NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID1266]

Pre-meeting briefing

Contains CIC

Abbreviations

DM	Distant metastases
DMFS	Distant metastases-free survival
ERG	Evidence review group
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
LR	Loco-regional recurrence
OS	Overall survival
PD-1	Programmed death-1 protein
PD-L1	Programmed cell death-1 ligand-1
PH	Proportional hazards
RFS	Recurrence-free survival
RS	Routine surveillance
QALY	Quality-adjusted life year

Clinical effectiveness issues (1)

- Does this represent a change in the treatment pathway for melanoma and would it affect the subsequent use or effectiveness of immunotherapy in the metastatic setting?
- Is the committee satisfied with the definition of high risk of recurrence defined in KEYNOTE-054 & what is the baseline risk?
  - patients had to have either Stage IIIA, IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition
  - The company has suggested that 90% will develop metastatic disease within 5 years - is this correct? (lower figures have been quoted previously)
- Do the baseline characteristics of patients in KEYNOTE-054 match those of patients in the NHS?
  - Practice not uniform in terms of resection within Stage III melanoma & the staging of melanoma has changed
  - Patients in KEYNOTE-054 had lower ECOG performance scores (all 0 or 1)

Clinical effectiveness issues (2)

- What conclusions can be drawn about recurrence-free survival (RFS)?
  - KEYNOTE-054 RFS data is limited to 16 months follow up → median RFS for pembrolizumab not reached
  - Proportional hazards assumption may not hold for RFS
- Is it reasonable to assume RFS is an appropriate surrogate outcome for OS?
- Would the frequency of administration of pembrolizumab place a high burden on NHS nursing and pharmacy staff?
- Does pembrolizumab have a tolerable safety profile, both short a long term in patients with no known disseminated disease?

Advanced fully resected melanoma

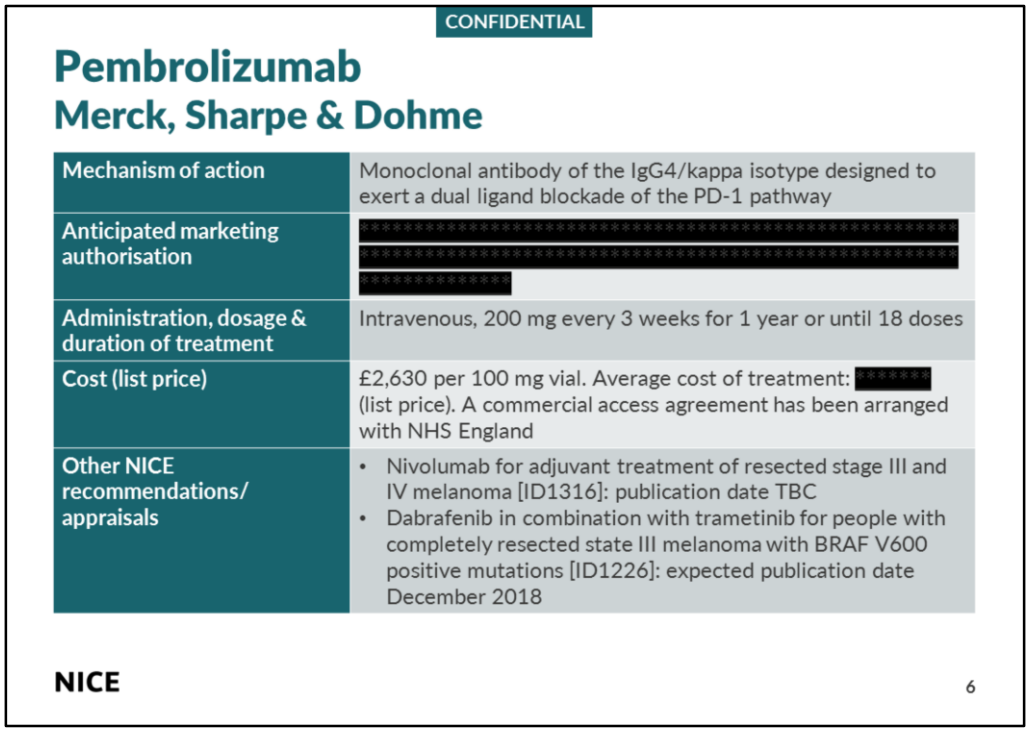
- Melanoma 5th most common cancer in the UK
  - rates increased steadily since 1990s, incidence up by 50% in last decade
- Disease stage describes the extent of disease
  - Stage I and II: (commonest presentation) no evidence that melanoma has spread anywhere else in body
  - Stage III: melanoma is present in the skin, lymph vessels, or nearby lymph glands
  - Stage IV: melanoma has spread to other distant parts of the body

