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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence

[ID 1266]

Confidential until published

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID 1266]

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LIST OF ABBREVIATIONS

AE	adverse event
AEOSI	adverse events of special interest
AIC	Akaike information criteria
AJCC	American Joint Committee on Cancer
BRAF	a human gene that encodes a protein called B-Raf
CAA	Commercial Access Agreement
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CS	company submission
CSR	clinical study report
CT	computed tomography
CTLA	cytotoxic T-lymphocyte-associated protein
DM	distant metastases
DMFS	distant metastasis free survival
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life – 3 Dimensions Questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
HRQoL	health related quality of life
HR	hazard ratio
IA1	first interim analysis
IARC	International Agency for Research on Cancer
ICER	incremental cost effectiveness ratio
IPD	individual patient data
KEYNOTE-054	key trial that informs the clinical effectiveness and cost effectiveness evidence
K-M	Kaplan-Meier
ITT	intention to treat
LR	locoregional recurrence
MRI	magnetic resonance imaging
MSD	Merck Sharp & Dohme
MSE	mean square error
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PD-1	programmed death-1 protein
PD-L1	programmed cell death-1 ligand 1
PH	proportional hazards
PRO	patient reported outcomes
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality adjusted life year
QLQ-C30	quality of life questionnaire C30
Q3W	treatment every 3 weeks
RCT	randomised controlled trial
RF	recurrence free
RFS	recurrence free survival
SAE	serious adverse events
SEER	Surveillance, Epidemiology, and End Results Program
SLNB	sentinel lymph node biopsy
SmPC	summary of product characteristics
TNM	tumour, node, metastases

1 SUMMARY

1.1 Scope of the submission

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 Sharpe & Dohme Limited (MSD) in support of the use of pembrolizumab (Keytruda®) for adjuvant treatment of resected melanoma with a high risk of recurrence.

1.2 Critique of the decision problem in the company submission

Population

The population described in the final scope issued by NICE is people with completely resected melanoma at high risk of recurrence. This population can be considered to be the same as the population addressed in the company submission (CS).

The ERG has been unable to identify any definitive definitions of high risk of either death or disease recurrence for patients with Stage III melanoma. It is, therefore, unclear whether all patients in the KEYNOTE-054 trial can be considered to be at high risk of death or disease recurrence.

Intervention

The company has made an application to the Committee for Medicinal Products for Human Use (CHMP) and expects an opinion to be published [redacted]. The company's proposed wording for the indication is [redacted] Pembrolizumab does not currently have a UK marketing authorisation (MA) for this indication.

Comparators

The comparator specified in the final scope issued by NICE is routine surveillance. The ERG notes that currently (August 2018) two NICE STAs, for related populations, are ongoing:

- ID1316: Nivolumab for the adjuvant treatment of completely resected stage III and IV melanoma (expected publication date: to be confirmed)
- ID1226: Dabrafenib in combination with trametinib for people with completely resected stage III melanoma with BRAF V600 positive mutations (expected publication date: December 2018).

This means that there is also evidence available for the clinical effectiveness of active adjuvant treatments other than pembrolizumab, i.e., nivolumab and dabrafenib in combination with trametinib.

Outcomes

Clinical evidence is presented in the CS for three of the five outcomes specified in the final scope issued by NICE: recurrence-free survival (RFS), adverse effects of treatment (AEs) and health-related quality of life (HRQoL). Due to the immaturity of trial data, the company only provided limited results for overall survival (OS) or distant metastases-free survival (DMFS). The company reports that as of [redacted]. The company expects OS results to become available in [redacted] and DMFS results to become available in [redacted]

Subgroups

No subgroups were specified in the final scope issued by NICE.

Other considerations

- A commercial access arrangement (CAA) means that pembrolizumab is available to the NHS at a (confidential) discounted price
- All of the treatments included in the company's economic model are available to the NHS at confidential discounted prices (either via a CAA or a patient access scheme [PAS])
- The company has not identified any equality issues
- The company has not presented a case for pembrolizumab to be assessed against the NICE End of Life criteria

1.3 Summary of the clinical evidence submitted by the company

The company conducted a broad literature search. This did not lead to the identification of any relevant randomised controlled trials (RCTs) other than the KEYNOTE-054 trial. The KEYNOTE-054 trial is an international, randomised, double-blind, ongoing Phase III trial of the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group designed to assess adjuvant immunotherapy with pembrolizumab versus placebo. The KEYNOTE-054 trial includes 1019 patients with completely resected Stage III melanoma.

The company presents results from the first interim analysis (IA1) of the KEYNOTE-054 trial (date of data cut: 2nd October 2017). At a median duration of follow-up of 16 months, median RFS in the intention-to-treat (ITT) population had not been reached in the pembrolizumab arm and was 20.4 months (95% confidence interval [CI]: 16.2 to not estimable) in the placebo arm. In comparison to placebo, treatment with pembrolizumab was demonstrated to deliver a

statistically significant and clinically meaningful improvement in RFS (hazard ratio [HR]=0.57; 98.4% CI 0.43 to 0.74; p<0.0001).

Only limited data for OS and DMFS are presented in the CS as, at the time of data cut-off for IA1, the minimum number of events required to enable these outcomes to be analysed had not been reached.

The company reported that most patients in the KEYNOTE-054 trial experienced at least one AE (93.3% in the pembrolizumab arm versus 90.2% in the placebo arm). Compared with the placebo arm, more patients in the pembrolizumab arm experienced AEs leading to treatment discontinuation (13.8% versus 3.6%). Drug-related Grade 3 to 5 AEs affected 14.5% of patients in the pembrolizumab arm and 3.4% of patients in the placebo arm. The company states that the most frequent AEs experienced by patients in the pembrolizumab arm were colitis [redacted] and type 1 diabetes mellitus [redacted]. The company states that colitis and type 1 diabetes mellitus are AEs that are known to result from treatment with pembrolizumab. Rates of immune-related AEs of any grade were 34% in the pembrolizumab arm and 7.6% in the placebo arm. The incidences of immune-related AEs were mostly categorised as Grade 1 and Grade 2 and included endocrine disorders. The company states that most of these events were manageable either by treatment interruption or discontinuation, with or without treatment with corticosteroids. It is also noted by the company that the nature of these events was generally consistent with the characteristics previously observed in trials that assessed the clinical effectiveness of pembrolizumab for the treatment of other indications.

HRQoL data were collected during the KEYNOTE-054 trial using the QLQ-C30 questionnaire and the EQ-5D-3L questionnaire. The results from the QLQ-C30 questionnaire are not currently available, as the data have not yet been analysed. Adjusted data from the EQ-5D-3L questionnaire are used to inform the company's cost effectiveness model.

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

The ERG is satisfied with the company's search strategy and their stated inclusion and exclusion criteria. The ERG is confident that the literature searching was carried out to an acceptable standard and the ERG is not aware of any additional studies that should have been included in the company's systematic review.

The ERG is satisfied that the patients recruited to the KEYNOTE-054 trial are representative of patients with resected Stage III melanoma who are treated in the NHS and appear to match

the population specified in the final scope issued by NICE. The ERG has been unable to identify any definitive definitions of high risk of either death or disease recurrence for patients with Stage III melanoma. It is, therefore, unclear whether all patients in the KEYNOTE-054 trial can be considered to be at high risk of death or disease recurrence.

Clinical advice to the ERG is that approximately 20% of patients treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than those participating in the KEYNOTE-054 trial (ECOG PS 0: 94.4%, ECOG PS 1: 5.6%). In addition, 83.3% of patients included in the KEYNOTE-054 study were defined as having programmed death ligand 1 (PD-L1) positive disease and, as PD-L1 testing is not routinely carried out in the NHS, it is not known whether a similarly high proportion of NHS patients have PD-L1 positive disease.

The ERG considers that the KEYNOTE-054 trial is a good quality trial and is well conducted. However, the ERG is concerned by the current lack of data available from this trial. The ERG notes that median RFS has not yet been reached in the pembrolizumab arm of the trial and that only limited analyses of the OS and DMFS data have been conducted due to the immaturity of the data.

The HRs for RFS presented in the CS are estimated using a Cox proportional hazards (PH) model. The ERG considers that, in the KEYNOTE-054 trial, although the company has not carried out any formal testing, the PH assumption is unlikely to hold for RFS. The ERG highlights that a HR estimated using a Cox PH model has no meaningful interpretation when the PH assumption is violated. Therefore, the HRs for the presented RFS analyses should be interpreted with caution. Given the recognised departures from PH for survival data collected during immunotherapy trials, the ERG suggests that, in order to generate meaningful results, designers of future trials of immunotherapies should consider including approaches to modelling survival data that do not rely on the assumption of PH.

The company is confident that the improvement in RFS demonstrated in the KEYNOTE-054 trial will result, in a future OS benefit. In support of this claim, the company cites evidence from a meta-analysis that was published in 2018. The meta-analysis included individual patient data from 13 RCTs conducted in patients with Stage II or Stage III melanoma. The authors of the meta-analysis conclude that RFS appears to be a valid surrogate endpoint for OS in RCTs of adjuvant treatment with interferon or a checkpoint inhibitor. The ERG considers that there is no reliable evidence, at present, to determine the extent (if any) to which adjuvant treatment of Stage III melanoma with immunotherapies delivers OS benefit.

The company considers that treatment with pembrolizumab was well tolerated by patients in the KEYNOTE-054 trial (CS, p48).

Clinical advice to the ERG is that AEs (Grade 2 or higher) arising from treatment with pembrolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs and that this places a high burden on NHS staff.

1.5 Summary of cost effectiveness evidence submitted by the company

Due to the absence of any relevant published information, the company developed a de novo cohort-based state transition model in Microsoft Excel to compare the cost effectiveness of treatment with pembrolizumab versus routine surveillance for the treatment of patients with completely resected Stage III melanoma. The company model comprised four health states: recurrence-free (RF), locoregional recurrence (LR), distant metastasis (DM) and death. All patients entered the model in the RF state and, at each cycle, were able to transition to a worse health state (transitions to less severe health states were not permitted). The company model time horizon was set to 46 years and the cycle length was 1 week. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE.

The RFS data from the KEYNOTE-054 trial was deconstructed into time to first recurrence event, which could either be LR, DM or death. These data were used to model the three transitions from the RF health state. Transitions from the LR health state to the DM or death health states were estimated using patient-level data from the Flatiron database. Estimates of the rates of transitions from the DM health state to the death health state were obtained from the KEYNOTE-006 trial. Duration of treatment was obtained from the time on treatment data from the KEYNOTE-054 trial. There was sufficient time on treatment data from the KEYNOTE-054 trial so data extrapolation for the model was not required.

Utility estimates in the company model were derived from the EQ-5D-3L data collected during the KEYNOTE-054 trial and from an observational study in which the general public were asked to value the HRQoL of people living with different stages of melanoma. Resource use estimates were obtained from the KEYNOTE-054 trial and from two previous NICE technology appraisals of pembrolizumab for advanced melanoma (TA357 and TA366).

Results from the company's base case comparison showed that treatment with pembrolizumab dominated routine surveillance, being both cheaper (-£3,988) and more effective (+3.18 life years, +2.73 QALYs). Results from the company's probabilistic sensitivity

analysis also showed that, compared with routine surveillance, treatment with pembrolizumab was the dominant strategy (incremental cost: -£3,970, incremental effectiveness: +2.62 QALYs).

The company carried out a range of deterministic sensitivity analyses. The most influential parameter was the parametric function used to model transitions from the RF health state to the LR health state. In all deterministic analyses performed by the company, the incremental cost effectiveness ratio (ICER) for the comparison of treatment with pembrolizumab versus routine surveillance was never greater than £10,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The company developed a de novo economic model to evaluate the cost effectiveness of pembrolizumab as an adjunctive therapy compared to routine surveillance for patients with Stage III melanoma. The ERG is satisfied that the company model is correctly implemented.

The company did not use the mature RFS data from the KEYNOTE-054 trial to populate their model; instead, they used data on first recurrence event (LR and DR) to indirectly model OS and DMFS. The ERG notes that these first recurrence events were not pre-specified outcomes in the KEYNOTE-054 trial analysis plan. In addition, the ERG considers that as OS and DMFS data from the KEYNOTE-054 trial were considered to be too immature to be analysed and/or presented fully in the CS, these data are too immature to be included in an economic model. At the time of writing the CS, the OS and DMFS data were not expected to reach maturity until [redacted] respectively. The ERG notes that immature data can lead to spurious projections of OS, especially in cancer studies.

To assess the clinical plausibility of the company model projections, the company compared the estimated 5-year OS and 5-year DMFS for the routine surveillance arm in the company model against reported data from the EORTC 18071 trial (ipilimumab for adjunctive therapy versus placebo for resected Stage III melanoma). The ERG notes that this comparison showed that the model projects slightly higher OS and, at the same time, much lower DMFS for the routine surveillance arm than the placebo arm of the EORTC 18071 trial.

The ERG used digitised versions of the OS data from the 2010 Surveillance, Epidemiology, and End Results (SEER) program database to generate curves by disease stage subgroup (Stage IIIA, Stage IIIB and Stage IIIC) and a composite curve (weighted by the percentage of patients, in the KEYNOTE-054 trial, in each disease stage). This composite OS curve provides an approximation of the expected OS for the routine surveillance arm in the company model. The trajectory of the OS curves suggests that, after 10 years, the company model projected

OS curve for the routine surveillance arm would lie below that of patients with only Stage IIIC disease in the 2010 SEER database, which is clinically implausible from the ERG's perspective.

The company has assumed that, over the 46-year model time horizon, the hazard rate of a first recurrence event (LR or DM) is always higher for patients in the routine surveillance arm than for those in the pembrolizumab arm. This assumption has a significant impact on model outcomes, for example:

- if the treatment effect for pembrolizumab were to be stopped at 3 years, the company model would predict that treatment with pembrolizumab would stop being cost saving and would become cost incurring (£22,848 per patient).
- if the time horizon of the company model were to be limited to 16 months (the median length of follow-up data available from then KEYNOTE-054 trial), i.e., no extrapolation, the ICER generated by the company model would be circa £750,000 per QALY gained for the comparison of treatment with pembrolizumab versus routine surveillance.

These analyses highlight the sensitivity of company model results to the estimates of treatment effect, a parameter which, with the current level of data maturity, cannot be accurately measured.

The ERG considers that the company's estimated ICERs per QALY gained are unreliable. Furthermore, given the immaturity of the data, the ERG was unable to produce ICERs per QALY gained that were more reliable than those presented in the CS.

1.7 Summary of company's case for End of Life criteria being met

The company (appropriately) did not present a case for pembrolizumab to be assessed against the NICE End of Life criteria.

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

1.8.1 Strengths

Clinical evidence

- The ongoing KEYNOTE-054 trial is of good quality and is well conducted
- EQ-5D-3L data are being collected as part of the KEYNOTE-054 trial
- Part 2 of the KEYNOTE-054 trial is designed to assess the clinical effectiveness of re-challenge with pembrolizumab

Cost effectiveness evidence

- The ERG is satisfied that the company model is correctly implemented
- The company used TTD to cost study treatments

- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- The main weakness of the clinical evidence supplied by the company is that there are only limited OS or DMFS data available from the KEYNOTE-054 trial to support the use of pembrolizumab for the adjuvant treatment of resected melanoma with high risk of recurrence
- Median RFS in the pembrolizumab arm of the KEYNOTE-054 trial has not yet been reached
- The HRs relevant to RFS outcomes presented in the CS are derived from data that are unlikely to meet the PH assumption. The HRs relevant to RFS that are reported in the CS should, therefore, be treated with caution
- In the patient population under consideration, the definition of high risk is unclear and it is uncertain whether, in the NHS, the whole of the KEYNOTE-054 trial population would be considered at high risk of death or disease recurrence
- Clinical advice to the ERG is that AEs (Grade 2 or higher) arising from treatment with pembrolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs
- Data relevant to HRQoL are limited to the company's report of the outcome of the analysis of the EQ-5D-3L responses. The ERG is unable to comment on the analysis, as the company has not provided the number of patients who responded to the questionnaire or stated the time points when the responses were collected
- Although sentinel node mapping is used in the NHS as a means of diagnosing Stage III melanoma, clinical advice to the ERG is that, currently, not all patients in the NHS have access to sentinel node mapping. If pembrolizumab is recommended for use in the NHS by NICE as an adjuvant treatment, limits to access to sentinel node mapping may affect access to pembrolizumab as an adjuvant treatment
- Pembrolizumab is recommended by NICE for treating patients with advanced melanoma not previously treated with ipilimumab (TA366). If pembrolizumab were to be recommended for use in the adjuvant setting, it is unclear how this recommendation would impact on treatments in the advanced (metastatic) setting
- In view of the ongoing NICE appraisals of nivolumab and dabrafenib in combination with trametinib for the treatment of Stage III melanoma, it would be informative to consider the relative effectiveness of pembrolizumab versus these other treatments

Cost effectiveness evidence

- RFS, the outcome for which data from the KEYNOTE-054 trial demonstrate that treatment with pembrolizumab is clinically and statistically significant, is not used in the model as it cannot be linked directly to costs or QALYs
- The model is constructed using outcomes from the KEYNOTE-054 trial that were not pre-specified in the trial statistical analysis plan (first DM or first LR event). These outcomes are used as intermediate outcomes for DMFS, which itself is an intermediate outcome that is used to determine OS. The company expects that DMFS and OS data from the KEYNOTE-054 trial will not be mature until [redacted]

- Over 99% of the QALY gain predicted by the company model for pembrolizumab comes from projections rather than actual trial data and these projections are based upon outcomes that were not pre-specified in the trial statistical analysis plan
- The company's use of the KEYNOTE-054 trial data produces model estimates of DMFS and OS that are not clinically plausible
- The ERG considers that data from the KEYNOTE-054 trial are too immature to produce a robust estimate of the pembrolizumab treatment effect on DMFS or OS
- The company assumes that everyone entering the DM state has systemic therapy and, therefore, effectively assumes that everyone in this health state has unresectable Stage IV cancer. The company did not provide sufficient evidence to support this assumption
- The company model does not generate results by Stage III melanoma (Stage IIIA, IIIB and IIIC/IIID). The differentials in OS and melanoma-specific survival rates are considerable, which suggests that the cost effectiveness of pembrolizumab for these subgroups will also be substantially different to that for the whole population.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

Given the immaturity of DMFS and OS data that are derived from the KEYNOTE-054 trial, the ERG did not consider that any robust ICERs per QALY gained could be produced. Therefore, no exploratory or sensitivity analyses were undertaken by the ERG.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B1.3.1 of the company submission (CS) [1]. The Evidence Review Group (ERG) considers that the company's description presents a reasonable summary of the underlying health problem for melanoma globally; however, the company has provided only limited information relevant to Stage III melanoma. Key points made by the company, and considered by the ERG to be of particular relevance to the current appraisal, are presented in Box 1. The ERG notes that the company has not discussed the impact of Stage III melanoma on patients and carers.

Box 1 Key points from the company's description of the underlying health problem

Description of disease
Melanoma is a malignant tumour that arises from the melanocytes found in the basal layer of the skin; these cells are responsible for the production of melanin skin pigment. Malignant melanoma is a heterogeneous and complex disease with multiple clinical subtypes including, but not limited to, superficial spreading melanoma and nodular melanoma, both of which are characterised by the site of primary tumour, radial growth and histopathology.

The main risk factors associated with the development of melanoma, include a familial history of melanoma, fair skin type and fair hair colour, high density of moles, previous history of melanoma, and additional environmental factors, such as intense or chronic exposure to ultraviolet light [2-4].

Melanoma is classified using the AJCC Tumour, Node, Metastases (TNM) staging system [5]. Stage III melanoma, the focus of the current appraisal, is typically characterised by regional nodal involvement and primary tumour ulceration. Stage III melanoma is further sub-categorised to IIIA, IIIB, and IIIC depending on the presence of micro-, macro- or satellite-metastases respectively.

Epidemiology
Malignant melanoma is one of the most aggressive types of skin cancer, contributing to over 90% of all cutaneous tumour deaths globally [6]. Melanoma has also been identified as the most commonly diagnosed cancer among adolescents and young adults globally [7]. Melanoma has an incidence of 4% of all new cancers diagnosed in the UK in 2015 [8, 9]. The incidence of melanoma has increased by 128% in the UK since the early 1990s [8].

Burden of disease
The 5-year OS rates reported in the 2009 AJCC Cancer Staging Manual 7th edition [7], for patients with Stage IIIA, IIIB and IIIC melanoma were 78%, 59%, and 40%, respectively. Recurrence of melanoma is associated with substantial patient morbidity and mortality.

AJCC= American Joint Committee on Cancer; CRUK=Cancer Research UK; OS=overall survival
Source: adapted from CS, Section B1.3.1

The ERG notes that in England, in 2015, almost 14,000 people were diagnosed with malignant melanoma of the skin [8]. Men and women were similarly affected, 51% and 49% respectively [8]. Most melanomas in England are diagnosed at an early stage, 91% at Stage I or Stage II [8]. In the UK in 2012, 3% of melanomas were diagnosed at Stage III [10]. The ERG notes that the incidence of 3% may not include patients who present with Stage I and Stage I disease and who later progress to Stage III. Clinical advice to the ERG is that there are no robust data

available to allow an estimate of the numbers of patients with disease progression to Stage III following a diagnosis at Stage I or Stage II.

Stage III melanomas are regarded as intermediate or high risk melanomas as they have a high probability of progressing to Stage IV melanomas that have spread to distant parts of the body [10]. Patients who have had surgery to remove Stage III tumours are at high risk of relapse and death.[11]. NICE reports that 5-year relapse-free survival for patients with Stage III melanoma is 28% to 44% [11].

Survival rates at 5 years of between 52% and 55% are reported for patients in England with Stage III melanoma [12]. The survival rates are based on data from the Anglian Cancer Network collected between 2002 and 2006. Data from Cancer Research UK indicate that survival from melanoma skin cancer in the UK has doubled in the last 40 years [12].

