ID1266 ERG REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

## [ID1266]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/109/17

Completed 23rd August 2018

CONTAINS IN COMMERCIAL IN CONFIDENCE DATA



UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 22 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are presented here. The ERG has also corrected an error identified during the preparation of this erratum (p20 of the ERG report).

Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Where an amendment was made to information marked as CiC, the ERG's amendments are indicated within square brackets [ ]

# 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)

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 health state 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

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
- Text removed.
- 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]

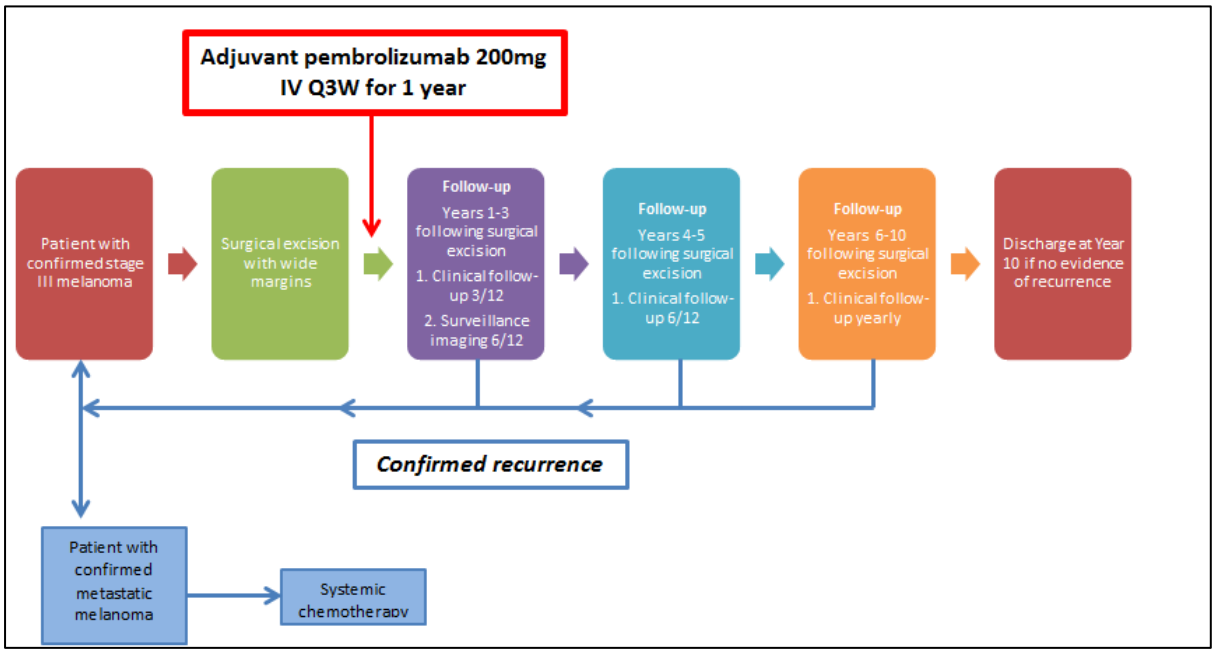


Figure 1 Current clinical pathway of care showing the context of the proposed use of the technology

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 RFS rates and survival rates in European patients with Stage III melanoma report RFS rates of 28% to 44% and survival rates of 41% to 71% [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 recurrence 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.

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] | July 2018 | 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:

**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 (1.4% versus 0.6%) 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.

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 notes that the patient response rates to the EQ-5D questionnaire were high across the timepoints reported (Weeks 12 to 48). Response rates ranged between 88.4% and 94.1%.

## *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 compared interferon (IFN) to no IFN (observation. The authors of the meta-analysis [32] suggest that results indicate that 'RFS was highly

## *4.1 Conclusions of the clinical effectiveness*

- 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. The authors of the publication conclude that RFS

appears to be a valid surrogate endpoint for OS in RCTs of adjuvant treatment with interferon or a checkpoint inhibitor. Given the ERG's critique of the methods of the meta-analysis, the ERG questions whether the results from the meta-analysis can be used to 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 discussion of the EQ-5D-3L data which were also collected during the KEYNOTE-054 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 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, adjuvant drug acquisition costs, adjuvant 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 [redacted]. 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 advanced or metastatic 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<br>• 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<br>• Life tables for England & Wales (2014-2016) | No direct LR-to-death transitions in the Flatiron database. The company assumed that the mortality hazard for LR and RF health states are the same |
| DM | DM-to-death | • KEYNOTE-006<br>• NMA comparing treatments for advanced melanoma<br>• 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

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 survival (where survival means reaching the DM state) 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.