  ~ 8% (total N=1,000) patients diagnosed at Stage III or IV disease in 2014 in England but may progress from earlier stages
- No UK-wide statistics available for melanoma survival by stage; data from former Anglia Cancer Network for people diagnosed between 2002-2006 - five-year survival approximately 50-55% for stage III disease and 8-25% for stage IV disease
- People who have had surgery to remove stage III or IV tumours are at high risk of relapse and death; 5-year relapse-free survival is 28-44% for stage III melanoma
- Principle of adjuvant therapy after complete surgical clearance is to remove any microscopic disease either locally or in the bloodstream to reduce the rate of it recurring and resulting in death from disseminated disease

NICE 5

Source:

Lead team slides for ID1316, Committee August 2018.



Source:

Company submission: Section B1.1 (page 9), Section B1.2 (page 11), Section B1.3.1 (page 12)

The ERG note (page 8 of ERG report) the other NICE appraisals that are ongoing. They highlight that there is also evidence available for the clinical effectiveness of active adjuvant treatments other than pembrolizumab, i.e. nivolumab and debrafenib with trametinib.

Pembrolizumab currently has a marketing authorisation covering the following indications:

• KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

• KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

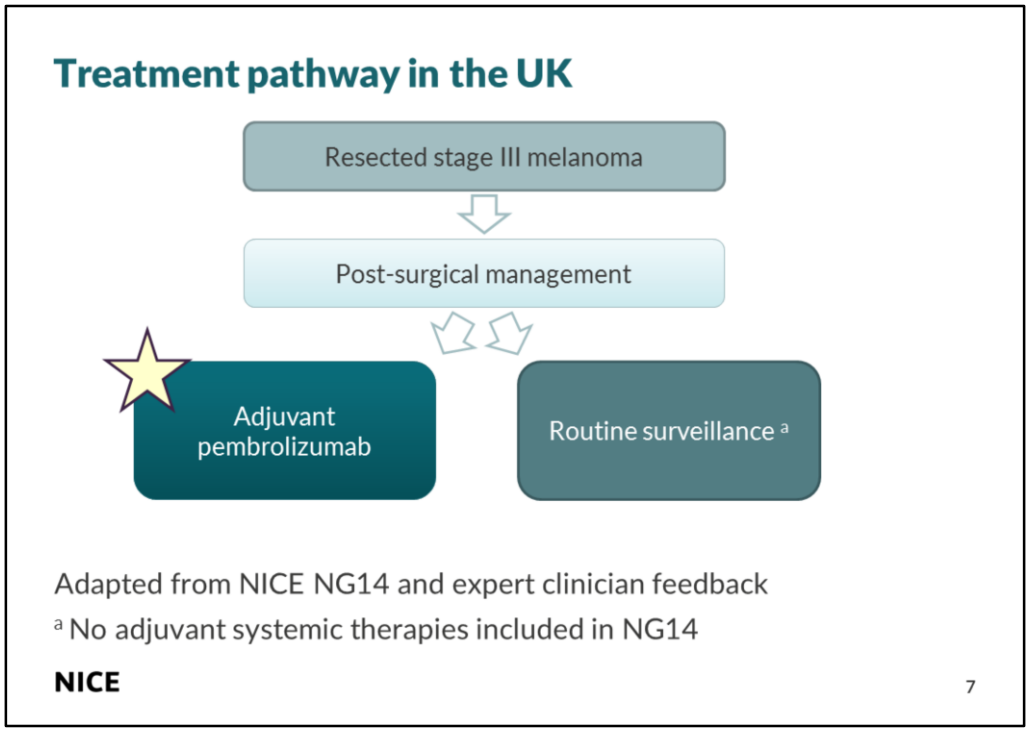
• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express

PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. People with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

• KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.