AJCC staging and classification

The company states that the staging of melanoma is based on the TNM staging system described in the AJCC Cancer Staging Manual.[5] The company highlights (CS, p14) that the staging system as set out in the 7th edition of the manual [7] was in use at the time of the protocol development for, and the recruitment of, patients to the KEYNOTE-54 trial, the trial discussed in the CS. The company reports that in 2018, the 8th edition of the AJCC manual came into effect [13]. In the 8th edition, the number of Stage III categories increased from three (A to C) to four (A to D). A comparison of the classifications in the 7th and 8th edition is provided in Table 3 of the CS. The company is confident that the changes made to the Tumour, Node, Metastasis (TNM) classification system from the 7th to the 8th editions of the AJCC manual do not have any impact on the clinical relevance of the patient population recruited to the KEYNOTE-054 trial. Clinical advice to the ERG supports the company's opinion.

The company highlights (CS, Table 3) the improved survival rates of patients with Stage III melanoma cited in the 8th edition of the manual compared with the survival rates cited in the 7th edition. The 5-year melanoma specific survival rates reported 8th edition [13] for patients with Stage IIIA, IIIB, IIIC and the new classification of Stage IIID melanoma are 93%, 83%, 69% and 32% respectively, compared with overall survival of 78%, 59%, and 40% in 2009 7th edition [7].

2.2 Company's overview of current service provision

The ERG considers that the company's overview of current service provision (CS, Section B1.3.2) represents an accurate summary and describes the company's key points in Box 2.

Box 2 Key points from the company's overview of current service provision

Diagnosis and management

- Patients typically present with an alteration in a pre-existing pigmented mole or a new pigmented lesion. For a confirmatory diagnosis of Stage III melanoma, patients undergo either an excision biopsy or a complete excision with normal skin margins and is confirmed by pathology. Patients with suspected Stage III melanomas are also offered a sentinel lymph node biopsy.

Treatment

- The primary treatment for Stage III melanoma includes wide excision of the primary tumour together with a lymph node dissection of the involved nodal basin.
- At present, NICE [14] does not recommend the use of adjuvant therapies for patients with surgically resected Stage III melanoma at high risk of recurrence. However, both the ESMO [15] and the NCCN [16] recommend the use of adjuvant therapies, including the use of immunotherapies.

Recurrence management

- As the risk of melanoma recurrence is at its highest within 5 years of the primary diagnosis, NICE clinical guidelines [14] recommend a period of observation of 5 years for patients with Stage III melanoma (16). A position paper [17] reporting the consensus view of the majority of UK clinicians recommends follow-up of 10 years following surgical excision of Stage III melanoma.

ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network
Source: adapted from CS, Section B1.3.2

As stated in the CS, in the NICE Guideline NG14 [14], NICE has not recommended any adjuvant treatment for patients with Stage III melanoma at high risk of recurrence following surgical resection. The ERG notes that in the European Society for Medical Oncology guidelines [15], interferon is recommended as an adjuvant therapy (in selected patients), whilst in the National Comprehensive Cancer Network guidelines [16], a range of adjuvant therapies, including nivolumab (for Stage IIIB or Stage IIIC only), dabrafenib in combination with trametinib, ipilimumab, and interferon alfa are recommended.

Within the context of the KEYNOTE-054 trial, the company describes (CS, p26) three categories of recurrent disease and these include new melanoma lesions that are either local, regional or distant. Local recurrence is defined as a new lesion that occurs within 2cm of the excised tumour bed. Regional lymphatic and nodal recurrences are defined as either in transit metastases (new lesions that are more than 2cm from the primary lesion but are not beyond the regional nodal basin) or regional node recurrence (lesions occurring within a previously dissected nodal basin and are at the periphery of the previous surgical site). Distant metastases occur in non-visceral sites, for example, skin, subcutaneous tissue and lymph nodes. Visceral sites for metastases include lung, brain, liver, gastrointestinal tract and bone.

The ERG considers that Figure 3 in the CS provides an accurate depiction of the current treatment pathways for patients in the NHS who have Stage III melanoma. The company has positioned treatment with pembrolizumab as an adjuvant treatment to surgical excision. Treatment with pembrolizumab is given intravenously at a dose of 200mg every 3 weeks for 18 administrations (approximately 1 year).

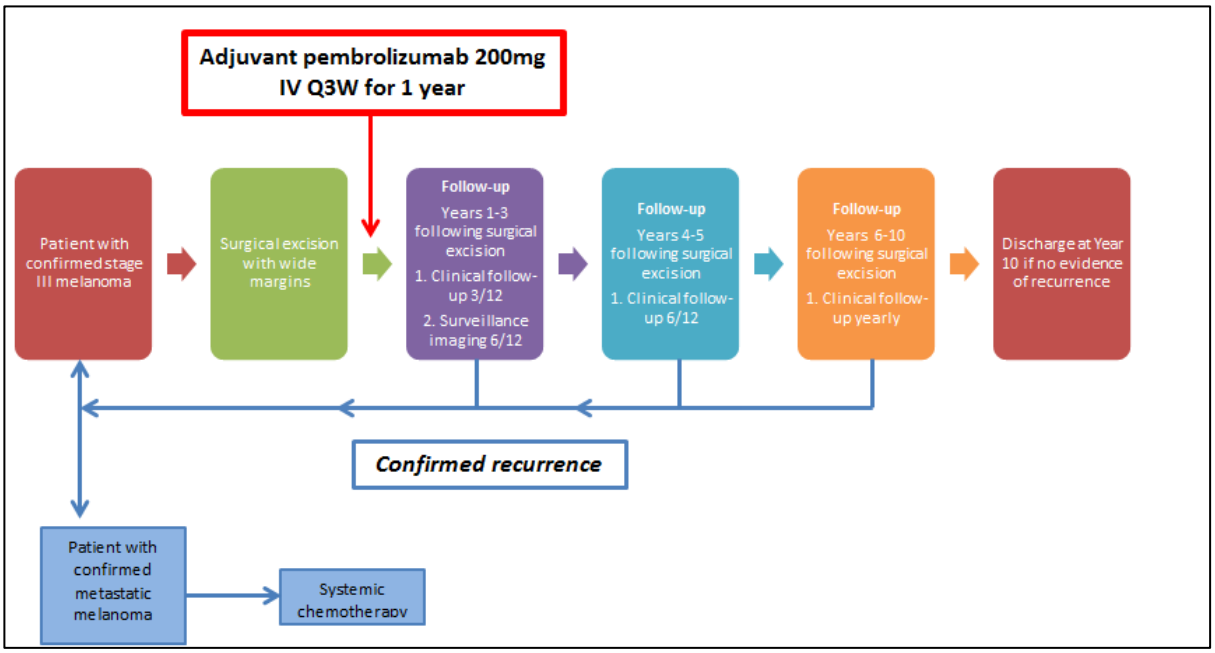

Figure 1 Current clinical pathway of care showing the context of the proposed use of the technology

Source: CS, Figure 3

The ERG notes that NICE's recommendations for the routine follow-up of patients in the NHS with completely resected Stage III melanoma are set out in NG14 [14]. NICE recommends that patients with Stage III melanoma are followed up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years. Patients may be discharged 5 years after treatment. NICE recommends considering surveillance imaging as part of the follow-up for patients who might be eligible for systemic therapy as a result of early detection of metastatic disease if there is a clinical trial of the value of regular imaging, or, if the specialist skin cancer multi-disciplinary team agrees to a local policy and specific funding for imaging every 6 months for 3 years is identified. However, the ERG is aware that, in the position paper authored by UK clinicians [17] the recommend imaging schedule is at baseline, every 6 months up to 3 years and annually up to 5 years. Patients should then be reviewed annually for a further 5 years.

The company's rationale (CS, p18) for the use of pembrolizumab as an adjuvant treatment is that surgery is not curative for most patients with Stage III melanoma [6, 18]. The company proposes that adjuvant systemic therapy has an impact on any residual micro-metastatic disease and thereby improves recurrence-free survival (RFS) and, ultimately, overall survival (OS) for patients with Stage III melanoma. The ERG notes that the authors of a systematic review of stage-specific recurrence rates and survival rates in European patients with Stage III melanoma report recurrence rates of 28% to 48% and survival rates of 35% to 58% [19].

The recurrence and survival rates indicate that more than half of patients with resected Stage III melanoma experience disease recurrence or die of their disease.

The company acknowledges that pembrolizumab is recommended by NICE as a treatment option for Stage IV melanoma. The company states (CS, p53) that the clinical efficacy of re-treatment with pembrolizumab after adjuvant treatment at Stage III is unknown. A second part of the KEYNOTE-054 trial is underway and is designed to assess the clinical effectiveness of re-challenge with pembrolizumab following progression at Stage III; however, the company states that the results from the second part of the KEYNOTE-054 trial will not be available for some years.

2.3 Innovation

The company states (CS, p49) that patients with Stage III melanoma who have undergone a complete resection of their primary tumour and lymph nodes remain at significant risk of disease recurrence for 5 years post-diagnosis [6, 18]. The company states that, until recently, few treatments have been available that could reduce the risk of disease recurrence. The company is confident that the use of pembrolizumab represents a durable and well-tolerated treatment for patients with completely resected melanoma at high risk of recurrence.

The ERG notes that adjuvant treatment with immunotherapies is not available in the NHS. However, treatment with immunotherapies is established practice in the NHS for patients with Stage IV melanoma. The ERG notes that NICE is currently appraising nivolumab for the adjuvant treatment of completely resected Stage III and Stage IV melanoma [20] and dabrafenib in combination with trametinib for patients with completely resected Stage III melanoma with BRAF V600 positive mutations [21]. NICE expects to publish recommendations for the use of dabrafenib in combination with trametinib in December 2018. The expected publication date for NICE's recommendations for the use of nivolumab is yet to be confirmed; however, the NICE Appraisal Committee is due to meet on 16th August 2018.

2.4 Number of patients eligible for treatment with pembrolizumab

In Section A of the CS (p21), the company estimates that, in England, the maximum number of patients who would be eligible for adjuvant treatment with pembrolizumab is 780 annually. The ERG is unable to comment on the company's estimate as the methods used to calculate the estimate were not included in the CS.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE [22] and that addressed within the CS is presented in Table 1. Each parameter in Table 1 is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 1 Comparison between NICE scope and company decision problem

Final scope issued by NICE Parameter and specification	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS**
Population People with completely resected stage III melanoma at high risk of recurrence	Adults with completely resected melanoma at high risk of recurrence (CS, Table 5, p20)
Intervention Pembrolizumab	Pembrolizumab
Comparators Routine surveillance	Routine surveillance (data are derived from the placebo arm of the KEYNOTE-054 trial)
Outcomes OS, RFS, DMFS, AEs,HRQoL	The company has presented final results for RFS, AEs and provides limited HRQoL findings The company explains that the final results for DMFS and OS have not been presented as, at the time of submission, these data from the KEYNOTE-054 trial were immature
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness has been assessed using ICERs per QALY gained
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	The model time horizon is 46 years (mean patient age at baseline is 53.8 years)
Costs will be considered from an NHS and Personal Social Services perspective	Costs have been considered from an NHS perspective
The availability of any patient access schemes (PAS) for the intervention or comparator technologies will be taken into account	Model base case results have been calculated using the CAA for pembrolizumab. However, discounts to the NHS are available for the other treatments included in the model (nivolumab, ipilimumab, vemurafenib, dabrafenib in combination with trametinib); these prices are confidential and, therefore, not known to the company. The ERG has re-run the company's base case analysis using the discounted prices for all drugs. Results from this analysis are provided in a confidential appendix
Subgroups to be considered. None	-
Other considerations. None identified	The company did not identify any equity or diversity issues

AE=adverse effects of treatment; CAA=Commercial Access Agreement; CS=company submission; DMFS=distant metastases-free survival; ERG=Evidence Review Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; OS=overall survival; PSS=Personal Social Services; QALY=quality adjusted life year; RFS=recurrence-free survival
Source: NICE scope, CS and ERG assessment

The company's main source of clinical effectiveness evidence for this appraisal is the KEYNOTE-054 trial. This is a randomised, double-blind, ongoing Phase III trial assessing the clinical effectiveness of pembrolizumab versus placebo in patients who have undergone complete surgical resection of Stage III melanoma.

3.1 Population

3.1.1 Risk of recurrence

The population described in the final scope issued by NICE [22] is people with completely resected Stage III melanoma at high risk of recurrence. Within the CS, the company describes the patient population in the KEYNOTE-054 trial as having completely resected melanoma at high risk of recurrence.

There is no definition of high risk of recurrence in the final scope issued by NICE. The ERG also highlights that there is no explicit definition of high risk of recurrence within the CS. Furthermore, there is no explicit definition of high risk of recurrence within the company's main peer-reviewed journal publication [23]; the most relevant statement within this publication [23] is that, "…The patients had to have either Stage IIIA melanoma or Stage IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition".

3.1.2 Risk of death

In the CS, the company compares the AJCC staging classifications described in the 7th and 8th editions (based on data from the Surveillance, Epidemiology and End Results (SEER) Program database [24]) and presents information on risk of death for each of the staging subgroups in the KEYNOTE-054 trial. Data in Table 2 show survival estimates for patients with Stage III melanoma for the three/four individual AJCC staging classifications [7, 13]. Clinical advice to the ERG is that there is no agreed definition of high risk of death for patients with Stage III melanoma but that it is likely that patients with an expected 5-year survival of ≤50% would be considered to be at high risk of death. This means that strict adherence to the most recent (2018) AJCC criteria [13] would suggest that only patients with Stage IIID disease fall within the definition of high risk of death.

Table 2 AJCC estimated survival for patients with Stage III melanoma

Stage III completely resected melanoma sub-category	AJCC 7th Edition Estimated 5 year overall survival	AJCC 8th Edition Estimated 5 year melanoma specific survival
Stage IIIA	78%	93%
Stage IIIB	59%	83%
Stage IIIC	40%	69%
Stage IIID	NA	32%

Source: Balch 2009; Gershenwald 2017

The ERG has been unable to identify any definitive definitions of high risk of either death or disease recurrence for patients with Stage III melanoma. It is, therefore, unclear whether all patients in the KEYNOTE-054 trial can be considered to be at high risk of death or disease recurrence.

Clinical advice to the ERG is that approximately 20% of patients treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than those participating in the KEYNOTE-054 trial (ECOG PS 0: 94.4%, ECOG PS 1: 5.6%). In addition, 83.3% of patients included in the KEYNOTE-054 study were defined as having programmed death ligand 1 (PD-L1) positive disease and, as PD-L1 testing is not routinely carried out in the NHS, it is not known whether a similarly high proportion of NHS patients have PD-L1 positive disease.

3.2 Intervention

The intervention specified in the final scope issued by NICE [22], and discussed in the CS, is pembrolizumab. Pembrolizumab does not currently have a UK marketing authorisation (MA) for the adjuvant treatment of patients with Stage III melanoma at high risk of recurrence, although it does have European MA for the treatment of advanced (unresectable or metastatic) melanoma in adults, as well as for certain populations with non-small cell lung cancer, classical Hodgkin lymphoma, and urothelial carcinoma. The company has made an application to the Committee for Medicinal Products for Human Use (CHMP) and [redacted]. The company's proposed wording for the indication is [redacted]

Summary details of guidance relating to treatment with pembrolizumab that has already been published by NICE are provided in Table 3.

Table 3 Pembrolizumab guidance published by NICE

ID	Date of publication	Guidance (summary details)
Melanoma		
TA366 [22]	Nov 2015*	Advanced melanoma in adults not previously treated with ipilimumab
TA357 [25]	Oct 2015*	Advanced melanoma after disease progression with ipilimumab
Non-small cell lung cancer		
TA531 [26]	Jun 2017	Untreated PD-L1 positive metastatic non-small cell lung cancer in adults
TA428 [27]	Jan 2017*	Locally advanced or metastatic PD-L1 positive non-small cell lung cancer in adults
Urothelial cancer		
TA522 [28]	Jun 2018	Untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable
TA519 [29]	Apr 2018	Locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy

* Updated September 2017

It is explained in the CS (p11) that pembrolizumab is a monoclonal antibody which binds to the programmed death (PD-1) receptor and directly blocks the interaction between PD-1 and its associated ligands (PD-L1 and PD-L2) which appear on antigen-presenting or tumour cells. It is further explained within the CS (p11) that the effect of treatment with pembrolizumab is to release the PD-1 pathway-mediated inhibition of the immune response, and reactivate both tumour-specific cytotoxic T lymphocytes in the tumour micro-environment and anti-tumour activity.

Within the KEYNOTE-054 trial, the treatment regimen for pembrolizumab is a flat dose of 200mg delivered via an intravenous (IV) infusion which is administered in a hospital setting every 3 weeks (Q3W) for up to 18 administrations. Clinical advice to the ERG is that the Q3W protocol used to deliver pembrolizumab places a high burden on NHS nursing and pharmacy staff. Clinical advice to the ERG is that adverse events (AEs) of Grade 2 or higher arising from treatment with pembrolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

3.3 Comparator

The comparator specified in the final scope issued by NICE is routine surveillance. The comparator arm of the KEYNOTE-054 trial is placebo. Specifically, a normal saline solution prepared by the local pharmacist, dosed and administered in the same manner as the investigational product (i.e., IV infusion Q3W on day 1 of each 3-week cycle for a total of 18 administrations [approximately 1 year]).

The ERG notes that currently (August 2018) two related NICE STAs are ongoing:

- ID1316 [20]: nivolumab for the adjuvant treatment of completely resected stage III and IV melanoma (expected publication date: to be confirmed).
- ID1226 [21]: dabrafenib in combination with trametinib for people with completely resected state III melanoma with BRAF V600 positive mutations (expected publication date: December 2018)

The comparator specified in the final scopes [11, 30] issued by NICE for both of these appraisals is also routine surveillance.

3.4 Outcomes

Clinical evidence from the KEYNOTE-054 trial is reported for three of the five outcomes specified in the final scope issued by NICE: RFS, AEs and health-related quality of life (HRQoL). The company explains that final OS and final distant metastasis-free survival (DMFS), the other outcomes specified in the final scope issued by NICE, are not yet available as the data from the KEYNOTE-054 trial are currently too immature for analysis ([redacted]). The company expects OS results to become available [redacted] and DMFS results to become available in [redacted].

The company acknowledges the immaturity of the OS data from the KEYNOTE-054 trial (CS, p115) and explains that, in the economic model, data derived from the Flatiron registry [31] were used to estimate the transition from local recurrence to distant metastases and that data from existing trials in the advanced setting were used to estimate the transition from distant metastases to death.

The company is confident that the improvement in RFS demonstrated in the KEYNOTE-54 trial will be reflected in a future OS benefit. In support of the claim, the company cites evidence from a meta-analysis [32] published in 2018. The meta-analysis included individual patient data from 13 randomised controlled trials (RCTs) conducted in patients with Stage II or Stage III melanoma. The authors of the meta-analysis [32] conclude that RFS appears to be a valid surrogate endpoint for OS in RCTs of adjuvant treatment with interferon or a checkpoint inhibitor.

The ERG considers that there is no reliable evidence, at present, to conclude that adjuvant treatment of Stage III melanoma with immunotherapies has any OS benefit. The ERG further cautions that there is evidence that benefits shown with surrogate endpoints are not always realised when OS data become mature [33-35]. A detailed ERG critique of the plausibility of RFS as a surrogate outcome for OS in the context of this submission is presented in Section 4.10 of this ERG report.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 46-year time-period (a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

No subgroups were specified in the final scope issued by NICE.

3.7 Other considerations

The company did not identify any equity or equality issues. However, clinical advice to the ERG is that although in clinical trials and clinical practice people are increasingly being offered sentinel lymph node (SLN) mapping, there is inequitable access to the procedure across the UK.

Details relating to the Commercial Access Agreement (CAA) for pembrolizumab have been provided by the company. Discounts (in the form patient access schemes [PASs]) are also in place for all treatments used in the company model to treat advanced or metastatic melanoma (i.e. ipilimumab, nivolumab, vemurafenib, and dabrafenib in combination with trametinib). These discounted prices are confidential and are, therefore, not known to the company. The ERG has, however, re-run the company's base case analysis using the discounted prices for these treatments and these results are provided in a confidential appendix.

The company (appropriately) did not present a case for pembrolizumab to be assessed against the NICE End of Life criteria.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D of the CS. The ERG considered whether the review was conducted in accordance with the key criteria listed in Table 4. Overall, the ERG considers the methods used by the company in the systematic review of clinical effectiveness evidence were satisfactory. The ERG has run its own searches and is confident that no relevant publications were missed.

Table 4 ERG appraisal of systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the study eligibility criteria appropriate to the decision problem?	Yes
Were study selection criteria applied by two or more reviewers independently?	Yes
Were the study data extracted by two or more reviewers independently?	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not reported
Were appropriate methods used for data synthesis?	Not applicable

4.1.1 Literature search

The company explains (CS, p19) that, at the time of the literature search, only unpublished evidence from the KEYNOTE-054 trial was available. However, details of the KEYNOTE-054 trial were published [23] after the searches were complete and before the company submitted its evidence submission to NICE.

4.1.2 Data extraction

The company has not reported whether one or more reviewers conducted the data extraction exercise.

4.1.3 Quality assessment methods

The company has (appropriately) applied the criteria from the Cochrane Risk of Bias tool[36] to the KEYNOTE-054 trial (CS, Table 12, p36). It is not stated in the CS whether one or more reviewers conducted the quality assessment exercise.

4.1.4 Data synthesis

Clinical effectiveness evidence for the use of pembrolizumab as an adjuvant treatment for patients with resected Stage III melanoma at high risk of recurrence is only available from the KEYNOTE-54 trial. Data synthesis was not applicable.

4.2 ERG critique of clinical effectiveness evidence

4.2.1 Identified trial

The KEYNOTE-054 trial is the only identified RCT that provides evidence for the use of pembrolizumab versus placebo in the adjuvant treatment of patients with completely resected Stage III melanoma at high risk of recurrence. All information presented in this ERG report is taken directly from the CS, unless otherwise stated. The ERG notes that there are minor differences between the information provided in the CS and the information provided in the published paper.

4.3 Characteristics of the KEYNOTE-054 trial

4.3.1 Trial characteristics

The KEYNOTE-054 trial is an ongoing phase III, double-blind trial. Details of the trial are reported in the CS (p19). The trial is being conducted in 23 countries and patient recruitment took place between August 2015 and November 2016. Of the 1019 recruited patients, 677 were from centres in Europe, with 52 from UK centres.

