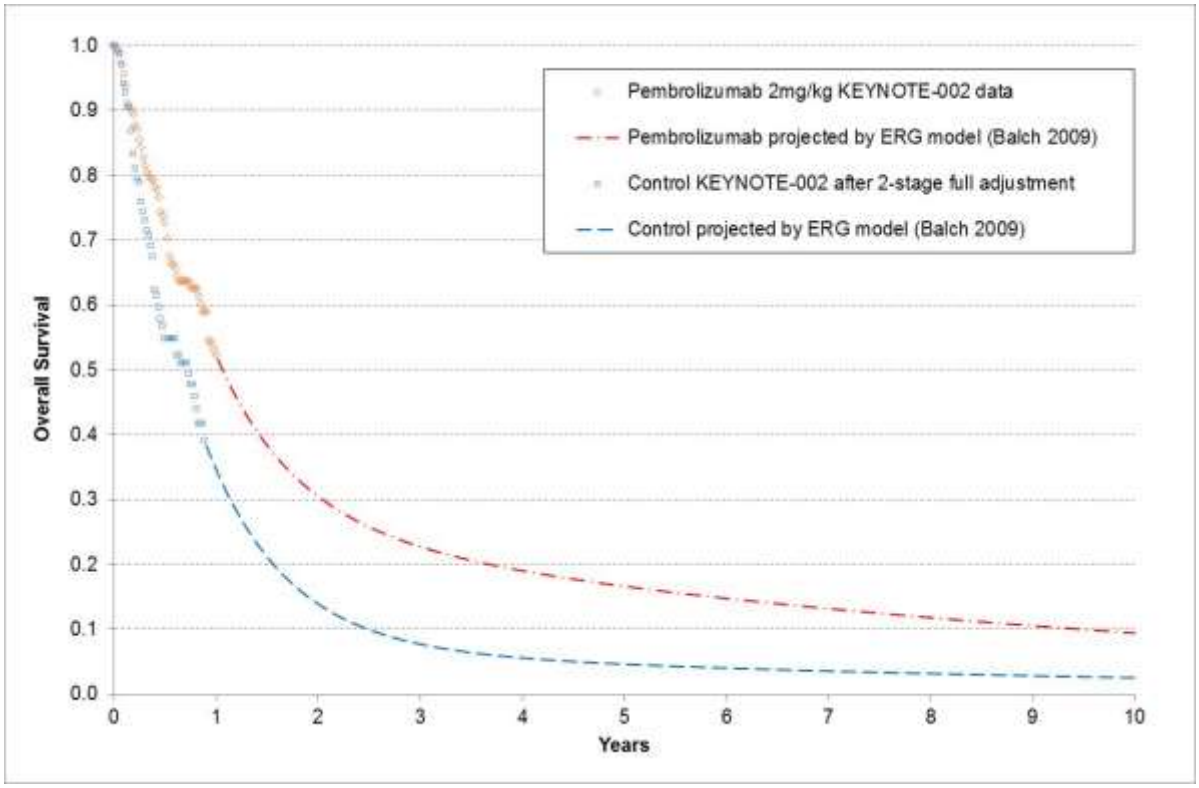

Figure 14 Long-term projection of survival beyond the available KEYNOTE-002 trial data, using a mixed exponential model

6.2 Effects of ERG model amendments on cost effectiveness

Table 39 summarises the various amendments made to the company's model and shows their impact on the ICER per QALY gained for pembrolizumab 2mg/kg Q3W compared with chemotherapy/BSC. Results are presented for two combined scenarios based either on the company's approach to OS projection or on the ERG's alternative method. Although individual amendments cause substantial changes (increase and decreases) in the estimated ICERs, it is noticeable that the net effect in both combined scenarios (B and C) is to increase the estimated ICER by less than £4,000 per QALY gained.

Table 39 Cost effectiveness results for pembrolizumab 2mg/kg Q3W vs chemotherapy/BSC with ERG revisions to company's base-case comparison

Model scenario ERG revision	**Pembrolizumab 2mg/kg Q3W**			**Chemotherapy/BSC**			**Incremental**			**ICER**	**ICER**
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
A. Company's base-case	**£66,955**	**2.262**	**3.912**	**£15,960**	**1.074**	**1.739**	**+ £50,995**	**+ 1.188**	**+ 2.174**	**£42,923**	**-**
R1) ERG Drug costs	£67,079	2.262	3.912	£15,970	1.074	1.739	+ £51,109	+ 1.188	+ 2.174	£43,019	**+ £96**
R2) ERG Admin costs	£66,955	2.262	3.912	£15,860	1.074	1.739	+ £51,095	+ 1.188	+ 2.174	£43,007	**+ £84**
R3) Dacarbazine <=6 cycles	£66,955	2.262	3.912	£16855	1.074	1.739	+ £51,100	+ 1.188	+ 2.174	£43,012	**+ £89**
R4) Life Table recalculation	£66,955	2.263	3.915	£15,960	1.075	1.739	+ £50,995	+ 1.189	+ 2.176	£42,898	**- £ 25**
R5) European utility data	£66,955	2.117	3.912	£15,960	1.008	1.739	+ £50,995	+ 1.110	+ 2.174	£45,960	**+ £3,037**
R6) ERG PFS estimates	£58,745	2.262	3.912	£15,948	1.074	1.739	+ £42,796	+ 1.188	+ 2.174	£36,022	**- £6,901**
R7) Time on treatment costs	£59,325	2.262	3.912	£16,862	1.074	1.739	+ £42,463	+ 1.188	+ 2.174	£35,742	**- £7,181**
R8) Remove no mortality period	£66,662	1.988	3.289	£15,878	0.966	1.508	+ £50,784	+ 1.023	+ 1.781	£49,663	**+ £6,740**
R9) Remove HR advantage after 10 years	£66,955	2.262	3.912	£15,997	1.127	1.879	+ £50,958	+ 1.136	+ 2.033	£44,863	**+ £1,940**
R10) ERG OS model	£66,842	1.903	3.107	£15,942	0.911	1.435	+ £50,900	+ 0.992	+ 1.672	£51,314	**+ £8,391**
R11} Temozolomide dose & costing formula errors	£66,995	2.262	3.912	£15,993	1.074	1.739	+ £50,961	+ 1.188	+ 2.174	£42,895	**- £28**
R12) Apply both utility methods together	£66,995	1.973	3.912	£15,960	0.908	1.739	+ £50,995	+ 1.065	+ 2.174	£47,888	**+ £4,965**
B. Base-case +R1-R9, R11, R12	**£58,036**	**1.736**	**3.292**	**£16,568**	**0.843**	**1.577**	**+ £41,468**	**+ 0.894**	+ 1.716	**£46,409**	**+ £3,486**
C. Base-case +R1-R12	**£58,143**	**1.661**	**3.107**	**£16,635**	**0.772**	**1.435**	**+ £41,508**	**+ 0.890**	**+ 1.672**	**£46,662**	**+ £3,739**

Costs and QALYs discounted; life years undiscounted
ERG=evidence review group; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years

7 END OF LIFE

In section 5.7.2 of the company submission, it is stated that:

> *"This incremental-cost effectiveness ratio (ICER) should be considered in the context of pembrolizumab being an end of life technology that presents an innovative nature."*

The NICE criteria for applying a less restrictive assessment of cost effectiveness for 'end of life' are that:

- The life expectancy of the patient population is short (less than 24 months)
- The number of patients who would be eligible for the treatment is small
- The increase in OS is greater than 3 months.