Follow-up

NICE clinical guidelines for the management of melanoma (NG14, 2015) recommends clinical follow-up with imaging for people with stage III disease following complete resection, at a schedule of every 3 months for the first 3 years post resection, then every 6 months for the next 2 years, and discharge at the end of 5 years. It states that adjuvant radiotherapy should not be offered in stage IIIA melanoma and should only offered in stage IIIB or IIIC melanoma, if a reduction in the risk of local recurrence outweighs the risk of significant adverse events.

Consider surveillance imaging as part of follow-up for people who have stage III melanoma and who would become 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**
- the specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging 6-monthly for 3 years is identified.

A consensus by UK doctors suggests that patients should be

followed up for up to 10 years. (https://melanomafocus.com/wp-content/uploads/2014/02/Cutaneous-Melanoma-Follow-Up-Position-Paper-30Jan14.pdf)

Decision problem

	Scope	Company
Population	People with completely resected melanoma at high risk of recurrence	Trial inclusion = ≥18 years → 'Adults'
Intervention	Pembrolizumab	✓
Comparators	Routine surveillance	✓
Outcomes	Overall survival (OS) Recurrence-free survival Distant metastases-free survival (DMFS) Adverse effects of treatment Health related quality of life	OS & DMFS data are immature Recurrence-free survival data used to assess the efficacy Other outcomes = ✓

ERG comment: Unclear whether all patients in KEYNOTE-054 can be considered to be at high risk of either death or disease recurrence → no definitive definition of high risk of either death or disease recurrence for patients with Stage III melanoma have been identified

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Source:

Final scope (page 2)

Company submission: Section B1.1 (Table 1, page 10)

ERG report: Section 3.1.1 (pages 23 and 24)

KEYNOTE-054 primary outcome measure was RFS in the ITT population and PD-L1 positive tumour subgroup. In the consultation comments table it was noted that there are no subgroups of people in whom pembrolizumab is expected to be more clinically effective or cost effective.

Clinical expert perspective

No submission received yet

Professional organisation perspective

- **Submission received from the British Association of Dermatologists (BAD) and endorsed by the Royal College of Physicians**
- Main aim of treatment is to stop progression → progression-free survival = clinically significant treatment response & overall survival = an important outcome
- Well defined pathway of care with clinical guidelines from NICE
- There is an unmet need → no adjuvant therapy available for earlier stage melanoma
- Interferon is generally not used in the UK because of side effects & lack of effectiveness
- Other adjuvant therapies are available through clinical trials: trametinib plus nivolumab or ipilumumab or dabrafenib
- Pembrolizumab = a new addition to treatment in secondary care specialist clinics → innovative & a step-change in management of stage III melanoma
- Study results suggest that pembrolizumab ↑ PFS → less resources used for more advanced melanoma & ↓ number of surgical interventions
- It is generally well tolerated but toxicity may limit treatment → likely have a defined period of treatment i.e. maximum of 12 months
- Reported side effects have been significant → endocrine & neurological

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Source:

Professional Organisation Submission: British Association of Dermatologists (BAD)

Email correspondence from the Royal College of Physicians (RCP)

Clinical effectiveness

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Company's clinical evidence: KEYNOTE-054

- Data from 1st interim analysis used in company submission (October 2017 cut-off)
- KEYNOTE-054 trial reported a median follow-up of 16 months

	KEYNOTE-054
Design	International, double-blind, routine surveillance-controlled phase 3 study
Population	Adults after complete resection of stage IIIA (>1mm lymph node metastasis), IIIB and IIIC melanoma (classified using the AJCC 7th edition)
Intervention	Pembrolizumab, 200 mg, every 3 weeks for a total of 18 administrations
Comparator	Routine surveillance
1◦ outcome	Recurrence-free survival in ITT population and subgroup with PD-L1 positive tumours (surrogate marker for overall survival)
2◦ outcomes	Adverse events, Distant metastasis free survival (DMFS) [redacted], DMFS in patients with PD-L1 positive tumour expression [redacted], OS [redacted], OS in patients with PD-L1 positive tumour expression [redacted]
Exploratory outcomes	Quality of life and health outcome evaluation

ERG comment: KEYNOTE-054 trial is a well-designed, good quality trial

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Source:

Table: Company submission: Section B.2.3, Section B2.3.2 (pages 21, 22, 26)

ERG report: Section 4.1 (page 53)