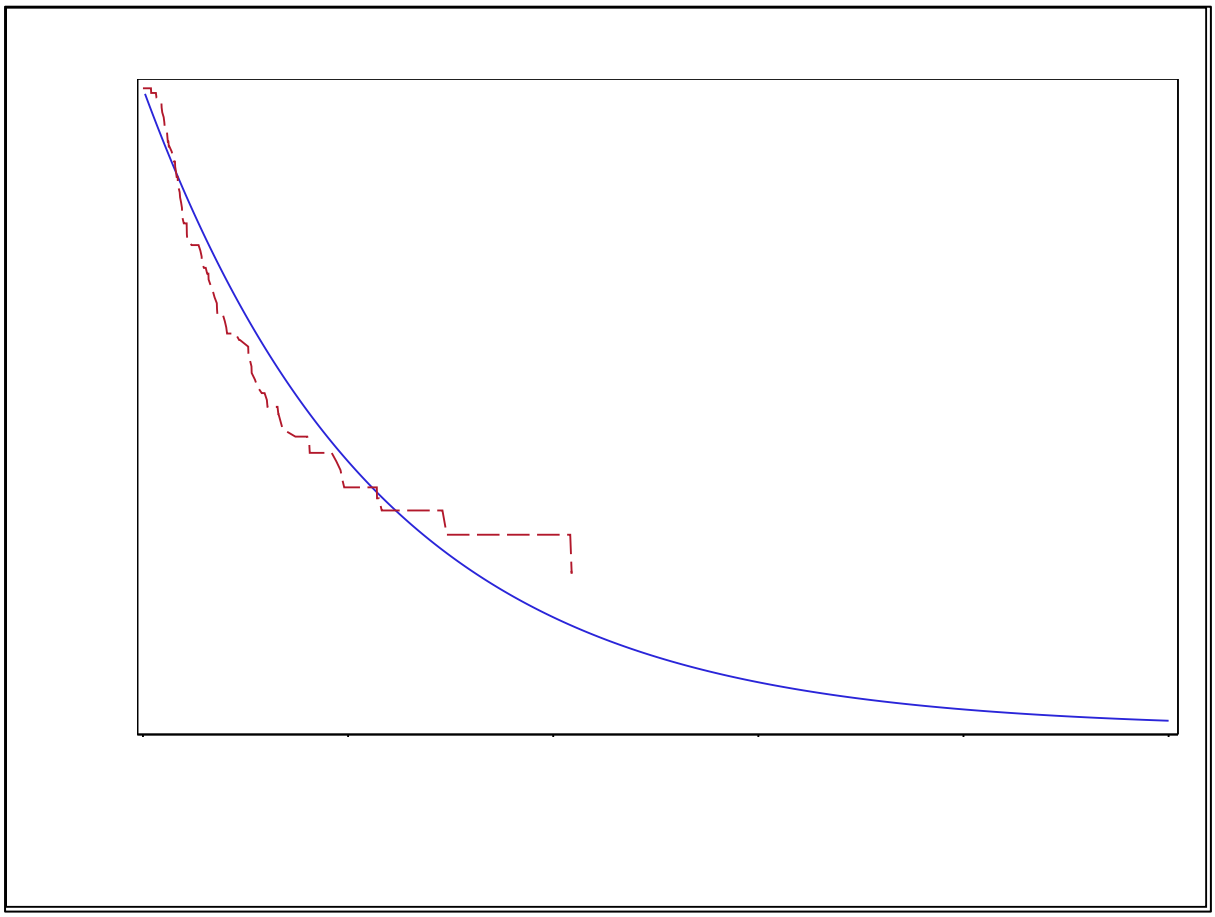

Figure 3 Exponential model fitted to the observed LR-to-DM data from the Flatiron database

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 after 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 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) | 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

### 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 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