The company argues that pembrolizumab meets the NICE end of life criteria (table 56 of CS) since:

- Patients with metastatic melanoma have a median survival of up to 9 months
- The patient population is small (approximately 628 in 2015 and approximately 300 annually thereafter);
- In KEYNOTE-002, pembrolizumab 2mg/kg Q3W offers both a mean and median extension to life >3 months (utilising the two-stage model to adjust for median OS).

The undiscounted mean life expectancy of eligible patients in the company's base case analysis is 20.9 months, and 17.2 months in the ERG's preferred scenario (C). (Table 39).

In section 6.2 of the CS, evidence is presented indicating that the number of patients eligible to receive pembrolizumab therapy in England is less than 1,000 per annum.

The undiscounted estimate of mean survival gain per patient attributable to pembrolizumab therapy compared with chemotherapy/BSC is 26.1 months in the company base case analysis, and 20.1 months in the ERG's preferred scenario (C).

These results suggest that pembrolizumab treatment in this population meets the NICE criteria for consideration as an 'end of life' technology.

8 DISCUSSION

8.1 Summary of clinical-effectiveness issues

The KEYNOTE-002 trial is the only RCT available that compares pembrolizumab 2mg/kg Q3W to (investigator choice) chemotherapy. In the NICE scope there are several comparators listed including dacarbazine; dacarbazine is one of the chemotherapy options permitted in the comparator arm of the trial. The KEYNOTE-002 trial is considered to be at low risk of bias and measures efficacy in terms of PFS, OS, AEs and HRQoL, all of which are outcomes that are important to clinicians and patients.

The company focuses on providing clinical evidence to support the use of the 2mg/kg Q3W dose of pembrolizumab as this is the dose for which the drug is anticipated to be licensed. Evidence from KEYNOTE-002 and from the supportive KEYNOTE-001 (Part B2) trial suggest that both the 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab are of equal efficacy. However, the ERG cautions that the number of patients in both of these trials is relatively small and the time period for which the data are available is relatively short. It is therefore difficult to determine conclusively that the two doses of pembrolizumab are of equal efficacy.

Interpretation of the survival data from the KEYNOTE-002 trial is challenging. First, as KEYNOTE-002 is an ongoing trial, OS data are not yet mature and currently only 12-month data are available for scrutiny. Second, in the KEYNOTE-002 trial, nearly half of the patients (48%) in the chemotherapy arm crossed over from chemotherapy to pembrolizumab and crossover was permitted early in the trial (after 12 weeks). To adjust for the effect of crossover on survival estimates, the company utilised a number of different methods (RPSFT, IPCW and two-stage models). The ERG and the company agree that, in this case, the most suitable method to use to adjust for crossover is a two-stage model. Results from the two-stage model (all covariates) show that median OS is statistically significantly improved by 3.5 months over chemotherapy for patients treated with pembrolizumab 2mg/kg Q3W (11.4 months vs 7.9 months). Nevertheless, the ERG urges caution in interpreting these OS findings and considers that, only when more mature OS data become available, will it be possible to determine the true difference in effect between treatments.

Evidence for efficacy was reported for a number of subgroups, including PD-L1 status. Given pembrolizumab is an anti-PD-1 agent and targeting PD-1 or its ligand PD-L1 is considered to be of promising therapeutic benefit,[68,69] outcomes may be expected to differ for patients with PD-L1 positive and negative tumours. Indeed, differences between pembrolizumab 2mg/kg Q3W vs chemotherapy (in terms of PFS, OS and ORR) were greater in patients with PD-L1

positive tumours than in patients with PD-L1 negative tumours. The company and the ERG notes that there were relatively few patients with PD-L1 negative tumours in the KEYNOTE-002 trial and also that there were imbalances in important baseline patient characteristics (BRAF status and LDH) between treatment arms. Furthermore, no statistically significant p-values for interaction were observed for PFS or OS (but were identified for ORR). As highlighted by the company, a treatment effect was observed with pembrolizumab 2mg/kg Q3W in patients with PD-L1 negative status. It remains uncertain, therefore, whether pembrolizumab 2mg/kg Q3W may have a greater effect on patients with positive, rather than negative, PD-L1 tumours.

Patients with BRAF positive melanoma included in the KEYNOTE-002 trial (23%) had all been previously treated with a BRAF or MEK inhibitor. However, it is noted by the company and the ERG that the treatment pathway for metastatic melanoma is evolving; increasingly, the use of BRAF inhibitors tends to be preferred by clinicians only if a rapid response to treatment is required. Therefore, in some instances, clinicians may also prefer to use BRAF inhibitors following treatment with pembrolizumab. There is however currently no available RCT evidence for patients with BRAF positive melanoma who have not been previously treated with a BRAF or MEK inhibitor.

8.2 Summary of cost effectiveness issues

The company submitted a decision model to estimate the cost effectiveness of pembrolizumab 2mg/kg Q3W vs chemotherapy/BSC in terms of incremental cost per QALY gained from the perspective of the NHS. The decision model submitted by the company is structured appropriately, and generally implemented correctly. The ERG notes that variants of the company's model structure have been used in a number of previous NICE STAs (TA268,[12] TA269[38] and TA321[14]).

The ERG implemented 12 corrections/modifications to the company's model. Seven of the changes were related to drug costs, utilities and life table mortality rates. Of these changes, only those related to utility methods (increase of £4,965 per QALY gained) and use of European utility data (increase of £3,037 per QALY gained) have any real impact on the size of the ICER per QALY gained.

The remaining five changes were related to the survival estimates employed in the model. The ERG's modifications led to lower ICERs per QALY gained when ERG PFS estimates were used (-£6,901) and when 'time on treatment' costs were revised (-£7,181). In contrast, ICERs per QALY gained were increased when the hazard ratio advantage (£1,940) and the

assumption of zero mortality (£6,740) were removed. Using the ERG's preferred OS model the ICER per QALY gained increased by £8,391.

Although individual amendments caused substantial changes (increases as well as decreases) to the size of the ICER, the net effect was only to increase the size of the ICER by less than £4,000 per QALY gained. In summary, the company's base case ICER was estimated to be £42,923 per QALY gained and the ERG's revised base case was estimated to be approximately £46,000 per QALY gained.