Briefly, patients over the age of 18 years were eligible to be randomised into the trial if they met the following criteria:

- had a complete resection of Stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to the lymph node classified as Stage IIIA (>1mm lymph node metastasis), any Stage IIIB, or Stage IIIC. No history of current in-transit metastases or satellitosis
- tumour sample evaluable for PD-L1 expression
- resection of Stage III lymph nodes must have been performed in complete compliance with the criteria for adequate surgical procedures for complete lymph node dissection
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
- interval from surgery to first study drug treatment ≤13 weeks
- adequate organ function.

Patients were randomised in a 1:1 ratio to receive treatment with an intravenous (IV) solution of pembrolizumab, IV infusion Q3W on day 1 of each 3-week cycle for a total of 18

administrations [approximately 1 year]). Stratification factors were disease stage and geographical region (North America, Europe, Australia and other countries as designated).

The primary outcome of the KEYNOTE-054 trial was RFS in the overall intention-to-treat (ITT) population and RFS in the subgroup of patients with PD-L1 positive tumour expression. Secondary outcomes include DMFS, OS and AEs. The data presented in the CS are derived from the first interim analysis (IA1) and are relevant to the outcomes of RFS and AEs only. The company explains (CS, p21) that too few DMFS and OS events had occurred at the time of the data cut off for IA1 to allow meaningful analysis.

The company reports (CS, p21) that the treatment phase of the KEYNOTE-054 trial is split into two parts. In part 1, patients receive adjuvant treatment for up to 18 cycles. In part 2, patients whose disease progresses can either crossover to treatment with pembrolizumab or patients can receive re-challenge with pembrolizumab. Only part 1 of the trial is discussed in the CS.

HRQoL data using the QLQ-C30 and the EQ-5D-3L questionnaires were collected during the trial. The results from the QLQ-C30 questionnaires are not reported in the CS as they are, at present, immature. The results from the analysis of the EQ-5D-3L questionnaires are used in the company's economic model.

Clinical advice to the ERG is that the trial eligibility criteria are reasonable, and, that the participating treatment centres are representative of treatment centres in the UK. Centres in Europe and the USA, in particular, have similar SLN protocols to those in place in the UK. The ERG is satisfied that the KEYNOTE-054 trial was well designed and well conducted. However, the ERG notes the immaturity of the data for the outcomes of DMFS and OS.

4.3.2 Baseline characteristics of patients enrolled in the KEYNOTE-054 trial

Patient characteristics summarised in the company submission

The baseline characteristics of the patients randomised in the KEYNOTE-054 trial are summarised in the CS (Table 9, p29). The ERG agrees with the company that the baseline characteristics (gender, age, geographic region, PD-L1 status, BRAF mutation status, ECOG PS) are well balanced across the two treatment arms. The overall mean age of patients was 53.8 years and 61.6% were men. Many patients (67%) were recruited from centres in Europe and the majority (94%) were of ECOG PS 0. Most patients (83.7%) tested positive for PD-L1 expression and almost half (49.8%) tested positive for a BRAF mutation.

Additional patient characteristics summarised in the trial publication and the clinical study report

Data relevant to patient baseline characteristics, including location of primary cutaneous melanoma, Breslow thickness, cancer by stage, number of lymph nodes, type of lymph node involvement, presence of ulceration and type surgery, are reported in the published paper and in the CSR. The ERG notes that the baseline characteristics of the patients are well balanced across the two treatment arms. Of key interest to this appraisal are the proportions of patients recruited to the trial with Stage IIIA, Stage IIIB and Stage IIIC disease (Table 5). The ERG notes that most patients had Stage IIIB or Stage IIIC disease. The patients recruited to the trial with Stage IIIA melanoma are those with lymph node metastases >1mm. For brevity, the ERG refers to this subgroup as Stage IIIA throughout this report.

Table 5 Proportions of patients according to disease stage

Disease stage	Pembrolizumab (N=514) n (%)	Placebo (N=505) n (%)	Total (N=1019) n (%)
At randomisation			
Stage IIIA	80 (15.6)	80 (15.8)	160 (15.7)
Stage IIIB	237 (46.1)	230 (45.5)	467 (45.8)
Stage IIIC (1 to 3 LN+)	95 (18.5)	93 (18.4)	188 (18.4)
Stage IIIC (≥4 LN+)	102 (19.8)	102 (20.2)	204 (20)

AJCC=American Joint Committee on Cancer; LN+=positive lymph nodes
Source: Eggermont 2018; CSR Table 10-4 (p7)

The ERG is satisfied that the patients recruited to the KEYNOTE-054 trial are representative of patients with resected Stage III melanoma who are treated in the NHS. However, the ERG notes that in the NHS, patients are not routinely tested for PD-L1 status, and, that approximately 20% of patients in the NHS with resected Stage III melanoma are of ECOG PS 2. In the KEYNOTE-054 trial, all patients were of ECOG PS of 0 or 1 and most patients were ECOG PS 0.

4.4 Risk of bias assessment for the KEYNOTE-054 trial

The company assessed the risk of bias of the KEYNOTE-054 trial using the Cochrane Risk of Bias tool [36]. In general, the ERG agrees with the company's assessment; however, the ERG disagrees with the company's rating of 'unclear risk' for the criterion of 'blinding of outcome assessment'. The company states that RFS was assessed by local investigators and not by an Independent Review Committee (IRC). The ERG understands, from the CS and the CSR that, in the KEYNOTE-054 trial, investigators were blinded to treatment allocation. In addition, [redacted]). The ERG considers that the risk of bias for the blinding of outcome assessment for RFS is low. Overall,

the ERG considers that the KEYNOTE-054 trial was generally well designed and well conducted and that the overall risk of bias for the trial is low.

Table 6 Assessment of risk of bias for the KEYNOTE-054 trial

Criterion	Company assessment of risk	Support for judgement	ERG comment
Random sequence generation (selection bias)	Low risk	Randomisation was conducted by a centralised voice-response system; minimisation technique was used for sequence generalisation	Low risk
Allocation concealment (selection bias)	Low risk	Randomisation was conducted by a centralised voice-response system	Low risk
Blinding of participants and personnel (performance bias)	Low risk	Both patients and investigators were blind to treatment allocation	Low risk
Blinding of outcome assessment (detection bias)	Unclear risk	RFS was assessed by local investigators, not an Independent Review Committee	Low risk
Incomplete outcome data addressed (attrition bias)	Low risk	Number of patients who discontinued treatment and reasons for discontinuation were specified and accounted for	Low risk
Selective reporting (reporting bias)	Low risk	Primary outcome (RFS) was reported; secondary endpoints (OS, DMFS, HRQoL) not yet reported	Low risk
Other sources of bias	Low risk	No other potential sources of bias were identified	Low risk

DMFS=distant metastasis-free survival; HRQoL=health-related quality of life; OS=overall survival; RFS=recurrence-free survival
Source: CS, Table 12 and ERG comment

4.5 Statistical approach adopted for the KEYNOTE-054 trial

In this section, the ERG describes and critiques the statistical approaches used to analyse data collected during the KEYNOTE-054 trial that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the CS, the CSR [1], the original trial protocol and trial statistical analysis plan (TSAP) which were available as supplementary documents to the KEYNOTE-054 trial publication [23].

4.5.1 Efficacy outcomes and statistical analysis approach

Sample size calculation

The primary objective of the KEYNOTE-054 trial is to determine whether pembrolizumab improves RFS, compared to placebo in patients with resected Stage IIIA, Stage IIIB and Stage IIIC melanoma with high risk of recurrence. The primary objective also included an assessment of whether pembrolizumab improves RFS compared to placebo in the subgroup with PD-L1 positive tumour expression.

The original sample size calculation of the KEYNOTE-054 trial was based on the results and distribution of stages (IIIA, IIIB and IIIC) of the EORTC 18071 trial [37]. Assuming RFS hazard rates of 0.54 in the first year (i.e. up to 12 months) post-randomisation and 0.25 from years 1 to 3 (i.e. 12 to 36 months) post-randomisation, a total of 409 RFS events (local recurrence, regional recurrence, distant metastases, death) would be needed to provide 95% power to detect a pembrolizumab hazard ratio (HR) of 0.70 or an increase in median RFS from 1.64 to 2.87 years, at a one sided alpha (α) level of 2.5% (CS, p32). By the multiplicity strategy employed in this sample size calculation, 409 RFS events would also provide 92% power to detect a HR of 0.70 at a one-sided α level of 2.5% (KEYNOTE-054 protocol, Section 8.1.1, p57). Therefore, the KEYNOTE-054 trial aimed to randomise 450 participants per arm with a further 2.5% additional participants enrolled to compensate for ineligible participants and early withdrawal of consent.

For the PD-L1 positive tumour expression subgroup, assuming the number of events in the subgroup ranges from 30% to 60% of the total 409 RFS events and assuming a subgroup HR of 0.55, 0.65 or 0.70, at a one sided α level of 2.5%, the statistical power under these scenarios for the subgroup ranges between 41% and 100% (KEYNOTE-054 protocol, Section 8.1.1, p57). Under these scenarios, the power for rejecting at least one RFS hypothesis (in the ITT population or in the PD-L1 positive tumour expression subgroup) is at least 93% (CS, p32).

Primary efficacy outcome

The primary efficacy outcome of the KEYNOTE-054 trial was RFS in the ITT population and RFS in the subgroup of patients with PD-L1 positive tumour expression. RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional, distant metastasis) or death, whichever occurred first. RFS was determined based on disease assessment as determined by the local investigator (see Section 2.3.2 of the CS for definitions of local cutaneous recurrence, regional lymphatic and modal recurrences and distant metastases and for methods of assessment of recurrences) or date of death. For patients who remained alive and whose disease had not recurred, RFS was censored on the date of the last visit or contact.

Kaplan-Meier (K-M) methodology was used to obtain estimates of RFS, the standard error of the estimates were computed using Greenwood's formula [38] and comparison of the time-to-event distributions between pembrolizumab and placebo were generated using the log-rank test stratified by stage i.e., IIIA versus IIIB versus IIIC (1-3 LN+) versus IIIC (≥4 LN+) as indicated at randomisation. Medians and 95% confidence intervals (CIs) were calculated based on the non-parametric method of Brookmeyer and Crowley [39] and the HR of pembrolizumab compared to placebo with (1 – 2α) x 100% CIs was estimated using a Cox

proportional hazards (PH) model (Efron's tie handling method), which was stratified by stage as indicated at randomisation, with treatment as a single covariate.

Secondary efficacy outcomes

The following secondary efficacy outcomes were pre-specified in the KEYNOTE-054 trial protocol (KEYNOTE-054 protocol, Section 2.4.2, p30):

- Distant metastasis-free survival (DMFS)
- DMFS in patients with PD-L1 positive tumour expression
- Overall survival (OS)
- OS in patients with PD-L1 positive tumour expression

The company states that analysis of the secondary outcomes is event driven ([redacted]) and that the minimum number of events required had not been achieved at the time of data cut-off (2nd October 2017). The company also states that the final analyses of DMFS are expected to be available in [redacted] and that the final analysis of OS is expected in [redacted]. The same statistical analysis approaches will be employed for these secondary endpoints as was used for the primary efficacy outcome RFS (KEYNOTE-054 protocol, Section 8.2.3, p64).

First interim analysis (IA1)

Positive RFS results, based on an interim analysis of the CheckMate 238 trial of adjuvant nivolumab versus ipilimumab, were announced in July 2017 and published in September 2017 [40]. Following this announcement, the KEYNOTE-054 trial protocol was amended to include an interim analysis of RFS following 330 events in the ITT population, [redacted] (Section 8.3, KEYNOTE-054 amended protocol, KEYNOTE-054 CSR, p956). The protocol amendment was finalised on 2nd October 2017, which was also the date of clinical data cut-off for the interim analysis. The interim analysis was performed by an independent statistician using a one-sided α level of 0.8% (corresponding to a 98.4% two-sided CI for the HR in the ITT population and a 95% two-sided CI in the PD-L1 positive tumour expression subgroup), based on 1019 randomised participants, with 351 RFS events reported in the ITT population. In December 2017, the Independent Data and Safety Monitoring Committee reviewed unblinded results and recommended the publication of the interim results for the primary outcomes and safety, which were subsequently published in May 2018 [23]. Due to the positive findings, the interim analysis of RFS in the ITT population is considered to be the final

analysis. For the future analysis of secondary outcomes, to preserve α error, a hierarchical testing approach will be applied, firstly to DMFS followed by OS (see Figure 5 of the CS, p32).

4.5.2 ERG critique of statistical approach

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Table 7. Having carried out these checks, the ERG considers that the pre-planned statistical approach employed by the company is adequate but highlights that, as acknowledged by the company in the company response to the ERG clarification letter, it is unlikely that the PH assumption is valid for the RFS analyses. Therefore, the ERG notes that all HRs for RFS generated from the KEYNOTE-054 trial must be interpreted with caution.

Table 7 ERG assessment of statistical approach used to analyse data from the KEYNOTE-054 trial

Item	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	The analysis populations are reported in Section 2.4.1 of the CS (p31). These populations were pre-defined in the KEYNOTE-054 trial protocol (Section 8.2.1, p63-64). Efficacy outcomes presented in the CS were analysed within the ITT population, defined as all randomised participants and summarised according to the treatment group at allocation. No randomised patients were excluded from analysis. Safety outcomes presented in the CS were analysed within the safety population defined as all randomised patients who received at least one dose of study medication and summarised by actual treatment received.
Were all protocol amendments carried out prior to analysis?	The original protocol of the KEYNOTE-054 trial was available as supplement to the trial publication [23]. All protocol amendments were provided in the KEYNOTE-054 CSR, in addition to the final protocol with all amendments incorporated. The rationale for amendments and details of changes made to the protocol were provided in the company response to the ERG clarification letter. Most amendments were administrative or related to policies of approval to release the document to Regulatory Agencies, Ethical Committees, Investigator sites or external parties. The largest amendment related to the first interim analysis (IA1) which is described in further detail in Section 4.5.1 of this ERG report. The ERG is satisfied with the rationale for the amendments and that all amendments that have been made to date were made before the data cut-off date for interim analysis (2nd October 2017). Therefore, amendments were not driven by the results of IA1.
Was an appropriate sample size calculation pre-specified?	The sample size calculation of the KEYNOTE-054 trial is reported in Section 2.4.2 of the CS (p31-32) and is described in more detail in Section 4.5.1 of this ERG report. The ERG is satisfied that the sample size calculations relating to all outcomes were appropriate and pre-specified in the KEYNOTE-054 trial protocol (Section 8.1.1, p56-63),
Were modelling assumptions (e.g. proportional hazards) assessed?	It was pre-specified in the KEYNOTE-054 trial protocol (Section 8.2.3, p64) that RFS, DMFS and OS would be analysed using a Cox PH model. Within the company response to the ERG clarification letter, the company stated that the PH assumption was not assessed for RFS analysis. The company notes that within immunotherapy studies (particularly studies of check-point inhibitors) that deviations from PHs have been shown and suggest that this may be due to an initial delay in the effect of the intervention [41]. The ERG acknowledges the importance of employing pre-specified statistical analysis methods to ensure the validity of phase III trial results. However, it should be noted that a HR estimated from a Cox PH model has no meaningful interpretation when the PH assumption is violated. Therefore, all HRs for RFS presented from the KEYNOTE-054 trial must be interpreted with caution.

Item	Statistical approach with ERG comments
Were all subgroup analyses pre-specified?	The ERG is satisfied that all of the subgroup analyses presented within Appendix E, Table 1 of the CS were pre-specified in the KEYNOTE-054 trial protocol (Section 8.2.5, p66-67). The ERG also notes that, within the KEYNOTE-054 protocol, it is stated that other variables may be assessed if new information becomes available during the study.
Were all sensitivity analyses pre-specified?	Two sensitivity analysis approaches are presented in Table 11 of the CS (p34) with different censoring rules to the primary analysis, and results of these two sensitivity analyses for RFS are reported in Table 14.2-26 and Table 14.2-27 of the CSR. Numerical results of the sensitivity analysis are very similar to two decimal places to those of the primary analysis and no change to conclusions. An additional sensitivity analysis is pre-specified in the KEYNOTE-054 trial protocol (Section 8.2.4, p64-65), namely "to ensure true randomisation via minimisation, a re-randomisation test will be performed." The company provides results for this sensitivity analysis in the company response to the ERG clarification letter and that sensitivity analysis results following re-randomisation tests were consistent with the main analysis. The ERG is satisfied that pre-specified sensitivity analyses and that all results available at the time of data cut-off have been provided.
Was the analysis approach for PROs appropriate and pre-specified?	HRQoL data were collected using the EORTC QLQ-C30 and the EQ-5D-3L questionnaires. The data collection schedule of the HRQoL questionnaires is available in Table 8 of the CS (p28). QLQ-C30 data were not available at the time of the submission; the planned statistical analysis approach of the QLQ-C30 data is outlined in the KEYNOTE-054 trial protocol (Section 10.5, p70-71). EQ-5D-3L data collected from the all subjects as treated population were analysed and base case utility values were derived via a linear mixed-effects model which was used to account for the correlation among repeated measures within an individual (visits with missing EQ-5D-3L data excluded). Further details of the statistical analysis approach and sample size calculations relating to HRQoL are provided in Sections 2.4.2 (p31-32) and 3.4 (p82-86) of the CS. The ERG is satisfied that the company's pre-specified HRQoL analysis methodology planned is appropriate. Base case utility values are reported in Table 31 of the CS (p84) and are discussed in Section 5.2.8 of this ERG report.
Was the analysis approach for AEs appropriate and pre-specified?	AEs were assessed using the International CTCAE version 4.0 and SAEs were defined using the GCP guideline. AEs and SAEs were recorded based upon investigator assessment as to whether those events were drug related (reasonable possibility, no reasonable possibility). Many summaries of AEs are provided in the KEYNOTE-054 CSR (p64 to 109); all AEs, AEs leading to treatment discontinuation, SAEs and deaths are summarised by grade by treatment arm, by system organ class and by demographic subgroups (age, sex and region). AEs of special interest are presented separately. Counts and percentages are presented and no formal statistical comparisons were made, as per the KEYNOTE-054 trial protocol (Section 8.2.3.2, p64). The ERG is satisfied that the methodology for presenting AEs was pre-specified and that all summary tables of AEs are presented within the CSR.

AE=adverse event; CS=company submission; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-3L=EuroQoL group 5 dimension three level; ERG=Evidence Review Group; GCP=good clinical practice; HRQoL=health related quality of life; QLQ-C30=quality of life questionnaire core 30; ITT=intention-to-treat; PH=proportional hazards; PRO=patient-reported outcome; SAE=serious adverse events; TSAP=trial statistical analysis plan
Source: adapted from the CS, KEYNOTE-054 CSR; KEYNOTE-054 trial protocol and TSAP (supplementary file to the KEYNOTE-054 trial publication [23]), the company's response to the ERG clarification letter, and ERG comment.

4.6 Efficacy results from the KEYNOTE-054 trial

4.6.1 Participant disposition and exposure to treatment

At the date of data cut-off (2nd October 2017), a total of 1019 participants were randomised in the KEYNOTE-054 trial and were included in the ITT population; 514 to pembrolizumab and 505 to placebo. The median duration of follow-up for patients in the ITT population reported in the CS (p29) was 16.0 months (range 2.5-25.3 months), which was also reported in the KEYNOTE-054 trial CSR. The KEYNOTE-054 trial publication [23] reported a median duration of follow-up of 15 months and the difference in results reported in the publication and the CSR was due to the different approaches to censoring. Both methods used a K-M approach to estimate median follow-up duration; within the publication, participants without an RFS event were censored when they left the study (i.e., censored at the latest disease evaluation performed according to the trial protocol) whilst, in the CSR, follow-up was measured from the time of randomisation to the date of death or database cut-off and participants were censored when they had an RFS event. The ERG agrees with the company that the approach employed within the CSR is the most appropriate method of estimating median duration of follow-up.

An additional 445 participants were enrolled in the trial but not randomised. Of these 445 participants, 46.5% had current disease, including loco-regional relapse, distant metastasis, or clinical evidence for brain metastases, 16.1% of participants met other exclusion criteria (see Appendix 1, Section 9.1), 23.1% of participants refused randomisation, 9.4% of participants could not be randomised within 12 weeks after clinic and for 4.3% of participants, central confirmation of PD-L1 expression was not available (CS, Table 10, p31 and Appendix 1, Section 9.1 of this ERG report).

A total of 1011 participants received at least one dose of the study treatment (509 received pembrolizumab and 502 received placebo) and were included in the safety population. Within the safety population, the median number of days on therapy and median number of doses received was the same in the pembrolizumab and placebo arms; [redacted] days on therapy (Table 10-5; KEYNOTE-054 CSR, p48) and median of [redacted] administrations [23]. The duration of exposure was slightly longer in the pembrolizumab arm compared with the placebo arm; 382 versus 364 person years for an exposure of at least 3 months and 364 versus 344 person years for an exposure of at least 6 months (CS, Table 17, p42).

At the time of analysis, 208 participants (40.9% of participants who had started treatment) had discontinued pembrolizumab and 202 (40.2%) had discontinued placebo [23]. The most common reason for discontinuation of treatment in both groups was recurrence, relapse or death due to progressive disease; 21.4% versus 35.6% in the pembrolizumab and placebo

arms, respectively. A further 13.8% of participants in the pembrolizumab withdrew from the regimen due an AE compared to 2.2% of the placebo arm [23].

4.6.2 Primary efficacy outcome: recurrence free survival

ITT population

The primary efficacy outcome of the KEYNOTE-054 trial was RFS in the ITT population and RFS in the subgroup of patients with PD-L1 positive tumour expression. RFS results in the ITT population are presented in Table 8.