Data presented by the company are from a data cut from the 2nd October 2017. They only report data for the primary end point (RFS) and adverse event data and health related quality of life data as the secondary outcomes. Other secondary outcomes were specified in the study and these will be published at a later date. These were not assessed at this time point because of an insufficient number of events. The specified secondary outcomes are:

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

KEYNOTE-054 primary outcome: recurrence-free survival

- Recurrence-free survival is defined in KEYNOTE-054 as the time between the date of randomisation and the date of first recurrence (local, regional, distant metastasis) or death, whichever occurs first
- The company report that recurrence-free survival has been established as a reliable surrogate efficacy marker & is an appropriate endpoint to assess the impact and safety profile of pembrolizumab in the adjuvant setting
- In a recent meta-analysis of 13 clinical studies (n>5,000 patients) involving adjuvant interferon in stage II-III melanoma, recurrence-free survival was shown to be a valid surrogate endpoint for overall survival
- For the EORTC 18071 ipilimumab study, a validated model predicted an overall survival benefit based on RFS → the study predicted that adjuvant studies with a hazard ratio ≤0.77 for RFS would demonstrate a treatment benefit of overall survival

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Sources:

Company submission: Section B2.3.1, B2.4.2, B2.13 (pages 25, 32, 49)

Meta-analysis: Suciu S, Eggermont AMM, Lorigan P, Kirkwood JM, Markovic SN, Garbe C, et al. Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy. J Natl Cancer Inst. 2018;110:87-96.

EORTC 18071 trial: Phase III, RCT that investigated the effectiveness of ipilimumab, compared with routine surveillance in people with resected Stage III melanoma.

Key baseline characteristics in KEYNOTE-054

		Pembrolizumab (n=514)	Routine surveillance (n=505)
Locations	23 countries with approximately two-thirds of people enrolled across Europe (n=677). N=52 enrolled from the UK		
Age	Median (range)	54.0 (19 to 88)	54.0 (19 to 83)
Melanoma stage at randominsat-ion	Stage IIIA, n (%)	80 (15.6)	80 (15.8)
	Stage IIIB, n (%)	237 (46.1)	230 (45.5)
	Stage IIIC with 1-3 +ve nodes, n (%)	95 (18.5)	93 (18.4)
	Stage IIIC with ≥ 4 +ve nodes, n (%)	102 (19.8)	102 (20.2)
ECOG score	0 or 1, (%)	514 (100)	505 (100)
PD-L1 status	Positive, n (%)	428 (83.3)	425 (84.2)
	Negative, n (%)	59 (11.5)	57 (11.3)
	Unknown, n (%)	27 (5.3)	23 (4.6)

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Source:

Company submission: Section B2.3.4 (Table 9, page 30), Melanoma stage from Eggermont et al. (2018)

KEYNOTE-054 patient population is young and have low ECOG score.

The company report that people with stage IIIA (lymph node metastasis >1mm) were included within this study as these groups of patients have a significantly higher risk of relapse and mortality compared to patients with ≤1mm nodal metastasis.

ERG comments: generalisability of KEYNOTE-054 data

- Clinical advice to the ERG highlighted that approximately 20% of patients treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than those in KEYNOTE-054 (KEYNOTE-054 = ECOG PS 0 = 94.4%, ECOG PS 1 = 5.6%)
- KEYNOTE-054 trial population included 83.3% of people whose disease was defined as programmed death ligand (PD-L1) positive
  - PD-L1 testing is not routinely carried out in the NHS so unsure if the trial population is similar to people seen in clinical practice
- 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

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Source:

ERG report: Section 1.4 (pages 10-11)

Key pembrolizumab clinical effectiveness results (ITT population)

	Pembrolizumab (n=514)	Routine surveillance (n=505)
Median follow-up (range)	16.0 months (2.5 to 25.3 months)	
Type of first event, n (%)		
Loco-regional recurrence	55 (10.7)	77 (15.2)
Distant metastasis	69 (13.4)	114 (22.6)
Death	2 (0.4)	1 (0.2)
Recurrence-free survival (95% CI)		
Median RFS in months	NR (NE to NE)	20.4 (16.2 to NE)
RFS rate at 6 months, %	82.2 (78.6 to 85.3)	73.3 (69.2 to 77.0)
RFS rate at 12 months, %	75.4 (71.3 to 78.9)	61.0 (56.5 to 65.1)
RFS rate at 18 months, %	71.4 (66.8 to 75.4)	53.2 (47.9 to 58.2)
HR (98.4% CI) and p-value	0.57 (0.43 to 0.74); p<0.0001	