Whether any of these ICERs per QALY gained are reliable is unclear. Both the company and the ERG survival models had to employ assumptions, which are arguably unreliable, to model 29 years of future survival. Currently, only 12-month survival data are available from the KEYNOTE-002 trial and, as patients in the chemotherapy arm were allowed to cross over to pembrolizumab therapy at 12 weeks, these data are compromised. In particular the ERG noted the following irregularities regarding the company's model:

- The company's approach to modelling OS introduces several aspects that are not clinically supportable or explained by trial protocol, such as a mortality rate of zero from year 6 to year 10 and a large, instantaneous leap in mortality rate at year 10
- In some cases the company used out of date or questionable external data to extrapolate survival beyond the trial period of 12 months
- The company assumed that additional survival benefit continued to accrue for pembrolizumab patients well beyond the treatment period, even if the treatment had been discontinued some 20 years earlier
- Progression-free survival in the pembrolizumab 2mg/kg Q3W arm is over-estimated. The company assumes that PFS continues indefinitely due to extrapolation, whereas all patients in the chemotherapy/BSC arm are assumed to have died or progressed at the period for which follow-up data are available
- In the company's base case there is no utility penalty associated with progressive disease and hence early progression is 'rewarded' as it results in a reduction in treatment costs.

In summary, for the comparison of pembrolizumab 2mg/kg Q3W vs chemotherapy/BSC, the company and the ERG have estimated ICERs that are less than £50,000 per QALY gained. However, the ERG cautions that these estimates are reliant on the use of immature survival data that have been compromised by crossover.

9 OVERALL CONCLUSIONS

Evidence presented by the company suggests that pembrolizumab 2mg/kg Q3W results in improved clinical efficacy and safety when compared with chemotherapy, regardless of BRAF mutation or PD-L1 status. The company and the ERG estimate the incremental cost per QALY gained for pembrolizumab 2mg/kg Q3W compared with chemotherapy/BSC to be under £50,000. However, the assessment of the cost effectiveness of pembrolizumab 2mg/kg Q3W versus chemotherapy/BSC depends largely on clinical data derived from a single Phase II trial (KEYNOTE-002) with only 12 months follow-up data available in which OS data are confounded (from 12 weeks) by crossover between treatments. The apparently stable estimated ICERs per QALY gained reported by the company and the ERG should not be taken to indicate an absence of uncertainty. The ERG emphasises that the assumptions required to anticipate 29 years of future survival experience based on the currently available data should not be under-estimated, nor the scope for substantial error that can arise from post-hoc manipulation of trial data compromised by crossover.

9.1 Implications for research

It is unlikely that a trial similar to KEYNOTE-002 will be carried out again in this patient population. Therefore, the only opportunity to improve the evidence base, and thereby somewhat mitigate the current extensive decision uncertainty, is to extend the follow-up period over which the survival outcomes for patients are monitored. The company expects that the final analysis data set will be complete by the end of 2015 (based on the target number of deaths), and therefore it would seem appropriate to review the evidence again as soon as practically possible after this date.

The crucial outcome required for the clarification of the nature and magnitude of patient benefit from use of pembrolizumab 2mg/kg Q3W and other treatments for malignant melanoma is long-term survival. If the company were able to commit to survival follow up of KEYNOTE-002 patients for 10 years or more, this would provide a very valuable resource for both the clinical research community and for healthcare decision-makers.

In the meantime, given pembrolizumab is an anti-PD-1 agent and targeting PD-1 or its ligand PD-L1 is considered to be of promising therapeutic benefit, data from ongoing studies of pembrolizumab may be useful for improving the evidence base regarding treatment efficacy and PD-L1 status. If a relationship is found to exist, further research into the clinical utility of using this biomarker to tailor treatment for patients with advanced melanoma would be required.

Further research into the clinical effectiveness of pembrolizumab in patients with BRAF positive melanoma who have not been treated previously with a BRAF (or MEK) inhibitor may also be of clinical value. Further research examining the optimal treatment pathway (for BRAF inhibitors, ipilimumab, pembrolizumab and possibly other promising drugs such as nivolumab) could also be tested in a clinical trial.

The remit of this STA has been to examine the effectiveness of pembrolizumab following progression with ipilimumab. The ERG believes that the majority of these patients seen in clinical practice are refractory to ipilimumab, as in KEYNOTE-002. However, patients may also benefit from pembrolizumab therapy if they have persistent (albeit stable) disease, as opposed to progressive disease. To test whether this is the case will require further research and a different remit to that of the current STA.

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11 APPENDICES

11.1 Appendix 1: Description and critique of search strategies for evidence of clinical effectiveness

11.1.1 Search for direct evidence

Searches were reported for the following databases: Medline, Embase and The Cochrane Library, Medline in Process was not listed as a source in the CS for this search (sections 4.1 and appendix 2 of the CS). The company also searched Toxline and limited the searches to only trials in the Cochrane Library. The company reported hand searches were undertaken to identify additional studies identified from the following sources: American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and Society of Melanoma Research (SMR) and clinicaltrials.gov. The submission did not include details of the search terms used to search these additional resources; therefore the ERG was unable to comment on these searches.

The date of the search and the full date span is included in the report; the searches were well reported and reproducible. The ERG noted that searches were limited to English language only, which may have resulted in the omission of potentially useful papers in other languages. The full search strategies included in appendix 2 of the CS indicate the search terms included were relevant and included medical subject headings (MeSH) and free text as well as a simplified RCT filter.

11.1.2 Search for indirect evidence and adverse reactions

The company carried out searches for indirect evidence and adverse reactions on the same databases reported above (reported in appendix 8 and appendix 12 respectively of the CS). The company carried out separate searches for each drug comparison; pembrolizumab, dacarbazine, best supportive care (BSC). The company then carried out another set of searches for pembrolizumab, dacarbazine, BSC, vemurafenib, dabrafenib, nivolumab and temozolimide in the same databases. It is unclear why each of these searches was carried out individually.

11.1.3 ERG summary and critique of searches

The CS adequately described the search strategies used to identify relevant studies relating to the use of pembrolizumab for metastatic melanoma, the searches were not specific to treatment after ipilimumab or ipilimumab-naïve melanoma. Despite the absence of potentially important databases and limiting the language, the ERG concluded that searching

was carried out to an adequate standard and accurately reflected the population and indication. The ERG is confident no relevant references have been missed by the company.

11.2 Appendix 2: Additional information and critique of supporting evidence trials

Key characteristics of the supporting evidence trials are provided in Table 40. The ERG considers that all of the trials are well designed and, within each trial, an appropriate approach was taken to address the main research questions of interest.

Only KEYNOTE-001 (Part B2) recruited patients who were all relevant to the decision problem issued by NICE. KEYNOTE-001 (Part B1) included some patients who were relevant to the decision problem since this non-randomised study included a mixture of patients previously treated with ipilimumab and ipilimumab-naïve patients.