Table 8 RFS results in the ITT population

	Pembrolizumab	Placebo
Number in ITT population	514	505
Number of events (%)	135 (26.3)	216 (42.8)
Type of first event: Locoregional recurrence (%)	55 (10.7)	77 (15.2)
Type of first event: Distant metastasis (%)	69 (13.4)	114 (22.6)
Type of first event: Both diagnosed within 30 days of each other (%)	9 (1.8)	24 (4.8)
Type of first event: Death (%)	2 (0.4)	1 (0.2)
Person months	6246.3	5566.3
Event rate per 100 person-months	2.2	3.9
Median RFS in months (95% CI)[a]	NR (NE to NE)	20.4 (16.2 to NE)
RFS rate at 6 months in % (95% CI)	82.2 (78.6 to 85.3)	73.3 (69.2 to 77.0)
RFS rate at 12 months in % (95% CI)	75.4 (71.3 to 78.9)	61.0 (56.5 to 65.1)
RFS rate at 18 months in % (95% CI)	71.4 (66.8 to 75.4)	53.2 (47.9 to 58.2)
HR (98.4% CI) and p-value[b]	0.57 (0.43 to 0.74); p<0.0001	

a. Median RFS estimated from product-limit (Kaplan-Meier) method for censored data
b. HR estimated from Cox regression model with treatment as a covariate, stratified by stage as indicated at randomisation. One-sided p-value based on log-rank test.

CI=confidence interval; HR=hazard ratio; ITT=intention to treat; LN=lymph nodes; NE=not estimable; NR=not reached; RFS=recurrence free survival

Source: CS, adapted from Table 13, Table 14 and Table 15

A total of 351 participants (31.4% of total participants in the ITT population) experienced an RFS event; 135 (26.3%) in the pembrolizumab arm and 216 (42.8%) in the placebo arm. The most common RFS event occurring first in both arms was distant metastasis occurring in 183 participants out of 351 participants with RFS events (52.1% of total events). Compared to the placebo arm, in the pembrolizumab arm, fewer distant metastases developed as the first RFS event (13.4% compared to 22.6% of participants) and fewer locoregional recurrences occurred as the first RFS event (10.7% compared to 15.2% of participants). Overall, 2.9% of participants were diagnosed with both locoregional recurrence and distant metastasis within 30 days of

each other, therefore for these participants their first RFS event was classified as both locoregional recurrence and distant metastasis in analysis; 1.8% of the pembrolizumab arm and 4.8% of the placebo arm and three participants (two in the pembrolizumab arm and one in the placebo arm) died without experiencing locoregional recurrence or distant metastasis.

At 6 months, 12 months and 18 months, the RFS rate was higher in the pembrolizumab arm compared to the RFS rate in the placebo arm (Table 8). Median RFS had not yet been reached at IA1 in the pembrolizumab arm and was 20.4 months in the placebo arm. From K-M data (CS, Figure 6), the company considers that the curves show separation of RFS rates after 3 months and these remain separated throughout the remainder of the evaluation period. The ERG considers that, after 3 months these K-M curves diverge to the end of the evaluation period, further demonstrating that the PH assumption is violated within this analysis (see Table 7 of this ERG report).

Pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in RFS in comparison to placebo (HR 0.57; 98.4% CI 0.43 to 0.74; p<0.0001). The ERG notes that the HR result must be interpreted with caution due to the likely violation of the PH assumption in this analysis. Clinical advice to the ERG is that a HR of 0.57 is a clinically meaningful result for RFS, however, a clinically meaningful OS benefit would be more important.

The company also states that "…the placebo arm in the KEYNOTE-054 trial performed similarly in regard to the rate of RFS over time to the ipilimumab control arm in the CheckMate 238 trial [40], supporting the magnitude of the RFS HR in KEYNOTE-054 of pembrolizumab versus placebo" (CS, p49). The ERG agrees that the RFS rates in the adjuvant ipilimumab control arm in the CheckMate 238 trial (12 month RFS rate of 60.8% and 18 month RFS rate of 52.7%) are similar to those in the placebo arm of the KEYNOTE-054 trial (Table 3). However, the ERG does not consider adjuvant ipilimumab to be equivalent to placebo as treatment with adjuvant ipilimumab was shown to significantly improve RFS compared to placebo in the EORTC 18071 study [37]. Therefore, the ERG does not agree that the similarity of control arm results in the KEYNOTE-054 and CheckMate 238 trials supports the magnitude of the RFS HR in the KEYNOTE-054 trial. The ERG also notes that there are differences between the patient characteristics in the CheckMate 238 trial and the KEYNOTE-054 trial. The CheckMate 238 trial includes patients with Stage IV disease and no patients with Stage IIIA disease. The KEYNO4TE-054 trial included patients with Stage IIIA disease and no patients with Stage IV melanoma. The ERG considers that the patient population in the CheckMate 238 trial are likely to have a worse prognosis than the patients in the KEYNOTE-

054 trial and therefore, the control arms of the two trials may not be comparable and such a comparison would favour the KEYNOTE-054 trial.

Cumulative incidence of distant metastasis as first type of recurrence

The ERG notes that within the publication of the KEYNOTE-054 trial [23], an additional analysis is presented which compares 78 participants (15.2% of the ITT population) in the pembrolizumab arm and 138 participants in the placebo arm (27.3% of the ITT population) in whom distant metastasis developed (alone or combined with locoregional recurrences). Within this analysis, other types of recurrence (locoregional alone) and death without any recurrence were considered as competing risks using the statistical model of Fine and Gray [42], stratified by stage of disease as provided at randomisation. The ERG considers that, in the presence of competing risks, this analysis approach is appropriate. The ERG notes that this analysis was not pre-defined in the KEYNOTE-054 original trial protocol or within any amended versions of the KEYNOTE-054 trial protocol provided in the KEYNOTE-054 CSR

The 12-month cumulative incidence of distant metastasis (alone or combined with locoregional recurrences) was 13.8% (95% CI 10.9% to 17.0%) in the pembrolizumab arm compared with 24.3% (95% CI 20.6% to 28.1%) in the placebo arm and the 18-month cumulative incidence was 16.7% (95% CI 13.3% to 20.4%) in the pembrolizumab arm compared with 29.7% (95% CI 25.1% to 34.3%) in the placebo arm. Pembrolizumab demonstrated a statistically significant advantage over placebo in terms of the cumulative incidence of distant metastases (alone or combined with locoregional recurrences) (HR 0.53; 99% CI 0.37 to 0.76). The ERG notes that this analysis represents the cumulative incidence of distant metastases as a first RFS event rather than an analysis of DMFS (i.e. incidence of distant metastases at any time).

AJCC 2010 cancer stage subgroups

Most of the ITT population had Stage IIIB melanoma according to the disease stage at randomisation (46% of the ITT population). The remaining participants had Stage IIIA melanoma (16% of the ITT population), Stage IIIC melanoma (1-3 LN+; 18% of ITT population) and Stage IIIC melanoma (≥4 LN+; 20% of ITT population).

RFS results by cancer stage in the ITT population are presented in Table 9. The ERG notes that across all cancer stage subgroups, more RFS events occurred within the placebo arms than within the pembrolizumab arms and, considering each type of first event, as many, or more, events occurred in the placebo arms compared to the pembrolizumab arms. Furthermore, across all cancer stage subgroups the RFS rate at 6 months, 12 months and 18 months is higher in the pembrolizumab arms than in the placebo arms.

More RFS events occurred across treatment groups in the Stage IIIC melanoma subgroups (36% of individuals with Stage IIIC (1-3 LN+) and 50% of individuals with Stage IIIC (≥4 LN +) experiencing an RFS event) than within the Stage IIIB subgroup (33% of individuals experiencing an RFS event) and the Stage IIIA subgroup (15% of individuals experiencing an RFS event). RFS rates at 6 months, 12 months and 18 months are highest in the Stage IIIA subgroup, decreasing across the cancer stages to the lowest RFS rates shown in the Stage IIIC (≥4 LN+) subgroup.

A statistically significant advantage for pembrolizumab over placebo is observed in the Stage IIIA, Stage IIIB and Stage IIIC (1-3 LN+) subgroups while no statistically significant difference between pembrolizumab and placebo is observed in the Stage IIIC (≥4 LN+) subgroup. No statistically significant difference between subgroups is observed according to the p-value of test for interaction (p=0.418, CS, Appendix E).

The ERG notes that HRs must be interpreted with caution due the likely violation of the PH assumption in RFS analyses. The ERG considers that, while no statistically significant differences between cancer stage subgroups have been observed, subgroup analysis results suggest that individuals with Stage IIIA (>1mm LN metastasis) have the best prognosis in terms of RFS while individuals with Stage IIIC, particularly individuals with Stage IIIC (≥4 LN+), have the worst prognosis in terms of RFS, whether treated with pembrolizumab or placebo.

Table 9 Recurrence-free survival results by AJCC 2010 cancer stage subgroups

AJCC 2010 staging classification	Cancer Stage IIIA (>1mm LN metastasis)		Cancer Stage IIIB		Cancer Stage IIIC (1-3 LN+)		Cancer Stage IIIC (≥4 LN +)	
	Pembrolizumab	Placebo	Pembrolizumab	Placebo	Pembrolizumab	Placebo	Pembrolizumab	Placebo
Number in subgroup	80	80	237	230	95	93	102	102
Number of events	6 (7.5%)	18 (22.5%)	60 (25.3%)	96 (41.7%)	25 (26.3%)	43 (46.2%)	44 (43.1%)	59 (57.8%)
Type of first event: Locoregional recurrence	4 (5.0%)	10 (12.5%)	23 (9.7%)	34 (14.8%)	10 (10.5%)	14 (15.1%)	18 (17.6%)	19 (18.6%)
Type of first event: Distant metastasis	1 (1.3%)	7 (8.8%)	35 (14.8%)	52 (22.6%)	12 (12.6%)	25 (26.9%)	21 (20.6%)	30 (29.4%)
Type of first event: Both diagnosed within 30 days of each other	0 (0.0%)	0 (0.0%)	2 (0.8%)	10 (4.3%)	2 (2.1%)	4 (4.3%)	5 (4.9%)	10 (9.8%)
Type of first event: Death	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Median RFS in months (95% CI)[a]	NR (NE to NE)	NR (NE to NE)	NR (NE to NE)	20.4 (15.6 to NR)	NR (NE to NE)	17.9 (11.0 to NR)	NR (9.6 to NE)	9.8 (5.5 to 15.4)
RFS rate at 6 months in % (95% CI)[a]	95.0 (87.1 to 98.1)	91.2 (82.5 to 95.7)	83.6 (78.2 to 87.8)	74.8 (68.6 to 80.0)	81.8 (72.4 to 88.3)	71.4 (61.0 to 79.6)	69.3 (59.3 to 77.3)	57.8 (47.7 to 66.7)
RFS rate at 12 months in % (95% CI)[a]	93.7 (85.5 to 97.3)	79.2 (68.3 to 86.8)	76.2 (70.0 to 81.2)	62.6 (55.9 to 68.6)	75.2 (65.0 to 82.8)	57.0 (46.1 to 66.4)	59.3 (49.1 to 68.2)	46.7 (36.8 to 56.1)
RFS rate at 18 months in % (95% CI)[a]	90.2 (77.5 to 95.9)	72.2 (57.3 to 82.6)	72.7 (66.1 to 78.3)	55.9 (48.6 to 62.5)	70.7 (58.8 to 79.7)	46.4 (31.5 to 60.0)	54.1 (43.1 to 63.9)	39.4 (29.3 to 49.4)
HR (95% CI) and p-value[b]	0.31 (0.12 to 0.79); p=0.014		0.56 (0.41 to 0.78); p<0.001		0.51 (0.31 to 0.83); p=0.007		0.69 (0.47 to 1.03); p=0.067	

a. RFS rates are estimated from the product-limit (Kaplan-Meier) method for censored data

AJCC=American Joint Committee on Cancer; CI=confidence interval; ITT=intention to treat; HR=hazard ratio; NE=not estimable; NR=not reached; PD-L1=programed death ligand-1; RFS=recurrence free survival

Source: CS, adapted from Table 1 (Appendix E), company response to ERG clarification letter (Table 5, Table 6, Table 7, Table 8)

Other subgroup analyses

The primary efficacy outcome of the KEYNOTE-054 trial was RFS in the ITT population, and also, within the subgroup of patients with PD-L1 positive tumour expression. Subgroup results by PD-L1 status are presented in Appendix 2, Section 9.2 of the ERG report. In summary, pembrolizumab demonstrated a statistically significant advantage in RFS over placebo both of the subgroup of the ITT population with PD-L1 positive tumour expression and the subgroup of the ITT population with PD-L1 negative tumour expression. However, there was no statistically significant difference between PD-L1 positive versus PD-L1 negative tumour expression subgroups according to the p-values of tests for interaction.

The following additional subgroups were pre-specified in the KEYNOTE-054 trial protocol (Section 8.2.5, p66-67); sex (male versus female), age (< 65 versus ≥ 65 years), lymph node involvement (micro- versus macro-involvement), ulceration (absent versus present versus unknown), number of lymph-nodes positive (1 versus 2-3 versus 4+), Breslow thickness (< 2 mm versus 2-<4 mm versus ≥ 4 mm), BRAF-mutation status (negative versus positive versus unknown).

Results of all RFS subgroup analyses are presented in Appendix E, Table 1 of the CS. Generally, subgroup results are consistent with ITT population results, with significantly improved RFS observed with pembrolizumab compared to placebo, regardless of age, sex, BRAF mutation status, number of lymph nodes positive, type of lymph node involvement, ulceration present or absent. There are no statistically significant differences between subgroups observed according to the p-values of tests for interaction.

4.6.3 Secondary efficacy outcomes

At the time of data cut-off (2nd October 2017), the minimum number of events required for the analysis of the endpoints of DMFS and OS had not been achieved.

The number of DMFS and OS events observed at the time of data cut-off in the ITT population, within the PL-D1 tumour expression subgroups and the AJCC cancer staging classification subgroups are shown in Table 10. Across the ITT population and all subgroups, more participants had experienced DMFS events in the placebo arm than in the pembrolizumab arm and as many, or more, participants had died in the placebo arm compared to the pembrolizumab arm. As within the subgroup analysis of RFS, across both treatment groups, more events (DMFS and OS) occurred in the subgroups with Stage IIIC melanoma (1-3 LN+ or ≥4 LN +) than in the Stage IIIB melanoma subgroup. The fewest DMFS and OS events occurred within the Stage IIIA melanoma subgroup.

Table 10 DMFS status and survival status at the time of interim analysis of RFS in the KEYNOTE-054 trial

Population or subgroup		DMFS status		Survival status	
		Pembrolizumab	Placebo	Pembrolizumab	Placebo
ITT population	N	514	505	514	505
	No event	416 (80.9%)	340 (67.3%)	489 (95.1%)	470 (93.1)
	Event	98 (19.1%)	165 (32.7%)	25 (4.9%)	35 (6.9%)
PD-L1 positive tumour expression	N	428	425	428	425
	No event	353 (82.5%)	294 (69.2%)	409 (95.6%)	399 (93.9%)
	Event	75 (17.5%)	131 (30.8%)	19 (4.4%)	26 (6.1%)
PD-L1 negative tumour expression	N	59	57	59	57
	No event	46 (78.0%)	33 (57.9%)	55 (93.2%)	50 (87.7%)
	Event	13 (22.0%)	24 (42.1%)	4 (6.8%)	7 (12.3%)
AJCC cancer stage IIIA (>1mm LN metastasis)	N	80	80	80	80
	No event	77 (96.3%)	67 (83.8%)	78 (97.5%)	78 (97.5%)
	Event	3 (3.8%)	13 (16.3%)	2 (2.5%)	2 (2.5%)
AJCC cancer stage IIIB	N	237	230	237	230
	No event	194 (81.9%)	159 (69.1%)	230 (97.0%)	217 (94.3%)
	Event	43 (18.1%)	71 (30.9%)	7 (3.0%)	13 (5.7%)
AJCC cancer stage IIIC (1-3 LN+)	N	95	93	95	93
	No event	74 (77.9%)	60 (64.5%)	89 (93.7%)	84 (90.3%)
	Event	21 (22.1%)	33 (35.5%)	6 (6.3%)	9 (9.7%)
AJCC cancer stage IIIC (≥4 LN+)	N	102	102	102	102
	No event	71 (69.6%)	54 (52.9%)	92 (90.2%)	91 (89.2%)
	Event	31 (30.4%)	48 (47.1%)	10 (9.8%)	11 (10.8%)

AJCC=American Joint Committee on Cancer; CI=confidence interval; ITT=intention to treat; LN=lymph node; N=number of participants in population or subgroup; PD-L1=programed death ligand-1; RFS=recurrence-free survival
Source: CS, adapted from Table 15, company response to ERG clarification letter (Table 3, Table 4, Table 5, Table 6, Table 7, Table 8),

4.7 Adverse events

4.7.1 Adverse events reported in the KEYNOTE-054 trial

Safety data for the KEYNOTE-054 trial are reported in the CS, Section 2.10.1 and in Appendix F of the CS. The ERG notes that the safety data presented in the CS are different to those reported in the published paper [23] due to differing methods of calculation.

Summary of adverse events

Table 11 is a summary of the AEs reported in the KEYNOTE-54 trial. Most patients reported at least one AE (93.3% in the pembrolizumab arm versus 90.2% in the placebo arm). However, the ERG notes that there are differences in the type and frequency of AEs recorded in the treatment arm compared with the placebo arm. These include a higher proportion of drug-related AEs (77.8% versus, 66.1%), any grade 3 to 5 AEs (31.0% versus 19.1%), grade 3 to 5 drug-related AEs (14.5% versus 3.4%), SAEs (25.1% versus 16.3%) and serious drug-related AEs (13.0% versus 1.2 %).

More of the patients in the pembrolizumab arm, compared with the placebo arm experienced AEs leading to treatment discontinuation. Treatment discontinuations were the result of an AE (13.8% versus 3.6%), a drug-related AE (12.2% versus 1.6%), a SAE (5.7% versus 2.2%) and a serious drug-related AE (4.3% versus 0.4%).

Two deaths were reported in the pembrolizumab arm, one of these was considered as drug-related (autoimmune myositis involving respiratory muscles).

Table 11 Summary of adverse events in the KEYNOTE-054 trial

Type of adverse event, n (%)	Pembrolizumab (n=509)	Placebo (n=502)
Any AE	475 (93.3)	453 (90.2)
Any drug-related AE	396 (77.8)	332 (66.1)
Grade 3 to 5 AE	158 (31.0)	96 (19.1)
Grade 3 to 5 drug-related AE	74 (14.5)	17 (3.4)
Any SAE	128 (25.1)	82 (16.3)
Any drug-related SAE	66 (13.0)	6 (1.2)
Death	1 (0.2)	0 (0.0)
Death (due to a drug-related AE)	1 (0.2)	0 (0.0)
AE leading to discontinuation	70 (13.8)	18 (3.6)
Drug-related AE leading to discontinuation	62 (12.2)	8 (1.6)
SAE leading to discontinuation	29 (5.7)	11 (2.2)
Drug-related SAE leading to discontinuation	22 (4.3)	2 (0.4)

SAE=serious adverse event
Source: CS Table 18

All drug-related adverse events

The company presents the full details of drug-related AEs from the KEYNOTE-054 trial in Table 3 of Appendix F of the CS. The company has reported the drug-related AEs that occurred with a reported incidence of >1% in either the pembrolizumab or placebo arm.

The most frequent drug-related AEs in the pembrolizumab arm were fatigue (28.1%), diarrhoea (18.5%), pruritus (16.7%), hypothyroidism (14.3%), nausea (11.4%), arthralgia (10.0%), and hyperthyroidism (9.6%). The most frequent drug-related AEs in the placebo arm were fatigue (26.9%, diarrhoea (16.3%), pruritus (9.8%), hypothyroidism (2.6%), arthralgia (9.4%) and nausea (8.6%). The company reports (CS, p46) that most of the drug related AEs were Grade 2 events.

Grade 3 to 5 adverse events

The company states that in the pembrolizumab and placebo arms of the trial, the commonly reported Grade 3 to Grade 5 AEs with an incidence of >0% included hypertension ([redacted] versus [redacted]), diarrhoea ([redacted] versus [redacted]), colitis ([redacted] versus [redacted]), blood creatinine phosphokinase increase ([redacted] versus [redacted]) and lipase increase ([redacted] versus [redacted]). The company states that all reported events were Grade 3.

Drug-related Grade 3 to 5 AEs

The company states that the most frequent drug-related AEs with an incidence of >0% in the pembrolizumab arm were colitis ([redacted]) and type 1 diabetes mellitus ([redacted]). The ERG notes that [redacted]. The company states that colitis and type 1 diabetes mellitus are recognised AEs that result from treatment with pembrolizumab (CS, p46).

Serious adverse events

In both the pembrolizumab and placebo arms, the most frequently reported SAE was basal cell carcinoma (3.3% versus 5.0%).

Other SAEs (Table 2, Appendix F) reported in the pembrolizumab and placebo arms were colitis (1.6% versus 0.0%), pneumonitis (1.4% versus 0.0%), squamous cell carcinoma (1.2% versus 0.6%), diarrhoea (1.0 versus 0.4%), cellulitis. The ERG notes that more patients in the placebo arm than in the pembrolizumab arm developed cellulitis (0.6% versus 1.4%) and malignant melanoma in situ (1.2% versus 0.2%).

Drug-related serious adverse events

Full details of the drug-related SAEs are reported in Table 3, Appendix F of the CS.

Drug-related SAEs occurred more frequently in the pembrolizumab arm (13.0%) compared with the placebo arm (1.2%) and included pneumonitis (2.9% versus 0.6%) and colitis (2.6% versus 0.2%). The company states (CS, p47) that colitis and pneumonitis are recognised SAEs that arise from treatment with pembrolizumab. The company also states that the severity of the cases of colitis and pneumonia reported in the KEYNOTE-054 trial are 'consistent with the established safety profile of pembrolizumab' (CS, p47).

Adverse events of special interest

Full details of the AEs of special interest (AEOSI) are presented in Appendix F, Table 4 (adrenal insufficiency), Table 5 (colitis), Table 6 (Guillain Barre Syndrome), Table 7 (hepatitis), Table 8 (hyperthyroidism), Table 9 (hypophysitis), Table 10 (hypothyroidism), Table 11 (infusion reactions), Table 12 (Myasthenic Syndrome), Table 13 (myocarditis), Table 14 (myositis), Table 15 (nephritis), Table 16 (pancreatitis), Table 17 (pneumonitis), Table 18 (sarcoidosis), Table 19 (severe skin reactions), Table 20 (thyroiditis), Table 21 (type 1 diabetes mellitus) and Table 22 (uveitis).