Abbreviations: NR: not reached; NE: not estimable

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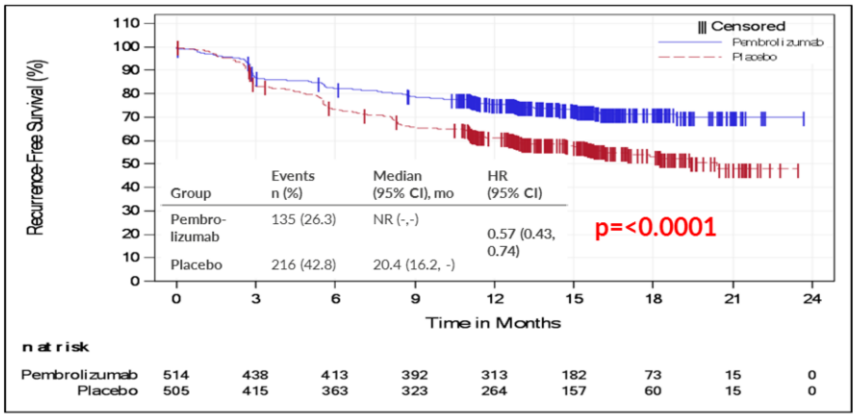
Source:

ERG report: Section 4.6.2 (Table 8, page 38)

Treatment effect was consistent in all subgroups analysed within the overall population.

Primary efficacy results: investigator assessed RFS (ITT population)

- Pembrolizumab gives a statistically significant and clinically meaningful improvement in RFS compared with placebo (HR = 0.57; 98.4% CI 0.43 to 0.74)
- HR estimated using a Cox proportional hazards model



NICE Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reached; RFS: relapse-free survival.; mo: months 17

Source:

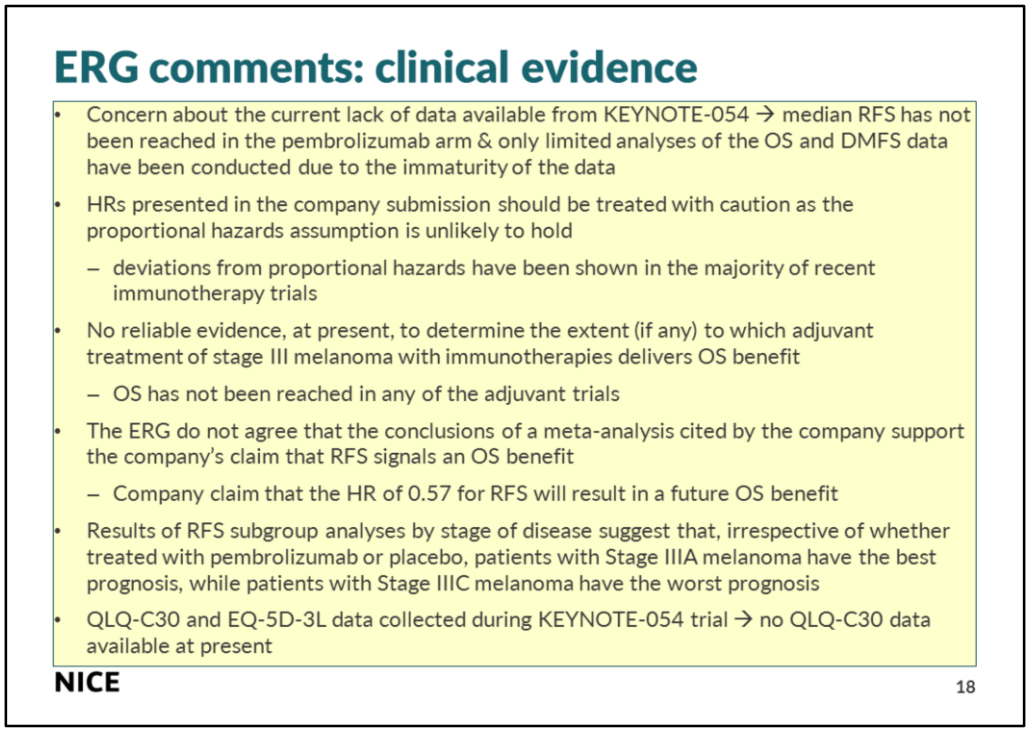
Company submission: Section B 2.6.1 (pages 39, 40)

Data cut off 2nd October 2017.