Table 40 Key characteristics of the supporting evidence trials

Parameter	KEYNOTE-001 (Part B2)	KEYNOTE-001 (Part B1)	KEYNOTE-006
Study type	KEYNOTE-001 initially designed as Phase I trial but evolved into multiple Phase II-like sub-studies. Part B2 is a Phase II RCT	KEYNOTE-001 initially designed as Phase I trial but evolved into multiple Phase II-like sub-studies. Part B1 is a Phase II non-RCT	Phase III RCT
Patient population	Patients with progressive locally advanced or metastatic melanoma, refractory to ipilimumab	Patients with measurable metastatic or locally advanced unresectable melanoma, both those who had received prior therapy with ipilimumab and those who had not	Patients with advanced (unresectable stage III or IV) melanoma who were naïve to prior ipilimumab therapy
Interventions/ comparators			
Pembrolizumab 2mg/kg Q3W	89	22 (all were ipilimumab naïve)	0
Pembrolizumab 10mg/kg Q3W	84	56 (24 were ipilimumab naïve)	277
Pembrolizumab 10mg/kg Q2W	0	57 (41 were ipilimumab naïve)	279
Ipilimumab	0	0	278

Parameter	KEYNOTE-001 (Part B2)	KEYNOTE-001 (Part B1)	KEYNOTE-006
Key eligibility criteria	Key inclusion criteria: • Histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that was not amenable to definitive local therapy with curative intent • Patients were ipilimumab-refractory • Measurable disease as defined per irRC • ECOG performance status of 0 or 1 Key exclusion criteria: • Chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who had not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier • Known history of a hematologic malignancy, primary brain tumour or sarcoma, or of another primary solid tumour, unless the patient had undergone potentially curative therapy with no evidence of that disease for 5 years • Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents • Received prior treatment targeting PD-1: PD-L1 axis or CTLA (with exception of ipilimumab), or was previously randomised in any pembrolizumab trial	Key inclusion criteria: • 18 years of age or older • Measurable metastatic or locally advanced unresectable melanoma • Adequate performance status and organ function (criteria listed in the protocol) • Patients who had not received prior treatment with ipilimumab had received no more than two prior regimens of systemic therapy • Patients who had received prior therapy with ipilimumab had full resolution of ipilimumab-related AEs and no history of severe immune-related AEs associated with ipilimumab therapy • Patients were eligible 6 weeks after the last dose of ipilimumab was administered • Patients with previously treated brain metastases were required to undergo baseline imaging by means of computed tomographic scanning or magnetic resonance imaging and to have had no evidence of central nervous system progression for 8 weeks Key exclusion criteria: • A melanoma of ocular origin • Prior therapy with a PD-1 or PD-L1 blocking agent • Current systemic immunosuppressive therapy • Active infections or autoimmune diseases	Key inclusion criteria: • Histologically or confirmed diagnosis of unresectable stage III or IV melanoma • Patients who had not received prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (1st line) or who had received one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (2nd line) were both eligible • BRAF mutational status must have been know, although previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels and no clinically significant tumour-related symptoms/evidence of rapidly progressive disease • ECOG performance status 0 or 1 • Provision of a tumour sample adequate for assessing PD-L1 expression Key exclusion criteria: • Patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors and those who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease
Outcomes	Primary outcome: • RR Secondary outcomes: • DCR • Response duration • PFS	Primary outcome: • Evaluation of safety profile of pembrolizumab Secondary/tertiary outcomes: • Preliminary analysis of the anti-tumour activity of pembrolizumab, both in patients who had received prior treatment with ipilimumab and in those who had not	Primary outcomes: • PFS and OS Secondary outcomes included: • ORR • Duration of response • Safety

BRAF= B-Raf proto-oncogene, serine/threonine kinase; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; CTCAE=common terminology criteria for adverse events; DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; irRC=immune-related response criteria; OS=overall survival; ORR=overall response rate; PD-1=programmed cell death 1; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival; RCT=randomised controlled trial; RR=response rate
Source: CS, adapted from sections 4.3.2, 4.4.1 and table 43

11.2.1 Statistical approach adopted for KEYNOTE-001 (Part B2)

KEYNOTE-001 was designed as a Phase I multi-centre, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumour activity of pembrolizumab in patients with locally advanced or metastatic melanoma (ipilimumab-naïve or previously treated with ipilimumab), NSCLC, or carcinoma. The trial was initially designed as a standard dose escalation trial (Part A), in which patients with melanoma were enrolled. The study was expanded to evaluate efficacy in melanoma in Part B (now Part B1). KEYNOTE-001 evolved into four Phase II-like melanoma sub-studies, known as Parts B1, B2, B3, and D.

The ERG considers that a seamless design has been used for the conduct of KEYNOTE-001. A seamless design allows the trial team to progress from one study to the next without delays or need for further protocol approvals, in the interest of time efficiency. The disadvantage of using this trial design is that there is no opportunity to reflect on the trial results or to modify the trial design if unexpected results have occurred in the first study. However, overall the ERG considers that a seamless design was an appropriate design to use.

In KEYNOTE-001 (Part A) patients received 1, 3 or 10mg/kg of pembrolizumab with 10mg/kg being the maximum tolerated dose. KEYNOTE-001 Part B2 randomised a new sample of 173 patients to receive pembrolizumab 2mg/kg Q3W or pembrolizumab 10mg/kg Q3W. It is not clear to the ERG whether results from Part A were used to determine whether a dose of 10mg/kg Q3W was safe to use in Part B2. If this was the case, the trial design would be considered to be an adaptive seamless design.

11.2.2 Risk of bias for KEYNOTE-001 (Part B2)

Aside from the KEYNOTE-002 trial, the company only presented an assessment of the risk of bias for KEYNOTE-001 (Part B2). This was conducted using the criteria recommended by NICE for company's submissions.[40] The risk of bias assessment is presented in Table 41. The ERG notes that the company indicates that KEYNOTE-001 (Part B2) includes an ITT analysis; however, there are no ITT analyses reported in the SAP or CSR. For all other risk of bias criteria, the ERG is satisfied with the assessments presented in the CS, and is therefore of the opinion that KEYNOTE-001 (Part B2) has an overall low risk of bias.

Table 41 Assessment of risk of bias for KEYNOTE-001 (Part B2)

Risk of bias criteria	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No
Were there any unexpected imbalances in drop-outs between groups?	Not clear	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	No

Source: CS, adapted from table 17

11.2.3 Findings from KEYNOTE-001 (Part B2)

KEYNOTE-001 (Part B2) provides supporting evidence for pembrolizumab 2mg/kg Q3W. There were no statistically significant differences identified between the pembrolizumab 2mg/kg Q3W arm and 10mg/kg Q3W arm for any of the efficacy outcomes reported in KEYNOTE-001 (Part B2).

As with KEYNOTE-002, the ERG notes that PFS determined by INV and reported at the October 2013 data-cut was markedly greater than the PFS determined by IRO. In the pembrolizumab 2mg/kg Q3W arm, median PFS determined by INV was 9 weeks greater than the corresponding assessment by IRO and in the 10mg/kg Q3W arm, it was 21 weeks greater than the corresponding assessment by IRO; PFS response as determined by INV at 6 months was 57% in both arms as opposed to 45% in the 2mg/kg Q3W arm and 37% in the 10mg/kg Q3W arm by IRO.

Although not statistically significant, the ERG observed that OS appeared to be improved in the pembrolizumab 10mg/kg Q3W arm in comparison to the pembrolizumab 2mg/kg Q3W arm with the opposite being the case for PFS (table 12 and figures 7 and 8 in appendix 6 of the CS). During the clarification process, the ERG therefore requested more context as to why the pembrolizumab 2mg/kg Q3W dose was preferred over the 10mg/kg Q3W dose. In response, the company reiterated that the positive CHMP opinion indicates that 2mg/kg Q3W dose will be the licensed dose and that the latest draft version of the European SmPC recommends that pembrolizumab 2mg/kg Q3W is “administered intravenously over 30 minutes every 3 weeks” (page 63 of company’s response to ERG clarification letter). Furthermore, the company agreed with the ERG that these findings were not statistically significant. The company also stressed that there were no clinically meaningful differences.