The ERG notes that, overall, more patients in the pembrolizumab arm reported AEOSI (34.0%) than patients in the placebo arm (7.6%). The company states that most of these events were manageable either by treatment interruption or discontinuation, with or without treatment with corticosteroids. It is also noted by the company that the nature of these events was generally consistent with the characteristics previously observed for pembrolizumab with its use in other indications.

[redacted]

Summary of adverse events from the KEYNOTE-054 trial

Overall, the company reports (CS, p48) that no new safety concerns associated with treatment with pembrolizumab treatment arose from the AE data reported for patients in the KEYNOTE-054 trial. The company considers that treatment with pembrolizumab was well-tolerated by patients in the KEYNOTE054 trial (CS, p48). The ERG notes that the 34% of patients treated with pembrolizumab experienced an immune-related AE of any grade, compared with 7.6% of patients in the placebo arm.

In addition, clinical advice to the ERG indicates that AEs (Grade 2 or higher) arising from treatment with pembrolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs, which places a high burden on NHS staff.

4.8 Health-related quality of life

The company states that HRQoL data were collected during the KEYNOTE-054 trial using the QLQ-C30 [43] questionnaire and the EQ-5D-3L [44] questionnaire. The company reports that the results from the QLQ-C30 [43] questionnaire are not available as the data have not yet been analysed.

The company describes the schedule for the administration of the HRQoL questionnaires (CS, Table 8). After the baseline assessment, patients were followed up every 12 weeks during the first and second year of participation in the trial. During year 3 and year 4, patients were followed up every 6 months. The company states (CS, 81) that both HRQoL questionnaires were administered to patients irrespective of any disease recurrence or progression or treatment status.

The use of the data from patient responses to the EQ-5D-3L [44] questionnaire are discussed in Section B3.4.1 of the CS. The ERG is unable to comment on the robustness of the results from the company's analysis of the EQ-5D-3L data, as the company has not provided any information relevant to numbers of patients who responded to the questionnaires.

4.9 ERG critique of the indirect evidence

No meta-analysis was performed as only a single study was identified in the SLR conducted by the company (see Section 2.2 of the CS, p19). No indirect treatment comparisons were performed as direct evidence was available for the intervention (pembrolizumab) and comparator (placebo, assumed to be equivalent to routine surveillance) outlined within the final scope issued by NICE. The ERG agrees that meta-analysis and indirect treatment comparisons were not required.

4.10 Additional work on clinical effectiveness undertaken by ERG

The company states that the HR of 0.57 for RFS (from the KEYNOTE-054 trial) is expected to predict an OS benefit (CS, p49). The company has based the statement on the findings of a meta-analysis [32] of 5826 participants with surgically resected Stage II-Stage III melanoma within 11 RCTs of adjuvant trials (and externally validated within a further 13 adjuvant RCTs). The trials included in the meta-analysis [32] compared interferon (IFN) to no IFN (observation). The authors of the meta-analysis [32] suggest that results indicate that "RFS was highly

predictive of OS at the patient level" and that the surrogate threshold effect for RFS was estimated to be 0.77; in other words, a HR of 0.77 or less would "predict a treatment impact on OS for future similar adjuvant studies."

The ERG notes that the meta-analysis (30) demonstrated a numerical OS benefit which is statistically significant, with a strong correlation to the HR for RFS. However, clinical advice to the ERG is that treatment with interferon is not considered to provide any long-term OS benefit.

The ERG has concerns about the robustness and the applicability of the meta-analysis, specifically:

- The objective of the meta-analysis was to evaluate "whether RFS is a valid surrogate endpoint for OS in adjuvant interferon melanoma studies" and, therefore, the ERG considers that the authors' conclusions may not be directly applicable to trials of checkpoint inhibitors such as pembrolizumab
- The HRs generated in the meta-analysis are likely to be uninterpretable as they are based on data that violate the assumptions of the Cox PH methodology
- There are differences between the patient population included in the KEYNOTE-054 trial and the patient populations included in the RCTs in the meta-analysis. Patients in the KEYNOTE-054 trial had resected Stage III melanoma at high risk of recurrence. The RCTs included in the meta-analysis were patients with resected Stage II-III melanoma, with 75% of participants in disease Stage III
- The median follow-up in the KEYNOTE-054 trial is shorter than in the trials included in the meta-analysis. The median follow-up in the KEYNOTE-054 trial is 16 months. The median follow-up of RFS and OS in the trials included in the meta-analysis is 6.8 years, with a minimum follow-up of 4.1 years
- The RCTs included in the meta-analysis [32] are relatively old, with trial publication dates ranging from 1996 to 2008. Surgical techniques used for melanoma have developed since 2008. Melanoma survival statistics indicate that survival rates for patients with melanoma have improved since 2008 [7, 13].

The ERG considers that these points should be considered when determining if RFS is a valid surrogate endpoint for OS in the KEYNOTE-54 trial, at the time of analysis presented in the CS.

ERG summary of key ongoing RCTs of adjuvant melanoma treatments

In Table 12, the ERG summarises key aspects of the phase III RCTs assessing the clinical effectiveness of immunotherapies as adjuvant treatments for resected melanoma.

The KEYNOTE-054 trial provides the evidence to inform the appraisal under discussion in this document. The CHECKMATE 238 [40] trial and the COMBI-AD [45] trial provide the clinical effectiveness evidence in NICE's ongoing appraisals of nivolumab [20] and dabrafenib in combination with trametinib [21], respectively. The companies that market vemurafenib and ipilimumab have advised NICE that they will not be applying to the EMA for a licence to market

vemurafenib or ipilimumab as adjunctive treatments for melanoma. NICE has suspended the appraisals [46, 47].

The ERG notes that median OS has not been reached in any of the trials listed Table 12. The ERG considers that the impact of adjuvant treatment with immunotherapy in completely resected melanoma is, at present, unknown.

Table 12 Summary of key ongoing RCTs of adjuvant melanoma treatments

Trial (date of publication) & Comparators	Disease stage	RFS/DFS definition	Duration of follow-up (median)	Median RFS/DFS (95% CI)	RFS/DFS Rate (95% CI)	OS events (95% CI)
Trial that informs this appraisal						
KEYNOTE-054 (2018) Pembrolizumab (n=514) vs Placebo (n=505) Total N=1019	Stage IIIA (16%) Stage IIIB (46%) Stage IIIC (1-3 LN) (18%) Stage IIIC (≥4 LN) (20%)	RFS: Time from randomisation until the date of the first recurrence (local, regional, or distant metastasis) or death	16 months	Pembrolizumab: Not reached	12m=75.4% (71.3 to 78.9) 18m=71.4% (66.8 to 75.4)	Not available
				Placebo: 20.4 months (16.2 to NE)	12m=61.0% (56.5 to 65.1) 18m= 53.2% (47.9 to 58.2)	Not available
				HR=0.57 98.4% CI:0.43 to 0.74		HR=not calculable
Other trials						
CheckMate 238 [40] (2017) Nivolumab (n=453) vs Ipilimumab (n=453) Total N=906	Stage IIIB (34%) Stage IIIC (47%) Stage IV (19%)	RFS: Time from randomisation until the date of the first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause	19.5 months	Nivolumab: Not reached	12m=70.5% (66.1 to 74.5) 18m= 66.4% (61.8 to 70.6)	Not available
				Ipilimumab: Not reached	12m=60.8% (56.0 to 65.2) 18m= 52.7% (47.8 to 57.4)	Not available
				HR= 0.65 (97.56% CI:0.51 to 0.83)		HR=not calculable
COMBI-AD [45] (2017) Dabrafenib+ trametinib (n=438) vs Placebo (n=432) Total N=870	Stage IIIA (18%) Stage IIIB (41%) Stage IIIC (40%) All BRAF V600+	RFS: Time from randomisation to disease recurrence or death from any cause	34 months	Dabafrenib+trametinib: Not reached	Proportion of disease recurrences at data-cut-off: 37%	60 deaths (14%)
				Placebo: 16.6 months (12.7 to 22.1)	Proportion of disease recurrences at data-cut-off: 57%	93 deaths (22%)
				HR=0.47 (95% CI 0.39 to 0.58)		HR=0.57 (0.42 to 0.79)

Trial (date of publication) & Comparators	Disease stage	RFS/DFS definition	Duration of follow-up (median)	Median RFS/DFS (95% CI)	RFS/DFS Rate (95% CI)	OS events (95% CI)
EORTC 18071 [37] (2016) Ipilimumab (n=475) vs Placebo (n=476) Total N=951	Stage IIIA (21%) Stage IIIB (38%) Stage IIIC (1-3 LN (25%) Stage IIIC (≥4 LN) (16%)	RFS: Time from randomisation until the date of first recurrence (local, regional, or distant metastasis) or death from any cause	64 months	Ipilimumab: 27.6 months (19.3 to 37.2)	5-year rate=40.8%	5-year rate=65.4% (60.8 to 69.6)
				Placebo: 17.1 months (13.6 to 21.6)	5-year rate=30.3%	5-year rate=54.4% (49.7 to 58.9)
				HR= 0.76 (95% CI: 0.64 to 0.89)		HR=0.72 (95.1% 0.58 to 0.88)
BRIM 8 [48] (2018) <u>Cohort 1</u> N=314 Vemurafenib (n=93) vs Placebo (n=91)	BRAF V600 Stage IIC (9% of Cohort 1) Stage IIIA (24% of Cohort 1) Stage IIIB (24% of Cohort 1) All BRAF V600+	DFS: Time from randomisation until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause, whichever occurred first	<u>Cohort 1</u> 30.8 months	<u>Cohort 1</u> Vemurafenib: Not reached	12m=84·3% (78·5 to 90·2) 24m= 72·3% (64·9 to 79·8)	16 deaths
				Placebo: 36.9 months (21.4 to NE)	12m=66·2% (58·7 to 73·7) 24m=56·5% (48·5 to 64·4)	28 deaths
				HR=0.54 (95% CI: 0·37 to 0.78)		
<u>Cohort 2</u> N=184 Vemurafenib (n=157) vs Placebo (n=157) Total N=498	Stage IIIC (100% of Cohort 2) All BRAF V600+		<u>Cohort 2</u> 33.5 months	<u>Cohort 2</u> Vemurafenib: 23·1 months (18·6 to 26·5)	12m=78·9% (70·5 to 87·3) 24m= 46·3% (35·4 to57·1)	19 deaths
				Placebo: 15·4 months (11·1 to 35·9)	12m=58·0% (47·8 to 68·1) 24m=47·5% (37·1 to57·9)	19 deaths
				HR=0.80 (95% CI 0.54 to 1.18)		

BRAF= a human gene that encodes the B-Raf protein; CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; LN=lymph node; RFS=recurrence-free survival

4.1 Conclusions of the clinical effectiveness section

- The ERG has been unable to identify any definitive definitions of high risk of either death or high risk of disease recurrence for patients with Stage III melanoma. It is, therefore, unclear whether all patients in the KEYNOTE-054 trial can be considered to be at high risk of death or disease recurrence.

- The KEYNOTE-054 trial is a well-designed, and good quality trial.

- Results presented within the CS are from IA1 in the ITT population (2nd October 2017 data cut) and show that, compared with placebo, treatment with pembrolizumab results in a clinically meaningful and statistically significant improvement in RFS (HR=0.57) as well as higher RFS rates at 6 months, 12 months and 18 months. However, at this time point, the minimum number of events required to analyse the secondary endpoints of OS and DMFS had not been reached.

- Safety data were also provided in the CS. The company states that AE data from the KEYNOTE-054 trial suggest that pembrolizumab is well-tolerated as a treatment for Stage III melanoma that has been completely resected. However, clinical advice to the ERG is that AEs (Grade 2 or higher) arising from treatment with pembrolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs and that this places a high burden on NHS staff.

- The ERG considers that the HRs presented in the CS should be treated with caution. The RFS K-M data presented within the CS suggest that, up to 3 months, RFS for patients in the pembrolizumab and placebo arms of the trials are the same. However, after 3 months the survival curves diverge until the end of the evaluation period. Based on examination of the K-M data the ERG considers that the PH assumption is unlikely to hold for RFS. Given the recognised departures from PH in immunotherapy trials [41], the ERG suggests that future trials of immunotherapy should consider alternative approaches to modelling survival data, i.e., ones that are not reliant on the validity of the PH assumption. interpretation of results.

- The company claims that RFS results for patients treated with pembrolizumab will be reflected in OS data (when these become available) and cites evidence from a meta-analysis, published in 2018 [32], to support this claim. The ERG, however, highlights that the meta-analysis [32] included individual patient data from 13 RCTs conducted in patients with Stage II or Stage III melanoma. Furthermore, the authors of the meta-analysis only

conclude that RFS appears to be a valid surrogate endpoint for OS in RCTs of adjuvant treatment with interferon or a checkpoint inhibitor. The ERG, therefore, questions whether results from this meta-analysis [32] support the company's claim. Furthermore, the ERG cautions that there is evidence that benefits shown with surrogate endpoints are not always realised when OS data become mature [33-35].

- Results of RFS subgroup analyses by stage of disease suggest that, irrespective of whether treated with pembrolizumab or placebo, patients with Stage IIIA melanoma have the best prognosis, while patients with Stage IIIC melanoma, particularly patients with Stage IIIC (≥4 LN+) melanoma, have the worst prognosis.
- The QLQ-C30 tool was used in the KEYNOTE-054 trial to collect HRQoL data. However, currently, no QLQ-C30 data are available. The CS does, however, include a limited discussion of the EQ-5D-3L data which were also collected during the KEYNOTE-054 trial.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of pembrolizumab for people with completely resected melanoma who have a high risk of disease recurrence. 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 has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Objective of the company's systematic review

The company performed a systematic review of the literature to identify studies that evaluated the cost effectiveness of treatment with pembrolizumab, compared with other therapies, for people with Stage III melanoma. The company searched the databases listed in Table 13 on 27 February 2018. The publication period of interest was restricted to 2008 onwards.

Table 13 Details of the databases searched for economic evidence

Database	Interface
Excerpta Medica Database (Embase®)	Elsevier.com
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	PubMed.com
MEDLINE® In-Process	Pubmed.com
Cochrane Library, including database of abstracts of review of effectiveness, National Health Service Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) database	Wiley.com
BioSciences Information Service of Biological Abstracts	proquest.com
EconLit®	Ebsco.com

Source: CS, Appendix G

The company also carried out searches to identify conference proceedings from January 1, 2016 to March 16, 2018 from:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- American Association for Cancer Research (AACR)
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- Society for Immunotherapy Cancer (SITC)
- Society for Melanoma Research (SMR).

Additionally, NICE, the Scottish Medicines Consortium (SMC) and the All Wales Medicine Strategy Group (AWMSG) websites were searched for relevant information from previous technology appraisals. Details of the search strategies used by the company are provided in Appendix G of the CS.

5.1.1 Eligibility criteria used in study selection

The main inclusion criteria used to select studies are shown in Table 14. The ERG is satisfied that the criteria meet the objectives set out in the decision problem.

Table 14 Economic review inclusion and exclusion criteria

Characteristic	Inclusion criteria	Exclusion criteria
Population	• Patients aged ≥18 years with melanoma • Stage III melanoma	• Patients who do not have Stage III melanoma • Patients with primarily other types of cancer or disease • Studies in animals but not humans
Interventions	• The list of included interventions was comprised of the following, whether alone or in combination with any other therapy: - Pembrolizumab - Dabrafenib+trametinib - Interferon alpha 2a and 2b - Ipilimumab - Nivolumab - Ipilimumab+nivolumab in combination - Vemurafenib - BCG or GM-CSF - Active observation	• Economic evaluations that do not investigate one of the interventions of interest in at least one of the study arms
Comparator	• No restriction; all therapies were included	• No exclusions based on comparator
Outcomes	• Direct costs by health state • Indirect or other costs • Cost per treatment success or per response or per QALY gained or ICER • Resource-use estimates by health state (e.g., number of hospitalisations and length of stay, drug utilisation, physician visits) • Utility weights by health state (e.g., EQ 5D, SF-6D, and HUI)	• Studies that report only clinical efficacy and safety data • Studies that report annual national disease costs (i.e., not per-patient or per–health-state costs)
Study design	• Economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequences, and cost-minimization analyses), including models • Prospective studies reporting costs or resource use (e.g., observational studies, clinical trials) • Utility studies (including studies where utility weights were mapped from other instruments, such as disease-specific patient-reported outcome measures) • Retrospective studies reporting costs or resource use (e.g., cost-of-illness, cross-sectional studies) • Systematic reviews of economic analyses, or utility, resource-use, or cost studies	• Commentaries and letters (publication type) • Editorials • News articles • Consensus reports • Nonsystematic reviews • Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden) • Conference abstracts published before 2016

BCG=Bacillus Calmette-Guérin; EQ-5D=EuroQol Group 5-Dimensions questionnaire; GM-CSF=granulocyte macrophage colony-stimulating factor; HUI=Health Utilities Index; ICER=incremental cost effectiveness ratio; LY=life years; QALY=quality adjusted life year; SF-6D=6-domain Short-Form Health Survey
Source: CS Appendix G, Table 1

5.1.2 Included and excluded studies

The company did not identify any cost effectiveness studies that matched the final scope issued by NICE. Details of the screening process and the reasons for the exclusion of the studies are presented in Section B.3.1 of the CS and Appendix G to the CS.

5.1.3 Findings from the company's cost effectiveness review

The company did not identify any studies that evaluated the cost effectiveness of pembrolizumab for the treatment of people with Stage III melanoma. The company suggests that the lack of relevant studies indicates that a de novo cost effectiveness model is needed to address the problem described in the final scope issued by NICE.

5.1.4 ERG critique of the company's review of cost effectiveness evidence

The ERG considers that the databases searched and the search terms used appear to be reasonable. The ERG updated the searches and is satisfied that the company has not missed any relevant economic studies.

5.2 Summary and critique of the company's submitted economic evaluation

5.2.1 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with pembrolizumab versus routine surveillance in people with completely resected Stage III melanoma at high risk of recurrence.

5.2.2 NICE Reference Case checklist

Table 15 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE: people with completely resected Stage III melanoma at high risk of recurrence	Yes
Comparator(s)	As listed in the scope developed by NICE: routine surveillance	Yes
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Data primarily taken from the KEYNOTE-054 study and NMA results	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – however, values from multiple sources were used to populate the company model
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; NMA=network meta-analysis; PSS=Personal social services; QALY=quality adjusted life year; RCC=renal cell carcinoma

5.2.3 Model structure

The company developed a cohort-based state transition model in Microsoft Excel. The model assesses the incremental cost effectiveness of treatment with pembrolizumab versus routine surveillance in people with completely resected Stage III melanoma at high risk of recurrence.

The model structure comprises four mutually exclusive health states designed to capture locoregional recurrence (LR), distant metastases (DM) and death as shown in Figure 2. The modelled population enters the model being recurrence-free (RF). At the end of every 1-week cycle, there is a risk of LR or DM. People who progress from RF health state to LR health state in a cycle have a risk of further progression to DM health state in subsequent cycles. Death is an absorbing health state that captures all-cause mortality from RF, LR and DM health states. Each health state has an attached cost and utility that individuals residing in that health state accrue every cycle.

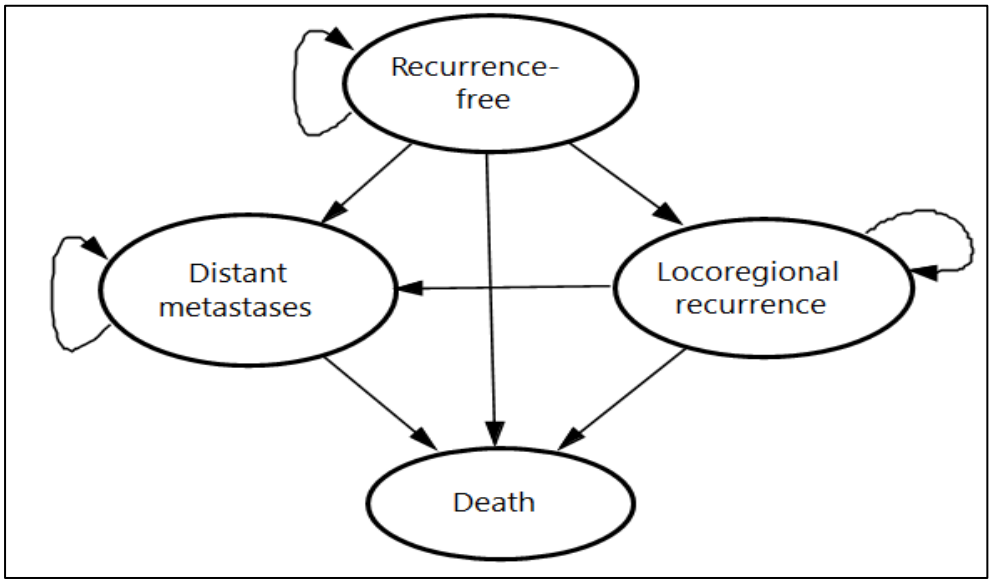

Figure 2 Health state structure of the company model

Source: CS, Figure 14

5.2.4 Population

People with completely resected Stage III melanoma at high risk of recurrence are considered in the company model, which is in line with the final scope issued by NICE. The mean baseline age of the cohort (54.0 years) and the percentage of males (61.6%) are based on the population recruited to the KEYNOTE-054 trial while the average weight of people in the model is obtained from the KEYNOTE-006 [49] trial.

5.2.5 Interventions and comparators

Intervention

Pembrolizumab is implemented in the model as per the anticipated licensed dosing regimen from the EMA marketing authorisation [50]. Pembrolizumab (200mg IV infusion over 30 minutes) is administered every 3 weeks for up to 1 year or until 18 doses.

Comparators

Routine surveillance is the comparator, which the company interprets to mean no systemic chemotherapy until LR or DM.

Discontinuation

To be consistent with the protocol for the KEYNOTE-054 study, the company states that the model reflects the assumption that adjuvant treatment with pembrolizumab following complete resection would continue until disease recurrence, toxicities leading to treatment discontinuation, physician's decision or 12 months of uninterrupted treatment (whichever occurs first).

5.2.6 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and personal social services (PSS). In line with NICE's Guide to the Methods of Technology Appraisal [51] the analysis excludes out-of-pocket expenses, carer costs and productivity costs. The cycle length is 1 week and the time horizon is set at 46 years, assuming a 100-year life expectancy. Both costs and utilities are discounted at 3.5% per annum. A half-cycle correction is applied to most costs and outcomes. The exceptions are AE utility decrement, drug acquisition costs, drug administration costs and AE costs.