The company assumes proportional hazards. The company confirmed during clarification that they did not test for proportional hazards.

Kaplan-Meier (K-M) methodology was used to obtain estimates of RFS, the standard error of the estimates were computed using Greenwood's formula 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 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.



Source:

ERG report: Section 4.6.2 (pages 39,40)

ERG report: Section 4.10 (page 48)

ERG report: Section 4.1 (pages 53, 54)

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, to support this claim. The ERG, however, highlights that the meta-analysis 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 company highlighted in their factual accuracy check that pembrolizumab is a checkpoint inhibitor. The ERG, questions whether results from this meta-analysis 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.

Adverse events in KEYNOTE-053: Investigator assessed

Event, n (%)	Pembrolizumab (n=514)	Routine surveillance (n=505)
Any AE	396 (77.8)	332 (66.1)
Grade 3 to 5 AE	74 (14.5)	17 (3.4)
AE leading to discontinuation	62 (12.2)	8 (1.6)
Any serious AE	66 (13.0)	6 (1.2)
Serious AE leading to discontinuation	22 (4.3)	2 (0.4)
Death	1 (0.2)	0 (0.0)

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Source:

ERG report: Section 4.7.1 (Table 11, page 45)

ERG comments: adverse events

- Clinical advice to the ERG is that adverse events (≥ grade 2) arising from treatment with pembrolizumab and other immunotherapies can place a high burden on NHS staff
  - These adverse events require careful monitoring by a specialist clinical team with experience to provide early recognition and management of immunotherapy related adverse events

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Source:

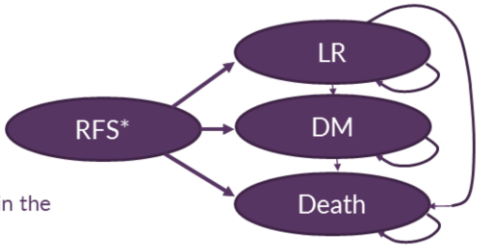
ERG report: Section 4.1 (page 53)

Cost effectiveness

Cost effectiveness issues

- Staying in the recurrence free state for longer gives cost savings from not incurring the cost of disseminated disease and QALY gains from not dying of disseminated disease. The long term projections of RFS are therefore important
- The company's model is reliant on DMFS and OS projections that the ERG suggests are clinically implausible. Is the model robust for decision making?
- Is a lifetime treatment effect with pembrolizumab plausible?
- What is the most plausible ICER per QALY gained?

Company's 4 state-transition model



*people enter the model in the RFS health state only

Factor	Chosen values
Model design	Markov model
Time horizon	46 years
Cycle length	7 days
Half cycle correction	Yes
Treatment waning effect	No
Discount rate	3.5% per year
Perspective	NHS and PSS

NICE

Abbreviations: RFS: recurrence-free survival; LR: loco-regional recurrence; DM: distant metastases; PSS: personal social services

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Source:

Company submission: Section B3.2.2 (pages 52 to 54). Presentation of diagram adapted from the company's submission.

The company uses a state transition model instead of a partitioned survival model given the lack of overall survival data from the KEYNOTE-054 trial.

Company model details

- RFS was defined in KEYNOTE-054 as the time from randomisation to loco-regional recurrence, distant metastases or death, whichever occurred first
- A proportion of people with LR are assumed to receive further salvage surgery – in line with KEYNOTE-054 and UK clinical practice. All received clinical surveillance
- People with DM could be eligible for treatment with a targeted therapy or immunotherapy in line with clinical practice in the metastatic setting
- People with DM receive best supportive care after stopping first or second line systemic treatment in the advanced setting
- Treatment benefit is assumed to be the same in both treatment arms in all health states except recurrence-free health state

ERG comment: Model structure is appropriate

NICE

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Source:

Company submission: Section B3.2.2 and B3.2.3 (pages 50, 51, 54)

ERG report: Section 5.3.3 (page 83)

Sources of clinical inputs to company model

Health states	Transition	Data sources
Recurrence-free	RF-to-LR	• KEYNOTE-054
	RF-to-DM	• KEYNOTE-054
	RF-to-death	• KEYNOTE-054 • Life tables for England & Wales (2014-2016)
Loco-regional recurrence	LR-to-DM	• Flatiron database
	LR-to-death	• KEYNOTE-054 • Life tables for England & Wales (2014-2016)
Distant metastases	DM-to-death	• KEYNOTE-006 • NMA comparing treatments for advanced melanoma • Life tables for England & Wales (2014-16)