Furthermore, during the clarification process the company also noted that the CS included KEYNOTE-001 (Part B2) data from the October 2013 data-cut whereas data from the April 2014 data-cut were now available. These data are reported in Table 42.

Table 42: Key efficacy endpoints in KEYNOTE-001(Part B2), April 2014 data-cut

Outcome	Pembrolizumab 2mg/kg Q3W	Pembrolizumab 10mg/kg Q3W
ORR by IRO (%)	25	25
PFS by IRO (median, months)	4.9	3.2
6-month PFS rate (%)	43	35
OS (median, months)	Not reached	18.3
6 month OS rate (%)	79	77

IRO=integrated radiology and oncology analysis; OS=overall survival; PFS=progression-free survival; ORR=overall response rate
Source: Company's response to ERG's clarification letter (table 53)

As highlighted by the company, the findings for OS and PFS are more impressive for both pembrolizumab arms in KEYNOTE-001 (Part B2) than KEYNOTE-002. As noted in Section 4.2 (Table 5), patients in KEYNOTE-002 had poorer ECOG status and more severe metastases than in KEYNOTE-001 (Part B2) which may explain these apparent differences in findings between trials.

11.2.4 Non-randomised study, KEYNOTE-001 (Part B1)

As noted by the ERG in Section 4.2, KEYNOTE-001 (Part B1) was the only study to include patients previously treated with ipilimumab who were not necessarily refractory to ipilimumab. It also included patients who were ipilimumab naïve. None of the patients previously treated with ipilimumab received pembrolizumab 2mg/kg Q3W; rather they only received pembrolizumab 10mg/kg (Q3W or Q2W). It is unclear to the ERG if this occurred by chance or design. However the company does state that patients were initially enrolled at a dose of 10mg/kg Q2W. Subsequently, additional patients were enrolled in concurrent (non-randomised) cohorts that received pembrolizumab 10mg/kg Q3W or 2mg/kg Q3W. As explored in Section 4.4.1, there is currently no evidence to suggest a difference between the Q3W doses. The remainder of this Section therefore concentrates on patients previously treated with ipilimumab in the pembrolizumab 10mg/kg Q3W arm (n=32).

Study characteristics of KEYNOTE-001 (Part B1)

Eligibility criteria stipulated that patients who had received prior therapy with ipilimumab must have had full resolution of ipilimumab-related AEs and no history of severe immune-related AEs associated with ipilimumab therapy. These patients must have waited 6 weeks from their last dose of ipilimumab before being included in the study. Clinical advice given to the ERG was that clinicians would not always wait 6 weeks before administering a new treatment in clinical practice.

Participant characteristics of KEYNOTE-001 (Part B1)

The company summarises the baseline characteristics for KEYNOTE-001 (Part B1) in table 44 of the CS. The ERG notes that in pembrolizumab 10mg/kg Q3W patients who were previously treated with ipilimumab, there was a higher proportion of patients with ECOG performance status of 0 in KEYNOTE-001 (Part B1) than in KEYNOTE-002 (53% compared with 61% in KEYNOTE-002). There were also marginally fewer males and patients were marginally younger in this arm of KEYNOTE-001 (Part B1) than in KEYNOTE-002 (Males: 53% vs 61% and mean age of 57.3 vs 60.1 respectively).

The company also notes that patients had characteristics suggestive of poor prognosis for patients with advanced melanoma. Specifically, the company highlighted (with ERG comment in parenthesis):

- >50% of the patients across all arms (n=135) had visceral metastases (stage M1c) (56% of patients treated at the 10mg/kg Q3W dose were previously treated with ipilimumab)
- Approximately 25% across all arms (n=135) had an elevated LDH level (22% of patients treated at the 10mg/kg Q3W dose were previously treated with ipilimumab)
- Around 9% across all arms (n=135) had a history of brain metastases (12% of patients treated at the 10mg/kg Q3W dose were previously treated with ipilimumab).

The ERG concurs these characteristics are indicators of poor prognosis. It is however noted that the incidences are still lower than seen in the population of patients in the KEYNOTE-002 trial, perhaps reflecting the fact that patients were refractory to ipilimumab and more heavily pre-treated in KEYNOTE-002.

Statistical approach employed for KEYNOTE-001 (Part B1)

The primary aim of KEYNOTE-001 (Part B1) was to assess the safety of pembrolizumab. The following efficacy outcomes were however assessed:

- ORR based on investigator-reported data (n=135) which was considered the primary measure for assessment of tumour response
- ORR based on independent central, blinded radiologic review assessed according to RECIST criteria (n=117)
- PFS (n=135)
- OS (n=135).

ORR was defined as the number of patients with a complete or partial response divided by the total number of patients who had measurable disease at baseline and received at least one treatment dose. The ORR and exact two-sided 95% confidence interval were calculated.

Median PFS was estimated by the K-M method for PFS in each treatment arm. Similarly, median OS was estimated by the K-M method for OS in each treatment arm.

Quality assessment of KEYNOTE-001 (Part B1)

The quality of KEYNOTE-001 (Part B1) was assessed using the Newcastle-Ottawa Scale[70] which considers:

- Selection of participants: both exposed and non-exposed cohorts, i.e.
  - Representativeness of the exposed cohort
  - Selection of the non exposed cohort
  - Ascertainment of exposure
  - Demonstration that outcome of interest was not present at start of study
- Comparability of cohorts on the basis of the design or analysis
- Outcomes, i.e.
  - Assessment of outcome
  - Was follow-up long enough for outcomes to occur?
  - Adequacy of follow up of cohorts.

A rating of one star considered the highest grading of quality. The company considered KEYNOTE-001 (Part B1) to have one star for selection and outcomes and two stars for comparability. The company's assessment is presented in appendix 10 of the CS.

The ERG notes that the company considers the exposed cohort to be patients treated with pembrolizumab 2mg/kg Q3W and the non-exposed cohort to be all patients treated with pembrolizumab 10mg/kg. It is unclear if this includes both pembrolizumab 10mg/kg Q2W and pembrolizumab 10mg/kg Q3W but would seem likely. The ERG also notes that no universally accepted standardised quality assessment tool exists for use in observational studies. For example, a review of non-randomised studies published in 2003[71] identified 194 tools that could be used to assess non-randomised studies. However, the Newcastle-Ottawa Scale was considered one of the most appropriate tools to use by this review. The ERG does not, therefore, have any concerns regarding the quality of KEYNOTE-001 (Part B1).

Findings from KEYNOTE-001 (Part B1)

As noted above, the primary aim of KEYNOTE-001 (Part B1) was to assess safety (see Appendix 4 for summary of AEs).