5.2.7 Treatment effectiveness and extrapolation in the base case

The company economic model largely relies on patient-level data from the KEYNOTE-054 trial. Other data sources in the economic model are patient-level data from the KEYNOTE-006 [49] trial and Flatiron database [31], results from an NMA [52] comparing treatments for advanced melanoma.

The primary outcome in the KEYNOTE-054 trial is recurrence-free survival (RFS), and not OS. RFS was defined in the KEYNOTE-054 trial as time from randomisation to LR, DM or death, whichever occurred first. The company states that the expected completion date that will allow for the OS analysis is in 2021. Given the lack of OS data from the KEYNOTE-054 trial, the company economic model takes the form of a state transition model instead of a

partitioned survival model, which is the modelling approach often used in economic evaluations of treatments for cancer.

The KEYNOTE-006 trial [49] is a Phase III randomised open-label trial that evaluated treatment with pembrolizumab versus treatment with ipilimumab in people with unresectable or advanced melanoma and who have not had previous treatment with ipilimumab. The primary outcome for the KEYNOTE-006 [49] trial was OS, which is defined as the time from randomisation to all-cause mortality. The Flatiron database [31] is an electronic health records database (EHR) used by cancer care providers in the US. The database [31] holds information on over 2 million active patients, including data on time to DM from LR.

The follow-up periods in the KEYNOTE-054 trial, KEYNOTE-006 [49] trial and Flatiron database [31] were shorter than the required duration of the economic evaluation, which is equivalent to a lifetime. Extrapolation of the RFS from the KEYNOTE-054 trial, OS data from the KEYNOTE-006 [49] trial, and time to DM from LR from the Flatiron database [31] were therefore necessary to enable the use of a fully functional state transition model.

Table 16 Summary of the data sources for health state transition probabilities in the cost effectiveness model

Health states	Transition	Data sources	Company justification
RF	RF-to-LR	• KEYNOTE-054	Main clinical evidence
	RF-to-DM	• KEYNOTE-054	Main clinical evidence
	RF-to-death	• KEYNOTE-054 • Life tables for England & Wales (2014-2016)	Main clinical evidence. Mortality hazard is set such that the maximum hazard from either the general population or the KEYNOTE-054 trial is chosen
LR	LR-to-DM	• Flatiron database	Part two of the KEYNOTE-054 trial, which contains information on people with locoregional recurrence and distance metastases is yet to be analysed. The Flatiron database holds information on population that the company considers to be similar to people in the KEYNOTE-054 trial.
	LR-to-death	• KEYNOTE-054 • Life tables for England & Wales (2014-2016)	No direct LR-to-death transitions in the Flatiron database. The company assumed that mortality hazard for LR and DM health state are the same
DM	DM-to-death	• KEYNOTE-006 • NMA comparing treatments for advanced melanoma • Life tables for England & Wales (2014-16)	Overall survival data are not available from the KEYNOTE-054 trial. The KEYNOTE-006 trial contains OS data on people with advanced or metastatic melanoma, including people who received first-line pembrolizumab

DM=distant metastases; LR=locoregional metastases; NMA=network meta-analysis; OS=overall survival
Source: Adapted from CS, Table 28

Transitions from recurrence-free health state

Using data from the KEYNOTE-054 trial, for each trial arm, the company assumed that RFS hazard is the sum of three competing cause-specific hazards as shown in Equation 1. The cause-specific hazards are the allowed transitions (or events) from the RF health state in the cost effectiveness model (a) RF-to-LR (b) RF-to-DM (c) RF-to-death.

Equation 1

$$\overline{h}_{RFS}(\mathrm{t}) = h_{ka}(\mathrm{t}) + h_{kb}(\mathrm{t}) + h_{kc}(\mathrm{t})$$

Where

$h_{ka}(\mathrm{t})$= RF-to-LR cause-specific hazard at week t

$h_{kb}(\mathrm{t})$= RF-to-DM cause-specific hazard at week t

$h_{kc}(\mathrm{t})$= RF-to-death cause-specific hazard at week t

To the estimate the transition probability for each event, first, the company developed a K-M curve for each cause-specific event. For each cause-specific K-M curve, for each trial arm, the company treated the failures from the other two hazards as censoring events [53, 54]. A concrete example is that to develop the K-M curve for RF-to-LR, the company considered the occurrence of DM and death as censoring events. The company then fitted six parametric models to the K-M curve for RF-to-LR and to the K-M curve for RF-to-DM while an exponential model was fitted to the K-M curve for RF-to-death. Next, the company computed a RFS hazard, which is the hazard of transitioning out of the RF health state due to any cause, with Equation 1. The RFS hazard was then converted to the probability of leaving the RF health state. Thereafter, the relative contribution of each cause-specific hazard was estimated as a ratio of that hazard to the RFS hazard. For example, the relative contribution of RF-to-LR cause-specific hazard is shown in Equation 2. Finally, the company derived the cause-specific probability of leaving the RF health state by multiplying the RFS probability by the relative contribution of that cause-specific hazard.

Equation 2

$$\text{Relative contribution of RF} - \text{to} - \text{LR hazard} = {h_{ka}(t)}\Big/{\overline{h}_{RFS}(\mathrm{t})}$$

For each treatment arm in the KEYNOTE-054 trial, 36 combinations of K-M curves were possible as six parametric models were fitted to the K-M curve for RF-to-LR and to the K-M curve for RF-to-DM. Mean squared error (MSE) and visual inspection were initially used to identify the survival model with the best fit. The company notes that Akaike information criteria

(AIC) which is often used as a goodness-of-fit measure for partitioned survival models is not suitable when modelling competing risks. The preferred models were, however, chosen primarily on how well the RFS fitted the European Organization for Research and Treatment of Cancer (EORTC) 18071 [37, 55] trial. The EORTC 18071 [37, 55] trial is a Phase III, RCT that investigated the effectiveness of ipilimumab, compared with routine surveillance in people with resected Stage III melanoma. The company notes that the observed 5-year RFS, DMFS and OS rates in the routine surveillance arm of the EORTC [37, 55] trial were 30% 39% and 54% respectively. The company's preferred models are the gompertz model (for the RF-to-LR) and generalised gamma model (for RF-to-DM). The company considered that these functional forms generated 5-year RFS, DMFS and OS predictions that were most consistent with the 5-year RFS, DMFS and OS values that were observed in the routine surveillance arm in the EORTC 18071 [37, 55] trial. The company states that, in line with recommendations in the NICE Decision Support Unit Technical Support Document (DSU TSD) 14 [56], the same functional form used for the RF-to-LR and RF-to-DM in the pembrolizumab arm the same as the functional forms in the routine surveillance arm.

Transitions from locoregional recurrence health state

The company conducted a retrospective database analysis of the Flatiron database [31] from January 1, 2011 to February 28, 2018 with the aim of estimating transition probabilities for LR-to-DM and LR-to-death. Adults with newly diagnosed Stage III, IIIA, IIIB or IIIC melanoma after complete resection were considered in the analysis. Eligible individuals (n=1166) were followed from the date of LR to DM, death, the last date of data availability, or February 28,

2018, whichever occurred earliest. The company compared the characteristics of people in the KEYNOTE-054 trial and in the Flatiron [31] study (Table 17).

Table 17 Baseline characteristics of participants in the KEYNOTE-054 trial and the Flatiron study cohort

Characteristics	KEYNOTE-054 (N=1019)	Flatiron study cohort (N=1166)
Sex, male, n (%)	628 (61.6)	742 (63.7)
Age, years, mean (SD)	53.8 (13.9)	57.3 (14.9)
BRAF-mutation detected, n (%)	507 (49.8)	524 (45.0)
Cancer stage		
• Stage IIIA	160 (15.7)	419 (35.9)
• Stage IIIB	467 (45.8)	373 (31.9)
• Stage IIIC		225 (19.3)
- Stage IIIC (1-3 LN+)	118 (18.4)	92 (7.8)
- Stage IIIC (>= 4 LN+)	204 (20.0)	130 (11.2)

LN=lymph node
Source: Adapted from Flatiron study report [31], Table 1

One hundred and forty seven eligible individuals in the Flatiron [31] database experienced LR after complete resection of their Stage III melanoma. The company developed a K-M curve using data for the LR population, with the event of interest being further progression to DM. The company reported that the median OS was 66 weeks and an exponential parametric function was fitted to the observed data (Figure 3). The company assumes that the LR-to-DM cause-specific hazard from the Flatiron [31] database is the same for the pembrolizumab arm and routine surveillance arm.

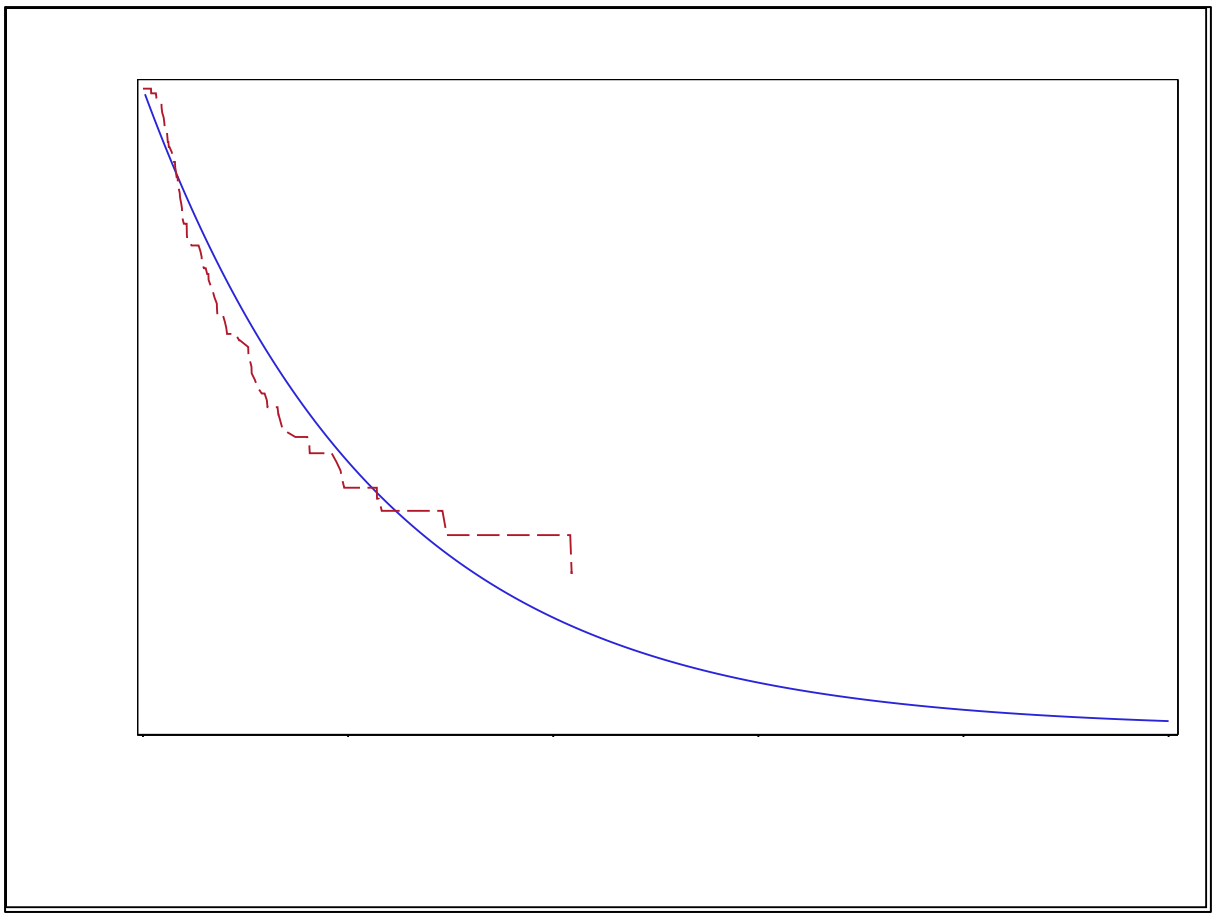

Figure 3 Exponential model fitted to the observed LR-to-DM data from the Flatiron database

Source: Company analysis of the Flatiron database [31], Figure 2

There was no direct LR-to-death transition amongst the eligible cohort in the Flatiron [31] study. Therefore, the cause-specific hazard for LR-to-death transition was approximated based on the exponential model of LR-to-death in the pembrolizumab arm of the KEYNOTE-054 trial. The company notes that people with LR in the cost effectiveness model are still at higher risk of death than those in the RFS health state because of the higher likelihood of developing DM and the higher associated mortality risk for the DM health state.

Transitions from distant metastases health state

The company assumed DM-to-death transitions depend on the distribution of first-line medications that people with advanced melanoma receive before the occurrence of DM. First-line treatment options considered by the company are pembrolizumab, ipilimumab, nivolumab, nivolumab plus ipilimumab, vemurafenib, dabrafenib, and dabrafenib plus trametinib. The distribution of the first-line medications corresponds to the market share of the medication (Table 18).

Table 18 Market share assumptions for advanced melanoma therapies (no re-challenge and with re-challenge)

Regimens in advanced setting	Market shares (%)				Reference
	Pembrolizumab (no re-challenge)	Routine surveillance	Pembrolizumab (re-challenge)	Routine surveillance	
Pembrolizumab	0.0%	27.8%	27.8%	27.8%	Ipsos Oncology Monitor, 2018 [57]
Ipilimumab	50.2%	5.8%	5.8%	5.8%	
Nivolumab	0.0%	3.8%	3.8%	3.8%	
Nivolumab+ipilimumab	0.0%	18.7%	18.7%	18.7%	
Vemurafenib	16.3%	14.4%	14.4%	14.4%	
Dabrafenib	0.0%	0.0%	0.0%	0.0%	
Dabrafenib+trametinib	33.4%	29.5%	29.5%	29.5%	

Source: CS, Table 40

To begin, the OS for pembrolizumab was obtained from the OS data in the pembrolizumab arm of the KEYNOTE-006 [49] trial, onto which an exponential model was fitted. Then, the company conducted a NMA of data from trials that investigated the effectiveness of various treatments in people with advanced melanoma [58]. Next, to obtain the OS for each alternative first-line treatment to pembrolizumab, as shown in

Table 18, the company applied the HR for that treatment (Table 19) to the OS for pembrolizumab. For ipilimumab, nivolumab, and nivolumab plus ipilimumab, HRs were based on NMA results for the first-line BRAF wildtype population. For vemurafenib, dabrafenib, and dabrafenib plus trametinib, HRs were based on the NMA [58] results for the first-line BRAF mutant positive population. For treatments not targeting BRAF, trial results for the all-comers population were used in both the BRAF wildtype and BRAF mutant positive NMAs, based on the assumption that BRAF status is not a significant effect modifier. The company states that the assumption was made because the treatment effects in subgroup analyses of the KEYNOTE-006 [49] trial were consistent in BRAF wildtype and BRAF mutant positive populations [49].

Table 19 HRs of OS and PFS failure for other first-line treatments versus pembrolizumab

Advanced regimen	HR of OS (versus pembrolizumab)		Expected mean OS (weeks)	Expected mean OS (weeks) weighted by market share	
	HR	SE of ln(HR)		Pembrolizumab	Routine surveillance
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib+trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HR=hazard ratio; ln=natural log; OS=overall survival; SE=standard error
Source: Adapted from CS, Table 26

Finally, OS for each group (pembrolizumab and routine surveillance) in the cost effectiveness model was calculated as the sum of the expected mean OS associated with different first-line treatments for advanced melanoma, weighted by their current market shares. For the pembrolizumab group, the company assumed that no further treatment with a PD-1 inhibitor was permitted. The market share for pembrolizumab, nivolumab, nivolumab plus ipilimumab was therefore assumed to be 0% in the base case. Market shares for the remaining advanced treatment regimens were proportionately increased, subject to the constraint that the total market share of BRAF inhibitors (i.e., vemurafenib, dabrafenib, and dabrafenib plus trametinib) cannot exceed the proportion of patients who were BRAF+ in the KEYNOTE-054 trial (i.e., 49.8%). See

Table 18 for the distribution of treatments used in the first-line advanced setting in the base case and sensitivity analysis [57]. For patients receiving routine surveillance, no further adjustments are made to the distribution of treatments used. Using the described company approach, the DM-to-death cause-specific HRs for pembrolizumab and routine surveillance are shown in Table 20.

Table 20 Hazards of death from distant metastases by adjuvant treatment arm, base case

Adjuvant regimen	Expected mean survival in DM health state (weeks): *Weighted average based on first-line advanced treatment market shares*			Hazard rate for DM-to-death (*based on expected OS*)
	OS	PFS	Ratio of PFS to OS	
Base case with no re-challenge				
Pembrolizumab	119	70	0.59	0.0084
Routine surveillance	153	83	0.55	0.0065

PFS=progression-free survival; OS=overall survival
Source: CS, Table 27

Time to treatment discontinuation

In the KEYNOTE-054 trial, individuals randomised to receive adjuvant pembrolizumab were treated for up to 1 year or until completion of 18 doses. The company states that there was sufficient follow-up data from the KEYNOTE-054 trial to directly observe time on adjuvant treatment, without the need for extrapolation. As illustrated in Figure 4, a small percentage of patients in the pembrolizumab arm of the KEYNOTE-054 trial remained on adjuvant therapy beyond 1 year. The company notes that the trial protocol allowed patients to complete all 18 doses past the 1-year point, if there had been earlier delays in treatment. Within the economic evaluation, the costs of adjuvant pembrolizumab treatment were modelled based on a fixed interval of every 3 weeks, and so the costs of the 18th dose were applied at t=49 weeks from baseline for the percentage of patients still on adjuvant treatment at this time point. Therefore, the model did not use the portion of the K-M curve beyond the scheduled 1-year treatment period (represented by the dashed line in Figure 4).

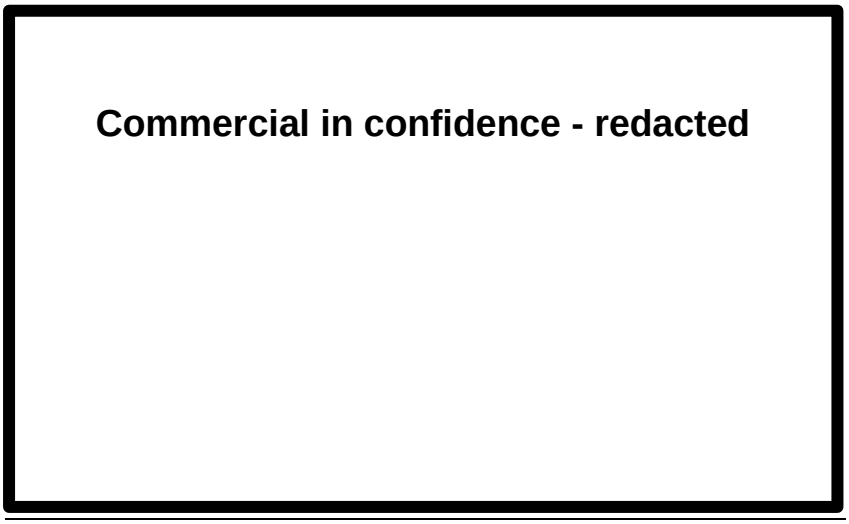

Figure 4 Observed Kaplan-Meier curve for time to treatment discontinuation in the pembrolizumab arm of the KEYNOTE-054 trial

Source: Company analysis of the Flatiron database. CS, Figure 19

The K-M curve from the KEYNOTE-054 trial was used to model duration of treatment for the RF health state. No systemic therapy was required for people in the LR health state as the mainstay of therapy is assumed to be surgery. For people in the DM health state, the PFS data from the KEYNOTE-006 [49] trial were assumed to be equivalent to the duration of treatment. Exponential rates of PFS failure were estimated using the same method for estimating the DM-to-death transition probability from the OS data in the KEYNOTE-006 [49] trial (see Section 5.2.7 in this report).

Table 21 Treatment duration and dose intensity for treatments in the advanced setting

Treatment	Drug component (for combination therapies)	Exponential rate of discontinuation	Maximum ToT (weeks)	Dose intensity
Pembrolizumab	n/a	0.016	No maximum	100%
Ipilimumab	n/a	0.029	12	100%
Nivolumab	n/a	0.016	No maximum	100%
Nivolumab plus ipilimumab	Ipilimumab (in combination)	0.012	12	100%
	Nivolumab (in combination)		12	
	Nivolumab (maintenance)[3]		No maximum	
Vemurafenib	n/a	0.014	No maximum	100%
Dabrafenib	n/a	0.012	No maximum	100%
Dabrafenib+trametinib	Dabrafenib (in combination)	0.008	No maximum	100%
	Trametinib (in combination)		No maximum	

ToT=time on treatment
Source: CS, Table 43

5.2.8 Health-related quality of life

Patients in the KEYNOTE-054 trial completed the EQ-5D-3L questionnaire at baseline and at 12-week intervals until week 48. Health status was assessed at each data collection point. Visits with missing EQ-5D-3L scores were excluded from the analysis. The company used a linear mixed-effect model to estimate utility value for each health state (RF, LR and DM). Unique identifiers for individuals were used as random effects to account for repeated measures per patient. Full results of the analysis are presented in Appendix N to the CS.

In the cost effectiveness model, the company used utility values for the RF and LR health states from the KEYNOTE-054 trial, using the linear mixed-effect model. To derive the utility estimate for the DM health state, the company first splits the DM health state into pre-progression and post-progression. The utility values for DM pre-progression and post-progression were obtained from the KEYNOTE-054 trial and a societal preference study [59] respectively. Then, the company calculated a single utility value for the DM health state as a weighted average of the DM pre-progression and DM post-progression utility values based on the proportion of time spent progression-free within the DM state.

Table 22 Base case health state utility value in the cost effectiveness model

Health state	Utility value, mean (SE)	Source
Recurrence-free (without toxicity)	0.870 (0.008)	KEYNOTE-054 trial
Locoregional recurrence	0.830 (0.016)	KEYNOTE-054 trial
Distant metastases (pre-progression)	0.775 (0.012)	KEYNOTE-054 trial
Distant metastases (post-progression)	0.590 (0.020)	KEYNOTE-054 trial and Beusterien [59]

Source: Adapted from CS, Table 31

Impact of age on health state utility

Further utility adjustments are made to account for the company's assumption that HRQoL decreases with age. The company uses a published linear algorithm [60] (Table 23) to calculate age-specific utility values in the general population.