The ORR for all 135 patients in KEYNOTE-001 (Part B1) was 37% (95% CI 29% to 44%) and for 117 patients blindly assessed independently it was 38% (95% CI 25% to 44%). The corresponding ORRs for patients previously treated with ipilimumab in the pembrolizumab 10mg/kg Q3W arm were markedly lower: 22% (95% CI 9% to 40%, n=32) and 27% (95% CI

12% to 48%, n=26) respectively. These are however similar to ORRs reported for both the pembrolizumab 2mg/kg Q3W arm and pembrolizumab 10mg/kg Q3W arm in KEYNOTE-002 (see Appendix 3).

The only findings reported for PFS are for all 135 patients, irrespective of previous treatment with ipilimumab and dose. In the CS it is simply stated that median PFS exceeded 7 months and the estimated median OS had not been reached. Since the findings are for a mixed population in that some patients had been previously treated with ipilimumab whereas others were ipilimumab naïve and since patients received three different doses of pembrolizumab (2kg/mg Q3W, 10mg/kg Q3W and 10mg/kg Q2W), the ERG considers the evidence for PFS and OS from this trial to be of no direct relevance to the company's decision problem.

11.3 Appendix 3: Evidence for overall response in KEYNOTE-002

There were four (2.2%) complete responses in the pembrolizumab 2mg/kg Q3W arm, whereas there were no complete responses in the chemotherapy arm. Disease control rate, as calculated by compete response + partial response + stable disease, was also higher in the pembrolizumab 2mg/kg Q3W arm than in the chemotherapy arm (38.9% vs 22.9%, respectively). Findings of ORR based on central review are provided in Table 43. Pembrolizumab 2mg/kg Q3W was found to statistically significantly increase confirmed response rate.

Table 43 Analysis of ORR based on independent central assessment (IRO) in KEYNOTE-002

Treatment arm	Number of overall responses	ORR (%) (95% CI)	Difference in % vs chemotherapy	
			Estimate (95% CI)*	p-value†
Pembrolizumab 2mg/kg Q3W,n=180	38	21.1 (15.4 to 27.8)	12.8 (7.0 to 20.6)	p<0.0001
Pembrolizumab 10mg/kg Q3W,n=181	46	25.4 (19.2 to 32.4)	18.4 (11.4,26.7)	p<0.0001
Chemotherapy, n=179	8	4.5 (1.9 to 8.6)		

CI=confidence interval; IRO=integrated radiology and oncology analysis; ORR=overall response rate
*Based on Miettinen & Nurminen method stratified by ECOG (0 vs 1) and LDH level (normal vs elevated) and BRAF mutation (mutant vs wild type).
† One-sided p-value for testing. H0: difference in %=0 vs H1: difference in % > 0
Source: CS, adapted from table 27 and appendix 6 (table 2)

The results from the ORR analysis based on assessment by INV are consistent with those from the ORR based on assessment by IRO (Table 44). Five (2.8%) patients had a complete response in the pembrolizumab 2mg/kg Q3W arm, while no patients in the chemotherapy arm experienced complete response.

Table 44 Analysis of ORR based on local investigator assessment (INV) in KEYNOTE-002

Treatment arm	Number of overall responses	ORR (%) (95% CI)	Difference in % vs chemotherapy	
			Estimate (95% CI)*	p-value†
Pembrolizumab 2mg/kg Q3W n=180	[redacted]	21.1 [redacted]	[redacted]	p<0.0001
Pembrolizumab 10mg/kg Q3W n=181	[redacted]	24.3 [redacted]	[redacted]	[redacted]
Chemotherapy n=179	[redacted]	5.0 [redacted]		

CI=confidence interval; IRO=integrated radiology and oncology analysis; ORR=overall response rate
*Based on Miettinen & Nurminen method stratified by ECOG (0 vs 1) and LDH level (normal vs elevated) and BRAF mutation (mutant vs wild type).
† One-sided p-value for testing. H0: difference in %=0 vs H1: difference in % > 0
Source: CS, adapted from appendix 6 and CSR (table 11-20)

Response duration: independent central assessment in KEYNOTE-002

A summary of time to response and response duration for patients with an overall response (assessed by central review) is provided in Table 45. The company also provides K-M estimates of overall duration of response based on central review in figure 14 of the CS.

In summary:

- Median time to response was comparable across the pembrolizumab 2mg/kg Q3W arm and the chemotherapy arm; both medians were 13 weeks. Both the company and ERG note that this was to be expected due to the time of the first post-baseline tumour assessment
- Median duration of response was found to be 37 weeks for the chemotherapy arm, although the median was not reached for the pembrolizumab 2mg/kg Q3W arm. Both the company and ERG concur that as only eight patients experienced a response in the chemotherapy arm, the median duration of response should be interpreted with caution
- The company highlights that of the patients with an overall response, 92% of patients in the pembrolizumab 2mg/kg Q3W arm had not progressed at the time of analysis vs 63% of patients in the chemotherapy arm.

Table 45: Summary of time to response & response duration for patients with overall response based on independent central assessment (IRO) in KEYNOTE-002

Treatment arm	Number of patients with response†	Time to response† (weeks)		Response duration‡ (weeks)	Number of non-progressing (non-PD) patients (%)
		Mean (SD)	Median (range)	Median (range)§	
Pembrolizumab 2mg/kg Q3W n=180	38	16 (5)	13 (12 to 30)	NR (6+ to 50+)	35 (92)
Pembrolizumab 10mg/kg Q3W n=181	46	16 (4)	15 (12 to 30)	NR (5+ to 48+)	40 (87)
Chemotherapy n=179	8	14 (3)	13 (12 to18)	37 (7+ to 41)	5 (63)

IRO=integrated radiology and oncology analysis; ITT=intention-to-treat; NR=not reached; PD=progressive disease; SD=standard deviation
† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only
‡ From product-limit (K-M) method for censored data
§ "+" indicates there is no progressive disease by the time of last disease assessment
Source: CS, adapted from table 29 and appendix 6 and CSR (table 14-9)

Subgroup analysis for overall response rate in KEYNOTE-002

The results suggest that the efficacy of pembrolizumab 2mg/kg Q3W was slightly greater in PD-L1 positive patients in comparison to chemotherapy. The ERG requested p-values for interaction for all performed subgroup analyses in order to investigate the statistical significance of subgroup effects, which the company provided in their clarification response. The subgroup effect for PD-L1 status was found to be statistically significant in terms of ORR (p=0.03) but not OS and PFS (see Section 4.4). Furthermore, it is noted by the ERG that the subgroup effect for PD-L1 status was not found to be statistically significant in terms of ORR for the pembrolizumab 10mg/kg Q3W compared with chemotherapy (p=0.120).

The company hypothesises that reduced efficacy in the PD-L1 negative subgroup may be due to imbalances in BRAF mutation status and elevated LDH across treatment arms within the PD-L1 subgroup. These imbalances may have confounded the efficacy results of the PD-L1 negative subgroup.