Table 23 Regression coefficients for estimating age-specific disutility

Parameter	Coefficient
Age (years)	-0.0002587
Age squared	-0.0000332
Male	0.0212126
Intercept	0.9508566

Source: CS, Table 32

5.2.9 Resources use and costs

Drug costs

A Commercial Access Agreement (CAA) discount ([redacted]) is in place for pembrolizumab is applied to list price of pembrolizumab in the base case analyses. Pembrolizumab is administered via IV infusion and, therefore, an additional treatment administration cost of £241.07 per dose was incurred. No vial sharing was assumed. Details of drug costs are presented in Section B3.5.1 of the CS and reproduced in Table 24 of this ERG report. No drug costs are associated with routine surveillance.

Table 24 Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per administration (list prices)

Drug	Dosing regimen	Cost per vial/pack	Vial size / tablets per pack	Vials per admin	Proportion of dose received	Total cost per administration
Pembrolizumab	200mg IV Q3W, up to 1 year	£2,630.00	100mg	2	99.7%	£5,260

IV=intravenous; Q3W=once every 3 weeks
Source: Adapted from company model, Table 34

Subsequent treatments

After treatment with adjuvant therapy following complete melanoma resection, individuals in the company model were modelled to receive subsequent therapy upon entering the DM health state. The company notes that the dosing schedule for each drug was based on the administration assessed and approved by NICE (Table 25)

Table 25 Drug doses and treatment cost per pack for each treatment given in the advanced setting

Treatment	Dosage	Pack size/ vial volume	Cost per pack/vial
Pembrolizumab	• 2mg/kg Q3W	• 100mg vial • 50 mg vial	£2,630 £1,315
Nivolumab	• 3mg/kg Q2W	• 100mg vial • 40mg vial	£1,097 £439
Nivolumab+ipilimumab	First four doses • Nivolumab: 1mg/kg Q3W • Ipilimumab: 3mg/kg Q3W	Nivolumab • 100mg vial • 40mg vial Ipilimumab 5mg/ml • 10ml (50mg) vial • 40ml (200mg) vial	Nivolumab £1,097 £439 Ipilimumab 5mg/ml £3,750 £15,000
	After four doses • Nivolumab: 3mg/kg Q2W	• 100mg vial • 40mg vial	£1097 £439
Vemurafenib	• 960mg twice daily	• 240mg 56-tab pack	£1,750
Dabrafenib	• 150mg twice daily	• 50mg, 28-cap pack • 75mg, 28-cap pack	£933.33 £1,400
Dabrafenib+trametinib	• Dabrafenib: 150mg twice daily • Trametinib: 2mg daily	• 2mg tablet, 30-tab pack • 2mg tablet, 7-tab pack	£4,800 £1,120

Cap=capsule; IV=intravenous; Q2W=once every 2 weeks; Q3W=once every three weeks; tab=tablet
Source: Adapted from CS, Table 41 and Table 42

Resource use by health state

Individuals in the RF health state incur costs for routine follow-up in addition to medication costs. The company obtained resource use estimates for routine surveillance from a position paper from UK clinicians [17]. Individuals without disease progression at 10 years were assumed to be discharged from follow-up. The company assumes that the main treatment of choice for individuals with LR is further surgery. The proportion of individuals receiving surgery and the types of surgery performed were taken directly from the KEYNOTE-054 trial. After surgery, individuals in the model were assumed to continue with routine follow-up as per the LR health state. The cost per cycle was estimated using the relevant NHS 2016/17 Reference Costs [61] for each resource use component. Resource use details for the RF and LR health states are shown in Table 26.

The primary treatment option for patients with confirmed advanced disease (i.e., unresectable or metastatic disease) is systemic treatment with one of the immunotherapies or targeted

agents (either as a monotherapy or combination therapy) approved by NICE and as outlined in the NICE Pathway for melanoma [62].

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Table 26 Monthly resource use detail and total weekly cost for recurrence-free health state and locoregional recurrence health state

Resource use element	Unit cost	RF (up to year 3)		RF (years 3 to 5)		RF (years 6 to 10)		LR (first month)		LR (subsequent months)	
		Patients	Resource use	Patients	Resource use	Patients	Resource use	Patients	Resource use	Patients	Resource use
Salvage surgery											
In-transit metastases resection or other surgery	£2,911.01	0%	0.00	0%	0.00	0%	0.00	[redacted]	[redacted]	0%	0.00
Lymphadenectomy	£2,076.83	0%	0.00	0%	0.00	0%	0.00	[redacted]	[redacted]	0%	0.00
Skin lesion resection	£497.41	0%	0.00	0%	0.00	0%	0.00	[redacted]	[redacted]	0%	0.00
Outpatient visits											
Medical oncologist	£161.13	100%	0.17	100%	0.08	100%	0.04	0%	0.00	100%	0.17
Radiation oncologist	£130.85	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
General practitioner	£32.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Plastic surgeon	£100.72	100%	0.08	100%	0.04	100%	0.02	0%	0.00	100%	0.08
Dermatologist	£103.05	100%	0.08	100%	0.04	0%	0.02	0%	0.00	100%	0.08
Cancer specialist nurse	£82.09	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Radiologic exams											
CT scan of abdomen/pelvis	£90.04	100%	0.17	100%	0.08	0%	0.00	0%	0.00	100%	0.17
CT scan of chest	£90.04	100%	0.17	100%	0.08	0%	0.00	0%	0.00	100%	0.17
MRI of brain	£142.32	100%	0.17	100%	0.08	0%	0.00	0%	0.00	100%	0.17
CT scan of brain	£90.04	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
PET/CT scan	£142.32	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Bone scintigraphy	£222.12	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Echography	£70.36	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Chest x-ray	£125.26	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Total cost		**£22.44 per week**		**£11.22 per week**		**£2.03 per week**		**£1,345.37 once**		**£22.44 per week**	

CT=computed tomography; LR=locoregional recurrence; MRI=magnetic resonance imaging; RF=recurrence-free
Source: Adapted from company model

The company assumed that individuals in the DM health state are eligible for treatment in the advanced setting. The distribution of therapies administered in the advanced setting is taken from the most recent market research of current UK treatment patterns [57]. In the base case scenario, patients receiving pembrolizumab in the adjuvant setting are assumed not to receive further treatment with a PD-1 inhibitor in the advanced setting (Table 18)

The company assumes that all individuals who stop first- or second-line systemic treatment in the advanced setting would receive best supportive care. Consequently, the cost of best supportive care was included for patients who entered the DM health state. Data for the components of best supportive care are taken from a previous appraisal of pembrolizumab,TA366 [22], in the advanced setting. This information was initially used in the appraisal of ipilimumab in the first-line setting for melanoma, TA319, [63].

Table 27 Monthly resource use detail and total weekly cost for distant-metastases health state

Resource use element	Unit cost	DM pre-progression (first month)		DM pre-progression (subs. months)		DM post-progression (subs. months)	
		Patient	Res. use	Patient	Res. use	% Pat.	Res. use
Salvage surgery							
Surgical resection	£2,911.01	[redacted]	[redacted]	0%	0.00	0%	0.00
Lymphadenectomy	£2,076.83	[redacted]	[redacted]	0%	0.00	0%	0.00
Skin lesion resection	£497.41	[redacted]	[redacted]	0%	0.00	0%	0.00
Outpatient visits							
Medical oncologist	£161.13	81%	3.60	0%	0.00	63%	0.90
Radiation oncologist	£130.85	6%	2.30	0%	0.00	6%	1.50
General practitioner	£32.00	4%	2.00	4%	2.00	78%	1.90
Palliative care visit	£151.12	0%	0.00	0%	0.00	29%	1.20
Psychologist	£139.33	0%	0.00	0%	0.00	4%	3.00
Plastic surgeon	£100.72	2%	1.50	2%	1.50	0%	0.00
Inpatient stays							
Oncology/general ward	£1,816.32	6%	2.80	5%	1.30	14%	3.60
Palliative care unit - inpatient	£397.65	0%	0.00	0%	0.00	26%	4.00
Home care							
Palliative care physician	£142.00	0%	0.00	0%	0.00	24%	1.00
Palliative care nurse	£102.00	0%	0.00	0%	0.00	58%	1.40
Home aide visits	98.00	0%	0.00	0%	0.00	22%	7.30
Laboratory tests							
Complete blood count	£3.00	100%	1.20	100%	1.30	0%	0.00
Complete metabolic panel	£1.00	100%	1.20	95%	1.30	0%	0.00
Lactate dehydrogenase	£1.00	100%	1.20	95%	1.30	0%	0.00
Radiologic exams							
CT scan of abdomen/pelvis	£90.04	100%	1.00	96%	0.40	0%	0.00
CT scan of chest	£90.04	100%	1.00	96%	0.40	0%	0.00
MRI of brain	£142.32	6%	1.00	21%	0.30	0%	0.00
CT scan of brain	£90.04	41%	1.00	11%	0.20	0%	0.00
PET/CT scan	£142.32	5%	1.00	2%	0.40	0%	0.00
Bone scintigraphy	£222.12	19%	1.00	1%	0.30	0%	0.00
Echography	£70.36	6%	1.00	12%	0.30	0%	0.00
Chest x-ray	£125.26	20%	1.00	30%	1.10	0%	0.00
Pain management							
Morphine - Oral	£5.45	0%	0.00	0%	0.00	51%	1.00
Morphine - IV	£100.95	0%	0.00	0%	0.00	22%	1.00
Morphine - Transdermal patch	£17.60	0%	0.00	0%	0.00	15%	1.00
NSAIDs (Ibuprofen)	£2.24	0%	0.00	0%	0.00	55%	1.00
Other: Paracetamol	£1.59	0%	0.00	0%	0.00	18%	1.00
Total Cost		**£3,672.09 once**		**£58.83 per week**		**£425.38 per week**	

CT=computed tomography; DM=distant metastasis; MRI=magnetic resonance imaging; PET=positron emission tomography; res=resource; subs=subsequent Source: CS, Table 41

Adverse event costs

Adverse event unit costs were derived from TA319 [63]. Costs were inflated to the 2017 price year or updated using the 2016/17 NHS Reference Costs [61] where appropriate. Table 28 shows the applied unit costs for AEs included in the company's cost effectiveness model.

Table 28 Adverse event unit costs

Type of adverse event	Cost per event (£)			Source for cost
	Original cost values	Original reporting year	Inflation-adjusted costs	
Diarrhoea	£684.01	2013	£749.12	Oxford Outcomes data reported in TA319 [63] inflated to 2017 GBP
Pneumonitis	£596.85	2017	£596.85	Assumption based on TA417 [64]
Hyperthyroidism	£473.72	2013	£518.81	Oxford Outcomes data reported in TA319 [63] (endocrine disorders), inflated to 2017 GBP
Fatigue	£173.89	2013	£190.44	Oxford Outcomes data reported in TA319 [63], inflated to 2017 GBP
Alanine aminotransferase increased	£0	2017	£0.00	Assumption of zero cost for laboratory abnormalities
Arthralgia	£151.46	2017	£151.46	NHS Reference Costs 2016/17 [61] Consultant-led outpatient attendances for 191 (pain management)
Headache	£0	2017	£0.00	Assumption based on TA319 [63]
Dyspnoea	£0	2017	£0.00	Assumption based on TA319 [63]

Source: CS, Table 49

5.2.10 Cost effectiveness results

Base case results

Table 29 shows the base case incremental cost effectiveness ratios (ICERs) per QALY gained for treatment with pembrolizumab versus routine surveillance. Treatment with pembrolizumab dominated routine surveillance by being £3,988 cheaper and generating 2.73 additional QALYs.

Table 29 Base case incremental cost effectiveness results – with list prices for pembrolizumab

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained (pembrolizumab vs routine surveillance)
				Cost	LYG	QALYs	
Pembrolizumab	£161,954	9.79	7.91				
Routine surveillance	£165,941	6.61	5.18	£-3,988	3.18	2.73	Dominant

LYG=life year gained; QALY=quality adjusted life year
Source: adapted from CS, Table 53

5.2.11 Sensitivity analyses

Deterministic sensitivity analyses

Results of one-way sensitivity analyses (OWSA) show that the extrapolation curve for estimating the transition probabilities from the RF health state to the LR health state, DM health state and death have the greatest impact as shown in Figure 5.

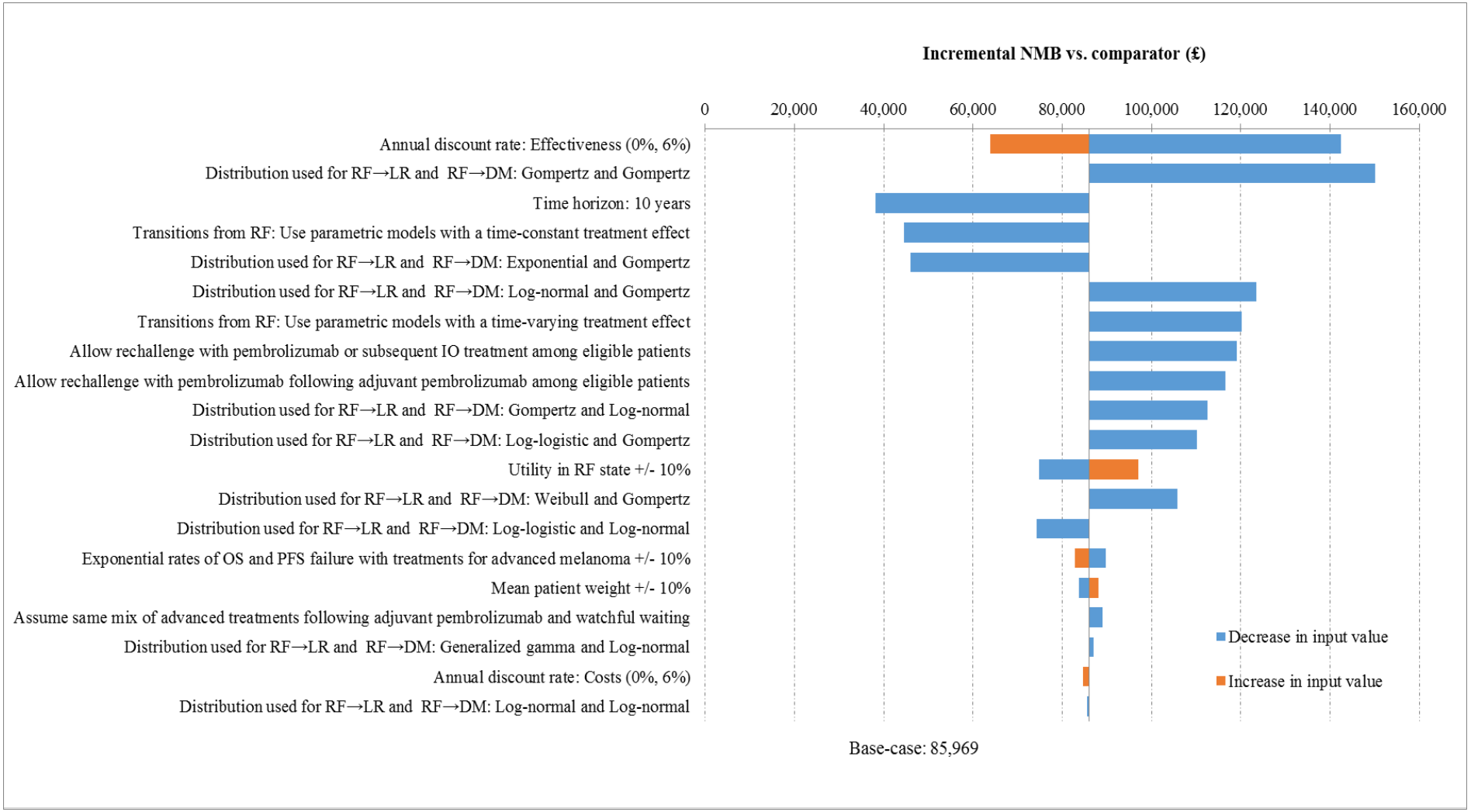

Figure 5 Tornado diagram shown one-way sensitivity analysis results for treatment with pembrolizumab versus routine surveillance DM=distant metastases; ICER=incremental cost-effectiveness ratio; IO=immune-oncology; LR=locoregional; OS=overall survival; PFS=progression-free survival; RF=recurrence-free
Source: CS, Figure 36

Probabilistic sensitivity analysis

The company varied a large number of input parameters in its probabilistic sensitivity analysis. The mean probabilistic ICER per QALY gained shows treatment with pembrolizumab to be the dominant strategy compared to routine surveillance (Table 30).

Table 30 Probabilistic incremental cost effectiveness results (list price for pembrolizumab)

Treatment	Total cost	Total QALYs	Incremental		Incremental cost per QALY gained
			Cost	QALYs	
Pembrolizumab	£163,093	7.97			
Routine surveillance	£167,063	5.36	£-3,970	2.62	Dominant

QALY=quality adjusted life year
Source: adapted from CS, Table 54

Figure 6 shows the uncertainty around the estimated mean cost per QALY difference between treatments with pembrolizumab versus routine surveillance. The cost effectiveness acceptability curve (Figure 7) shows that there is an approximate 91.5% probability of pembrolizumab being cost-effective when compared to routine surveillance at the £30,000 per QALY threshold.

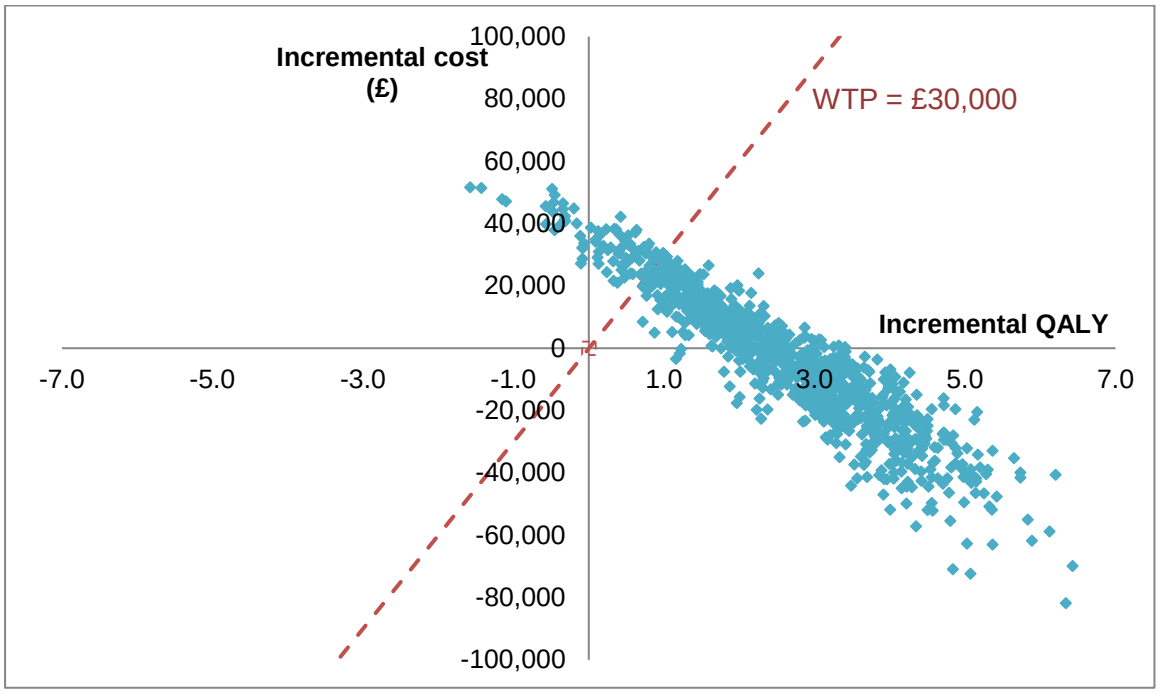

Figure 6 Scatter plot of incremental cost and incremental QALY for pembrolizumab versus routine surveillance (1000 iterations) ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; WTP=willingness-to-pay
Source: Company model, probabilistic sensitivity analysis worksheet

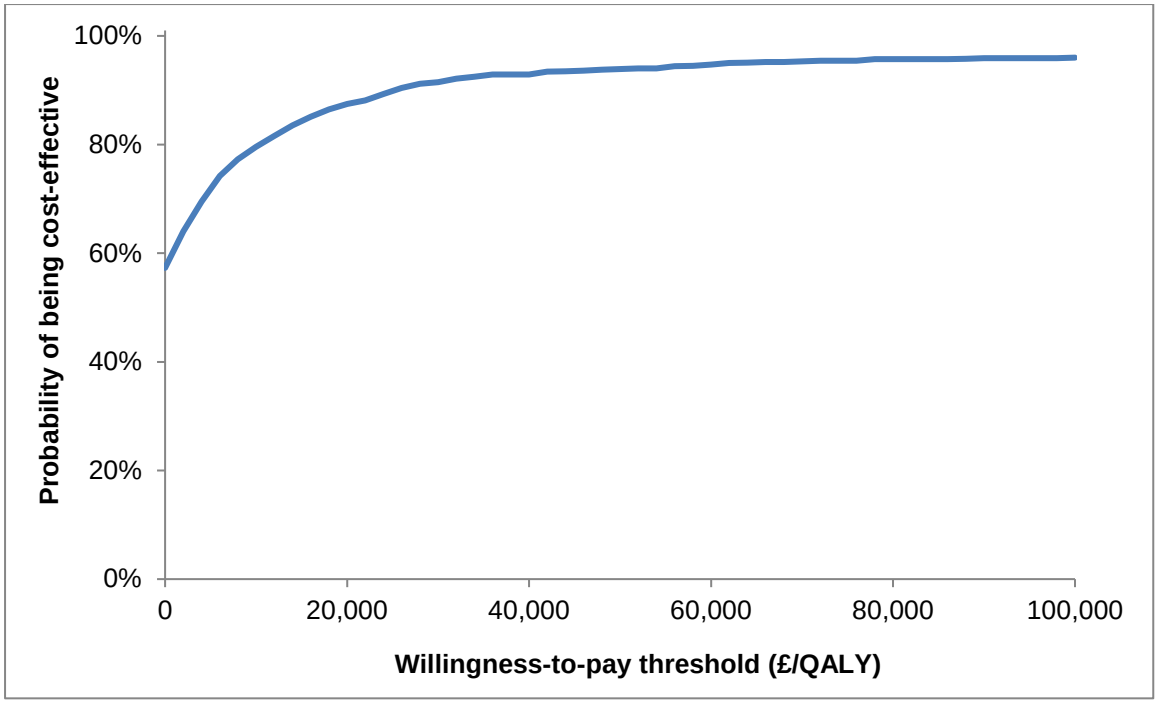

Figure 7 Cost effectiveness acceptability curve of treatment with pembrolizumab vs routine surveillance QALY=quality adjusted life year
Source: Company model, probabilistic sensitivity analysis worksheet

5.2.12 Model validation and face validity check

The company states that the predicted efficacy outcomes from the cost effectiveness model were compared to those observed in the KEYNOTE-054 trial. Additionally, external health economists assessed the model for implementation errors and from an overall health economics perspective.