11.4 Appendix 4: adverse event data from supportive trials in the company's submission

A summary of the broad types of AEs reported in the pembrolizumab 2mg/kg Q3W treatment arm of KEYNOTE-001 (Part B2), APaT population, is provided in table 53 of the CS. The ERG notes that, generally, similar incidences of AEs were reported in this trial as for KEYNOTE-002. Fatigue was the only specific drug-related Grade 3 or 4 AE reported by the company to occur in more than one patient: five (6%) patients experienced this in KEYNOTE-001 (Part B2); the CSR for KEYNOTE-001[72] notes [redacted].

Limited safety data are reported from the non-random KEYNOTE-001 (Part B1) study where only the incidence of patients reporting any type of AE (that occurred in at least 1% of patients) and the specific types of AEs are summarised in table 55 of the CS. The data reported in appendix 13 (table 11) of the CS are arguably more informative; the ERG notes that all Grade AEs were more common for patients receiving pembrolizumab 10mg/kg Q2W (91.2%) or 10mg/kg Q3W (73.2%) weekly as opposed to pembrolizumab 2mg/kg Q3W (63.6%). Specific types of AEs were also generally more common in both the 10mg/kg arms than in the 2mg/kg Q3W arm. However, caution must be exercised in interpreting these findings due to the small numbers of patients in the study (n=157), particularly the 2mg/kg Q3W arm (n=22). It should also be noted that the 10mg/kg arms included a mixture of patients pre-treated with ipilimumab and those who were ipilimumab naïve whereas the 2mg/kg Q3W arm only included patients who were ipilimumab naïve.

Finally, the company notes from KEYNOTE-006 that the incidence of drug-related Grade ≥3 AEs and permanent discontinuations for an AE attributed to treatment were lower with pembrolizumab than with ipilimumab. It is highlighted that this was despite exposure to treatment being approximately three times as long with pembrolizumab 10mg/kg as with ipilimumab.

11.5 Appendix 5: ERG Revisions to the company's model: pembrolizumab STA (ID760)

All revisions are activated by a binary logic switch with 0 = unchanged, 1 (or any non-zero number) = apply ERG modification.

Logic switches are indicated by range variables Mod_*n* where n = 1 – 12. The Mod numbers do not directly match the Table Row numbers.

A menu of revisions/Mod numbers appears on the 'Results' worksheet together with summary results as used to transfer to the ERG report.

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
R1. Drug costs	Mod_1	'Drug cost calculations'.xlsx	In Sheet 'Costs', Replace formula in cell **E45** by =IF(Mod_1=0,vials_kn002_european*$L$43,4728.97) Replace formula in cell **E54** by =CHOOSE(Mod_1+1,L78*d_DTIC,40.3643,40.3643,47.2237,47,2237) Replace formula in cell **E55** by =IF(Mod_1=0,L79*d_pac,33.4557) Replace formula in cell **E57** by =IF(Mod_1=0,L79*d_paccomb,33.4557) Replace formula in cell **F54** by =CHOOSE(Mod_1+1,SUMPRODUCT(L96:L98,O96:O98),40.8966,40.8966,47.7553,47.7553) Replace formula in cell **F55** by =IF(Mod_1=0,SUMPRODUCT(L104:L107,O104:O107), 34.1435) Replace formula in cell **F57** by =IF(Mod_1=0,SUMPRODUCT(L104:L107, P104:P107),34.1435) Replace formula in cell **F62** by =IF(Mod_11=0,CHOOSE(Mod_1+1, SUMPRODUCT(L130:L135,O130:O135),141.62,143.18, 141.62,143.18),39.09)
R2. Cost of drug administration	Mod_2	-	In Sheet 'Costs', Replace formula in cell **L29** by =IF(Mod_2=0,IF(K29="Outpatient",(IF(G29="Complex Chemotherapy", p_parenteral_outpatient,IF(G29="Oral Chemotherapy",p_oralchemo))), p_parenteral_inpatient),245.16965) Replace formula in cell **L32** by =IF(Mod_2=0,IF(K32="Outpatient",(IF(G32="Complex Chemotherapy", p_parenteral_outpatient,IF(G32="Oral Chemotherapy",p_oralchemo))), p_parenteral_inpatient),245.16965) Replace formula in cell **L33** by =IF(Mod_2=0,IF(K33="Outpatient",(IF(G33="Complex Chemotherapy", p_parenteral_outpatient,IF(G33="Oral Chemotherapy",p_oralchemo))), p_parenteral_inpatient),245.16965) Replace formula in cell **L34** by =IF(Mod_2=0,IF(K34="Outpatient",(IF(G34="Complex Chemotherapy", p_parenteral_outpatient,IF(G34="Oral Chemotherapy",p_oralchemo))), p_parenteral_inpatient),245.16965)
R3. Limit dacarbazine treatment to 6 cycles	Mod_3	-	In Sheet 'Patient flow - Comparator', Replace formula in cell **AH14** by =IF(Mod_3=0,IF(MOD(B14-1,p_d_freq_DTIC)=0,1,0), IF(B14<17,IF(MOD(B14-1,p_d_freq_DTIC)=0,1,0),0)) Copy formula in AH14 to range AH15:AH2101
R4. Age-sex adjusted Life Table mortality	Mod_6	-	In Sheet 'Life Tables', create new estimates as follows: *Male sub-cohort in column G* Cell **G11** =1000*ctrl_prop_male

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Cell **G12** =G11*(1-B11) Copy cell **G12** to range **G13:G61** *Female sub-cohort in column G* Cell **H11** =1000-G11 Cell **H12** =H11*(1-C11) Copy cell **H12** to range **H13:H61** *Sex Ratio in column H* Cell **I11** =G11/H11 Copy cell **I11** to range **I12:I61** *Annual mortality rate* Cell **J11** =(G11*B11+H11*C11)/(G11+H11) Copy cell **J11** to range **J12:J61** ERG per cycle mortality rate Cell **K11** =1-((1-J11)^(ctrl_cycle_length/365.25)) Copy cell **K11** to range **K12:K61** *Apply revised mortality* Replace formula in Cell **E11** by =IF(Mod_6=0,1-((1-D11)^(ctrl_cycle_length/365.25)),K11) Copy cell **E11** to range **E12:E61**
R5. Use European utility values	Mod_13	-	<u>In Sheet 'Utilities',</u> create tables of European EQ-5D values as follows: Cell **H25** =0.73, Cell **H26** =0.64, Cell **H27** = 0.54, Cell **H28** = 0.47, Cell **H29** = 0.4, Cell **H30** = 0.33 Cell **H35** =0.71, Cell **H36** =0.61, Cell **H37** = 0.54, Cell **H38** = 0.49, Cell **H39** = 0.44, Cell **H40** = 0.4 Cell **I35** =0.75, Cell **I36** =0.64, Cell **I37** = 0.53, Cell **I38** = 0.46, Cell **I39** = 0.39, Cell **I40** = 0.3 Replace formula in cell **E25** by =IF(Mod_13=0,0.78,**H25**) Replace formula in cell **E26** by =IF(Mod_13=0,0.62,**H26**) Replace formula in cell **E27** by =IF(Mod_13=0,0.62,**H27**) Replace formula in cell **E28** by =IF(Mod_13=0,0.52,**H28**) Replace formula in cell **E29** by =IF(Mod_13=0,0.52,**H29**) Replace formula in cell **E30** by =IF(Mod_13=0,0.42,**H30**) Replace formula in cell **D35** by =IF(Mod_13=0,0.76,**H35**) Replace formula in cell **D36** by =IF(Mod_13=0,0.64,**H36**) Replace formula in cell **D37** by =IF(Mod_13=0,0.64,**H37**) Replace formula in cell **D38** by =IF(Mod_13=0,0.54,**H38**) Replace formula in cell **D39** by =IF(Mod_13=0,0.54,**H39**) Replace formula in cell **D40** by =IF(Mod_13=0,0.47,**H40**) Replace formula in cell **E35** by =IF(Mod_13=0,0.79,**I35**)

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Replace formula in cell **E36** by =IF(Mod_13=0,0.6,**I36**) Replace formula in cell **E37** by =IF(Mod_13=0,0.6,**I37**) Replace formula in cell **E38** by =IF(Mod_13=0,0.5,**I38**) Replace formula in cell **E39** by =IF(Mod_13=0,0.5,**I39**) Replace formula in cell **E40** by =IF(Mod_13=0,0.37,**I40**)
R6. ERG PFS projections	Mod_9	ERG_PFS_OS_ToT_estimates.xlsx	Paste Worksheet **'ERG_PFS'** into model In Sheet 'PFS' Replace formula in cell **L45** by =IF(Mod_9=0,HLOOKUP(ctrl_select_comp_pfs, $F$44:$H$2132, OS!B54+2, FALSE),ERG_PFS!F18) Replace formula in cell **M45** by =IF(Mod_9=0,PFS!J45,ERG_PFS!G18) Copy range **L45:M45** to Range **L46:M2132**
R7. ERG Time on treatment projections	Mod_10	ERG_PFS_OS_ToT_estimates.xlsx	Paste Worksheet **'ERG_ToT'** into model In Sheet 'Patient Flow - Comparator' Replace formula in cell **AQ14** by =IF(ctrl_select_comp="Dacarbazine", AH14*c_DTIC,IF(ctrl_select_comp="BSC",(((AH14*prop_DTIC_BSC*(c_DTIC)+(AN14*prop_interferon*(c_interferon))+(AI14*prop_pac*(c_pac))+(AK14*prop_carbo*(c_carb))+(AO14*prop_vind*(c_vind))+(AL14*prop_paccomb*(c_paccomb))+(AP14*prop_temo*(c_temo))))),0))*IF(Mod_10=0,(IF(inc_hc_correction="Yes", P14, L14)),ERG_ToT!G10)*p_percentdose_chemo Copy cell **AQ14** to range **AQ15:AQ2101** In Sheet 'Patient Flow - Treatment' Replace formula in cell **AI13** by =IF(B13<ctrl_stoppingrule, AH13*c_pem* (IF(Controls!$C$78="Yes",1-ctrl_PAS1,1))*IF(Mod_10=0, IF(inc_hc_correction="Yes", P13,L13),ERG_ToT!F10),0)*p_percentdose_pembro Copy cell **AI13** to range **AI14:AI2100**
R8. Remove zero mortality period	Mod_4	-	In Sheet 'OS' Replace formula in cell **Q377** by =IF(Mod_4=0,HLOOKUP(ctrl_treatextrap, $J$53:$M$2141,(2+B377),FALSE),HLOOKUP(ctrl_treatextrap,$J$53:$M$2141,(B576),FALSE)) Copy cell **Q377** to range **Q378:Q2166**
R9. Remove HR advantage after 10 years	Mod_5	-	In Sheet 'OS' Replace formula in cell **P576** by =HLOOKUP(ctrl_select_comp_os, OS!$G$53:$I$2141, OS!B576+2, FALSE)*IF(Mod_5=0,1,Q576/Q575)

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Copy cell **P576** to range **P577:P2166**
R10. ERG OS projections	Mod_8	ERG_PFS_OS_ToT_estimates.xlsx	Paste Worksheet **'ERG_OS'** into model In Sheet 'Patient Flow - Comparator' Replace formula in cell **K14** by =IF(Mod_8=0,OS!P54,ERG_OS!T54) Copy cell **K14** to range **K15:K1578** In Sheet 'Patient Flow - Treatment' Replace formula in cell **K13** by =IF(Mod_8=0,OS!P54,ERG_OS!T54) Copy cell **K13** to range **K14:K1577**
R11. Temolozomide dosing and drug cost coding errors	Mod_11	-	In Sheet 'Parameters' Replace formula in cell **D101** by =IF(Mod_12=0,Costs!G59,Costs!G60) Replace formula in cell **D103** by =IF(Mod_12=0,Costs!G60,Costs!G62) In Sheet 'Costs' Replace formula in cell **F59** by =IF(Mod_11=0,SUM(E57:E58),SUM(F57:F58)) Replace formula in cell **F62** by =IF(Mod_11=0,CHOOSE(Mod_1+1, SUMPRODUCT(L130:L135,O130:O135),141.62,143.18,141.62,143.18),39.09)
R12. Apply both methods of utility estimation	Mod_7	First switch ctrl_source_utility_type to 'Progression ' then set Mod_12=1	In Sheet 'Utilities' Enter formula in cell **G26** =(F25-F26)*60/365.25 Enter formula in cell **G27** =(F$25-F27)*30/365.25 Copy cell **G27** to range **G28:G30** Enter formula in cell **G31** =SUM(G26:G30) Enter formula in cell **F36** =(D35-D36)*60/365.25 Enter formula in cell **F37** =(D$35-D37)*30/365.25 Copy cell **F37** to range **F38:F40** Enter formula in cell **F41** =SUM(F26:F30) Enter formula in cell **G36** =(E35-E36)*60/365.25 Enter formula in cell **G37** =(E$35-E37)*30/365.25 Copy cell **G37** to range **G38:G40**

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Enter formula in cell **G41** =SUM(G26:G30) <u>In Sheet 'Patient Flow – Treatment'</u> Enter heading in cell **A12** ERG End of Life disutility Enter formula in cell **A14** =-S14*MIN(C13,13)/13*IF(utility_KN002_type = "Pooled Utilities ", Utilities!$G$31,Utilities!$G$41) Copy cell **A14** to range **A15:A2100** Enter formula in cell **AG14** =IF(Mod_7=0,0,A14) Copy cell **AG14** to range **AG15:AG2100** Enter formula in cell **AS14** =IF(Mod_7=0,0,AG14*$H14) Copy cell **AS14** to range **AS15:AS2100** <u>In Sheet 'Patient Flow – Comparator'</u> Enter heading in cell **A13** ERG End of Life disutility Enter formula in cell **A15** =-S15*MIN(C14,13)/13*IF(utility_KN002_type = "Pooled Utilities ", Utilities!$G$31,Utilities!$F$41) Copy cell **A15** to range **A16:A2101** Enter formula in cell **AG15** =IF(Mod_7=0,0,A15) Copy cell **AG15** to range **AG16:AG2101** Enter formula in cell **AS15** =IF(Mod_7=0,0,AG15*$H15) Copy cell **AS15** to range **AS16:AS2101**

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