5.3 ERG detailed critique of company economic model

5.3.1 NICE Reference Case checklist

Table 31 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=personal social services

5.3.2 Drummond checklist

Table 32 Critical appraisal checklist 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?	No	DMFS and OS drive the company's model and these data, which were obtained from the KEYNOTE-054 trial, were too immature to be included in the model. The intermediate outcomes that the company chose to use generated clinically implausible results
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?	No	All patients entering the DM state were assumed to receive systemic therapies; however, no justification for this approach was provided
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?	Partly	A sensitivity analysis should have been performed around the percentage of people entering the DM state who had inoperable Stage IV disease and who received systemic therapy
Did the presentation and discussion of study results include all issues of concern to users?	No	Subgroup analysis of groups with differential risk of recurrence should have been considered

DM=distant metastases, DMFS=distant metastases free survival, OS=overall survival

5.3.3 ERG critique of the company model

The ERG is satisfied that the structure of the company model is appropriate for the assessment of the cost effectiveness of pembrolizumab as an adjunctive therapy versus routine surveillance for patients with Stage III melanoma. The ERG identified no errors in the algorithms used to construct the model and the parameter values used in the model appear to match those stated in the CS.

Immaturity of KEYNOTE-054 trial data

The company does not use the mature RFS data from the KEYNOTE-054 trial to populate the submitted de novo model; instead, they use data on first recurrence event (either distant metastases [DM], locoregional recurrence [LR] or death). In the company model, OS and DMFS were not projected or modelled directly; rather, they were indirectly based upon projections of first recurrence events. The ERG notes that the first recurrence events were not pre-specified outcomes in the KEYNOTE-054 trial statistical analysis plan. The ERG also notes that OS and DMFS are secondary outcomes of the KEYNOTE-054 trial and data for these outcomes are not expected to reach maturity until [redacted] respectively. In the CS (p25), the company states that 'The minimum number of events required to analyse the endpoints of OS and DMFS had not been achieved at the time of data cut-off (October 2017)'. As OS and DMFS data from the KEYNOTE-054 trial are too immature to be analysed and/or be presented fully in the CS, the ERG considers that these data are too immature to be included in an economic model. The ERG highlights that, at the October 2017 data cut, the OS data were only 15% mature. The ERG notes that previous research has identified that immature data can lead to spurious projections of OS, especially in cancer studies [65].

The company's total discounted QALY gain estimate for the comparison of the effectiveness of pembrolizumab versus routine surveillance is 2.73 QALYs. The ERG notes that only 0.03 QALYs (1.0% of the total QALY gain) is accrued during the first 16 months of the model time horizon, the median period for which follow up data from the KEYNOTE-054 trial were available.

Impact of immature data on model OS and DMFS projections

The company compared the estimated 5-year OS and DMFS results generated by their submitted model for patients in the routine surveillance arm against those reported in the EORTC 18071 [37, 55] trial, which assessed ipilimumab for adjunctive therapy versus placebo for resected Stage III melanoma. This comparison (CS, p58) showed predicted 5-year OS for patients in the routine surveillance arm of the company model was slightly higher than actual OS for patients in the placebo arm of the EORTC 18071 [37, 55] trial (55.2% versus 54.4%). It also showed that predicted 5-year DMFS for patients in the routine surveillance arm of the

company model was 8.7% lower than the actual 5-year DMFS data for patients in the placebo arm of the EORTC 18071 [37, 55] trial (30.2% versus 38.9%). The company model, therefore, projects slightly higher 5-year OS and, at the same time, much lower 5-year DMFS for routine surveillance than would be expected based upon similar data from the EORTC 18071 [37, 55] trial.

The EORTC 18071 [37, 55] trial was not the only evidence source that could have been used by the company to validate the OS and DMFS projections produced by the company model. Ten-year OS data are also available from the 2010 SEER database [24] for patients with Stage III melanoma by AJCC 7th Edition [7] staging classifications. In addition, 10-year melanoma-specific survival rates, based on the AJCC 8th Edition staging classifications using data from a 2017 analysis of the International Melanoma Database and Discovery Platform (IMDDP) [13], were released in 2017. Projected OS using data from the SEER and IMDDP databases [24] should be considered pessimistic for patients with Stage III melanoma in the routine surveillance arm of the company model as (i) all SEER [24] and IMDDP [13] data include patients who have not had a complete resection, (ii) 2010 SEER [24] data do not reflect improvements resulting from the use of sentinel lymph node biopsy and imaging [66], and (iii) the 2017 IMDDP [13] data do not reflect the benefits of widespread use of systemic therapies such as pembrolizumab for Stage IV cancer.

Using digitised versions of the OS data from the 2010 SEER [24] database (based upon AJCC 7th Edition staging classifications), the ERG generated a composite Stage III survival curve by combining the OS curves for Stage IIIA, IIIB and IIIC disease weighted by the proportions of patients in each of these stages in the KEYNOTE-054 trial. This composite OS curve provides an approximation of the expected OS for the placebo arm of the KEYNOTE-054 trial. The OS curves are shown in Figure 8.

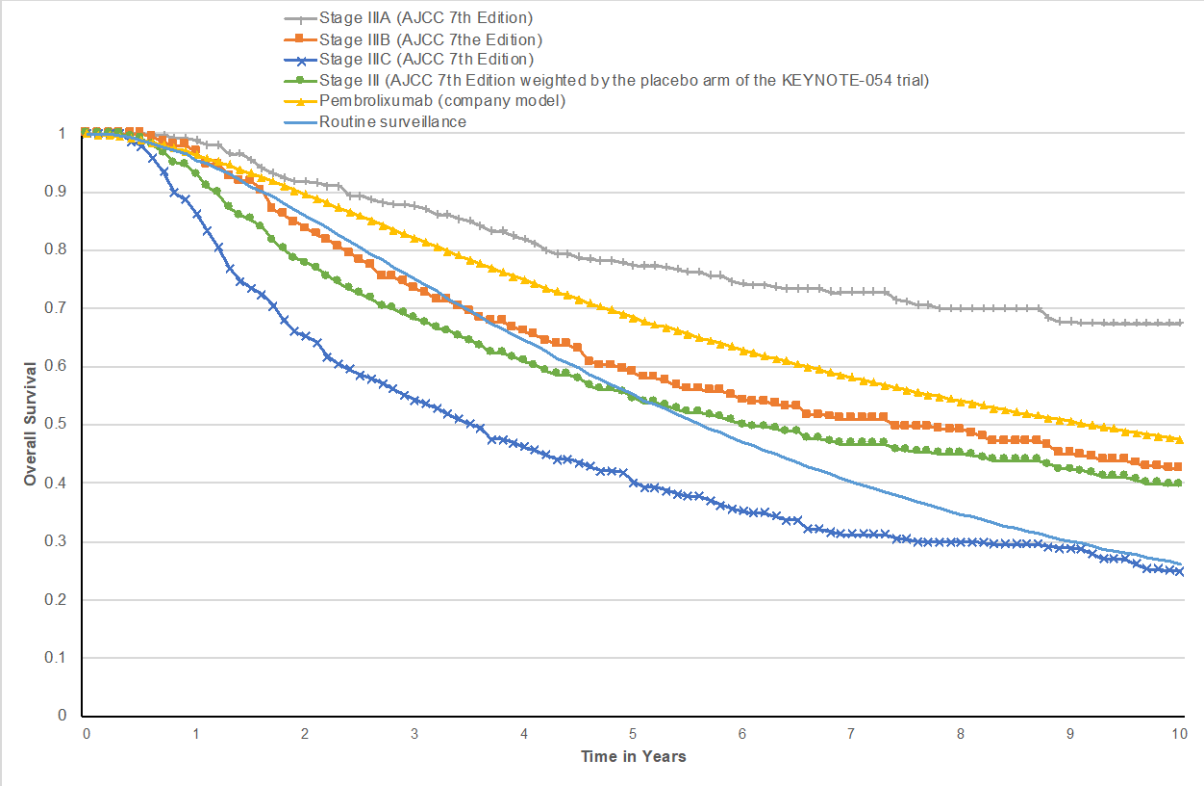

Figure 8 10-year OS for patients with Stage III melanoma: SEER data from 2010 based upon AJCC 7th Edition staging classifications and data from the pembrolizumab and routine surveillance arms of the company model

The OS curves in Figure 8 show that, for the first 5 years, projected OS in the routine surveillance arm of the company model is better than that demonstrated by the ERG's composite expected OS curve. After 5 years, the company model projected OS curve for the routine surveillance arm lies below the ERG's composite expected OS curve and then, by 10 years, the company model projected OS curve for the routine surveillance arm is approximately equal to the 2010 SEER [24] database OS curve for patients with Stage IIIC disease. The ERG considers that this is clinically implausible.

The 5- and 10-year melanoma-specific survival rates for different melanoma stages (AJCC 8th Edition classifications [13] are shown in Table 33 alongside the expected melanoma-specific survival for the population in the KEYNOTE-054 trial (where Stage IIIC [1-3LN+] and Stage IIIC [>=4LN+] were assumed to be equivalent to Stage IIIC and Stage IIID definitions in the AJCC 8th Edition [13] respectively).

Table 33 2018 IMDDP database 5- and 10-year melanoma-specific survival by staging classification in the AJCC 8th Edition

	5-year melanoma specific survival	10-year melanoma specific survival
Stage IIIA	93%	88%
Stage IIIB	83%	77%
Stage IIIC	69%	60%
Stage IIID	32%	24%
KEYNOTE-054 trial composite	72%	65%

Source: Gershenwald 2017

The company model predicts that, at 5 years, 68.7% of patients in the routine surveillance arm will have entered the DM state and that, of these patients, 43.7% will have died. Some patients will have died of causes other than cancer so this 43.7% only approximates to melanoma-specific mortality which, based on data from the 2017 IMDDP [13] dataset, was estimated to be 28%. The company model also predicts that, at 10 years, 81.5% of patients in the routine surveillance arm will have entered the DM state and that, of these patients, 71.8% will have died. Some patients will have died of causes other than cancer so this 71.8% only approximates to melanoma-specific mortality which, based on data from the 2017 SEER [13] dataset, was estimated to be 35%.

The company model projections of DM and death for patients in the DM state appear to be clinically implausible up to year 5, and increasingly more clinically implausible between years 5 and 10. Over the company model time horizon (46 years), the company model predicts that 91.6% of all people in the routine surveillance arm will have developed a DM (i.e., have Stage IV disease), which the ERG also considers is clinically implausible. Further, none of the exhaustive list of curves considered by the company produces results that are sensible for both DMFS and OS.

Impact of immature data on estimation of treatment effect

An analysis of DMFS data from the KEYNOTE-054 trial was reported in the main journal publication [23] but not in the CS. Results from this analysis show a statistically significant difference in the hazards for DMFS at 12 and 18 months between the pembrolizumab and placebo arms of the trial. However, a statistically significant difference in a hazard rate is insufficient to project hazards in both arms when the hazard rate changes over time. Trial data immaturity means there have not yet been sufficient events to fully understand the treatment effect of the intervention over a specified time period and that there are, therefore, insufficient data to construct robust projections of treatment effects.

The company has assumed that there is a lifetime treatment effect associated with treatment with pembrolizumab (i.e., over the 46-year time horizon of the model) as evidenced by the

hazard rate of a first recurrence event (LR or DM) is always higher for patients in the routine surveillance arm of the company model than for patients in the pembrolizumab arm of the company model. The ERG considers that the data are too immature to draw this conclusion and highlights that this assumption has a considerable impact on model outcomes, for example, if the:

- treatment effect for pembrolizumab were to be stopped at 3 years, the company model would predict that treatment with pembrolizumab would stop being cost saving and would become cost incurring (£22,848 per patient)
- time horizon of the company model was limited to 16 months (the median length of follow-up data available from then KEYNOTE-054 trial), i.e., no extrapolation, the ICER generated by the company model would be circa £750,000 per QALY gained for the comparison of treatment with pembrolizumab versus routine surveillance.

However, these estimates cannot be considered reliable as, as previously shown, the company's underlying projections of first events are not robust. These analyses simply highlight the sensitivity of company model results to the actual treatment effect which, with the current level of data maturity, cannot be accurately measured.

Subgroup analysis

Data in Table 33 show that melanoma-specific survival rates differ markedly depending on disease stage; this means that patient benefit and, therefore, the cost effectiveness of adjunctive therapy with pembrolizumab versus routine surveillance also varies by disease stage. During the clarification process, the ERG requested K-M data on time to first event for patients in the KEYNOTE-054 trial with Stage IIIA, B and C disease in the anticipation that it would be possible to separately generate estimates of cost effectiveness for these subgroups (clarification questions B1 and B2). However, the numbers of events were very small; for example, there were only 10 RF-LR events for patients with Stage IIIA disease and, therefore, the ERG did not carry out any further analyses using these data.

5.4 Impact on the ICER of additional clinical and economic analyses undertaken by the erg

In the company base case, treatment with pembrolizumab was estimated to generate an additional 2.73 QALYs and to lead to a cost saving of £3,988 compared to routine surveillance; this means that treatment with pembrolizumab as adjunctive therapy is a dominant strategy when compared to routine surveillance.

The ERG, however, considers that the KEYNOTE-054 trial data are too immature to produce a reliable ICER per QALY gained and, therefore, has not undertaken any additional or exploratory analyses. The ERG considers that this approach avoids generating spurious ICERs per QALY gained.

5.5 Cost effectiveness conclusions and research recommendations

The company has made significant efforts to make best use of the available data from the KEYNOTE-054 and other relevant trials to estimate the cost effectiveness of treatment with pembrolizumab versus routine surveillance. However, data from the KEYNOTE-054 trial are not sufficiently mature to enable robust ICERs per QALY gained to be generated. The immaturity of the trial data means that none of the projections undertaken by the company produces clinically plausible OS and DM estimates for the routine surveillance arm of the company model. Furthermore, the currently available data are too immature to be used to estimate the treatment effect of pembrolizumab. The ERG considers that the company's estimated ICERs per QALY gained are unreliable. Given the immaturity of the data, the ERG did not undertake any additional or exploratory analyses as they considered that results from such analyses could only generate spurious ICERs per QALY gained.

Research recommendations

Data from the SEER and IMDDP datasets [13, 24] demonstrate that long-term survival of patients with melanoma varies by Stage III classification; this suggests that patient benefit and, therefore, the cost effectiveness of adjunctive therapy versus routine surveillance also varies by Stage III classification. The ERG, therefore, considers that any future analyses of treatments for Stage III melanoma should be carried out using the different classification subgroups (e.g., AJCC 8th Edition [13] Stage IIIA, IIIB, IIIC and IIID definitions).

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7 APPENDICES

7.1 Appendix 1

Table 34 Reason participants were enrolled but not randomised

Reason participants were enrolled but not randomised	N (%)
Total not Randomized	445
Central Confirmation Of PD-L1 Expression Was Non-Eligible	19 (4.3%)
Patient Could Not Be Randomized Within 12 Weeks After CLND	42 (9.4%)
Patient's Refusal	103 (23.1%)
Patient Was Ineligible For Another Reason	281 (63.1%)
Did not have ECOG performance status of 0 or 1	1 (0.2%)
Did not have adequate organ function as defined by laboratory values specified in the protocol	3 (0.7%)
Did not have complete resection of stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as (AJCC, 2010) stage IIIA (>1 mm lymph node metastasis), any stage IIIB, or stage IIIC	13 (2.9%)
Did not have tumour sample evaluable for PD-L1 expression	2 (0.4%)
Had a diagnosis of immunodeficiency, systemic steroid therapy, or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment	1 (0.2%)
Had a history of another malignancy or a concurrent malignancy	11 (2.5%)
Had active infection requiring therapy	2 (0.4%)
Had current disease, including loco-regional relapse, distant metastasis, or clinical evidence for brain metastases	207 (46.5%)
Had interval from surgery to first study drug treatment >13 weeks	7 (1.6%)
Had prior therapy for melanoma except surgery for primary melanoma lesions	7 (1.6%)
Investigator/Physician discretion	14 (3.1%)
Known history of HIV, active Hepatitis B or Hepatitis C	2 (0.4%)
Post lymph node dissection radiotherapy was not completed within the 13 week post-surgery period and prior to treatment start	1 (0.2%)
Resection of stage III lymph nodes was not performed in complete compliance with the criteria for adequate surgical procedures for CLND outlined in the protocol	10 (2.2%)

AJCC=American Joint Committee on Cancer; CLND= chemiluminescent nitrogen detection; ECOG= Eastern Cooperative Oncology Group; HIV=human immunodeficiency virus; N=number of participants; PD-L1=programed death ligand-1;
Source: company response to ERG clarification letter, Table 2

7.2 Appendix 2

7.2.1 PD-L1 positive tumour expression subgroup

The majority of the ITT population had PD-L1 positive tumour expression; 853 out of 1019 participants (83.7%), 116 participants (11.4%) of participants had PD-L1 negative tumour expression and the remaining 50 participants (4.9%) had an undetermined PD-L1 expression before randomisation.

RFS results in the PD-L1 positive tumour expression subgroup of the ITT population are presented in Table 35. For comparison, the ERG also presents RFS results in the PD-L1 negative tumour expression subgroup of the ITT population, which were reported in the publication of the KEYNOTE-054 trial and the KEYNOTE-054 CSR (Table 11-5). As noted within the CSR (p58), results for the PD-L1 negative tumour expression subgroup were not pre-specified or multiplicity controlled so should be interpreted with caution and presented here only for information.

For the additional primary efficacy outcome of RFS in participants with PD-L1 positive tumour expression, results were comparable to those of the overall ITT population. Median RFS was not yet reached in either treatment group but RFS rate at six months and at 12 months was higher in the pembrolizumab group compared to the placebo group. From K-M data (CS, Figure 7), as for the ITT population, the company considers that the curves show separation of RFS rates after 3 months which was maintained throughout the evaluation period.

Table 35 Recurrence free survival results in the PD-L1 positive and PD-L1 negative tumour expression subgroups

Tumour expression subgroup	PD-L1 positive		PD-L1 negative	
	Pembrolizumab	Placebo	Pembrolizumab	Placebo
Number in subgroup	428	425	59	57
Number of events (%)	102 (23.8%)	176 (41.4%)	20 (33.9%)	27 (47.4%)
Type of first event: Locoregional recurrence (%)	39 (9.1%)	61 (14.4%)	11 (18.6%)	10 (17.5%)
Type of first event: Distant metastasis (%)	55 (12.9%)	93 (21.9%)	8 (13.6%)	15 (26.3%)
Type of first event: Both diagnosed within 30 days of each other (%)	6 (1.4%)	21 (4.9%)	1 (1.7%)	2 (3.5%)
Type of first event: Death (%)	2 (0.5%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Person months	5287.4	4830.1	[redacted]	[redacted]
Event rate per 100 person-months	1.9	3.6	[redacted]	[redacted]
Median RFS in months (95% CI)[a]	NR (NE to NE)	NR (17.1 to NE)	[redacted]	[redacted]
RFS rate at 6 months in % (95% CI)	83.8 (80.0 to 87.0)	75.4 (71.0 to 79.2)	[redacted]	[redacted]
RFS rate at 12 months in % (95% CI)	77.1 (72.7 to 80.9)	62.6 (57.7 to 67.0)	72.2 (58.6 to 82.0)	52.2 (38.2 to 64.5)
HR (95% CI) and p-value[b]	0.54 (0.42 to 0.69); p<0.0001		0.47 (0.26 to 0.85); p=0.01	

a. Median RFS estimated from product-limit (Kaplan-Meier) method for censored data
b. HR estimated from Cox regression model with treatment as a covariate, stratified by stage (IIIA [1>mm metastasis] vs IIIB vs IIIC 1-3 nodes vs IIIIC 4≥ nodes) as indicated at randomisation. One-sided p-value based on log-rank test.

CI=confidence interval; HR=hazard ratio; ITT=intention to treat; NE=not estimable; NR=not reached; PD-L1=programed death ligand-1; RFS=recurrence free survival

Source: CS, adapted from Table 16, company response to ERG clarification letter (Table 3, Table 4), KEYNOTE-054 CSR, Table 11-5, Eggermont et al 2018 [23]

Pembrolizumab demonstrated a statistically significant advantage in RFS over placebo in the subgroup of the ITT population with PD-L1 positive tumour expression (HR=0.54; 95% CI 0.42 to 0.69; p<0.0001).

The ERG notes that a statistically significant advantage in RFS for pembrolizumab over placebo was also observed in the subgroup of the ITT population with PD-L1 negative tumour expression (HR=0.47; 95% CI 0.26 to 0.85; p=0.01) and that no statistically significant difference between treatments was observed for those with undetermined tumour PD-L1 status (HR=0.88; 99% CI 0.29 to 2.72; p=0.77) [23]. The ERG encourages caution when interpreting these results due to small numbers of participants in these subgroups and lack of multiplicity control in the analysis of these subgroups. Additionally, as in the primary analysis of RFS, it is likely that the PH assumption has been violated so HRs must be interpreted with caution.

Subgroup analysis of RFS by PD-L1 status showed no statistically significant difference between PD-L1 positive versus PD-L1 negative tumour expression (p value for interaction test =0.671; CS, Appendix E).