- Flatiron database = an electronic health records database used by cancer care providers in the United States. Company selected eligible individuals for inclusion in their analyses
- KEYNOTE-006 = Phase III open-label RCT that evaluated treatment with pembrolizumab vs ipilimumab in people with unresectable or advanced melanoma. Primary outcome = OS, defined as the time from randomisation to all-cause mortality

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Source:
ERG report: Section 5.2.7 (Table 16, page 61 and page 61)

The company has provided justification for using each data source:

Recurrence-free survival:

RF to LR = main clinical evidence

RF to DM = main clinical evidence
RF to death = Main clinical evidence. Mortality hazard is set such that the maximum hazard from either the general population or the KEYNOTE-054 trial is chosen

Loco-regional recurrence:

LR to DM = Part two of the KEYNOTE-054 trial, which contains information on people with loco-regional 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 = 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

Distant metastases:
DM to death = 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

Company's modelling of transitions from RFS

- Kaplan-Meier curves generated for each event and for each trial arm : RF → LR, RF → DM and RF → death. Where another event occurred this was treated as a censoring event
- Parametric models were fitted to each of the Kaplan-Meier curves. Best fit was established by analysing:
  - Mean square error
  - Visual inspection
  - How well the RFS fitted the European Organisation for Research and Treatment of Cancer (EORTC) 18071 trial
- Company's preferred models for the cause-specific hazards, shown below, generated 5-year RFS, DMFS and OS predictions that were most consistent with the values that were observed in the routine surveillance arm in the EORTC 18071 trial

Treatment arm	RF → LR	RF → DM	RF → death
Pembrolizumab	Gompertz	Generalised gamma	Exponential
Routine surveillance	Gompertz	Generalised gamma	Exponential

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Source:

Company submission: Section B3.3.1 (pages 55 to 67)

ERG report: Section 5.2.7 (pages 62 to 63)

EORTC 18071 trial: Phase III, RCT that investigated the effectiveness of ipilimumab, compared with routine surveillance in people with resected Stage III melanoma.

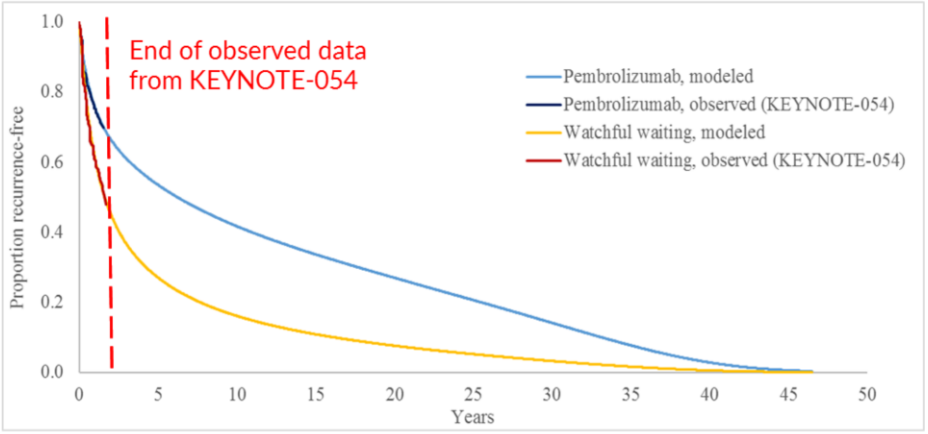
Exponential models were fitted to the transition from RF to death in each treatment arm due to the small number of direct transitions observed in KEYNOTE-054. RF to death: In KEYNOTE-054, 2 transitions in the pembrolizumab arm and 1 in the placebo arm.

Plausibility of long-term extrapolations: External data from the European Organization for Research and Treatment of Cancer (EORTC) 18071 trial were used to assess the appropriateness of different possible combinations of parametric functions in the routine surveillance arm. EORTC 18071 was a phase 3 trial comparing adjuvant ipilimumab vs. placebo in patients with resected stage III

melanoma. Observed RFS, distant metastases free survival (DMFS), and OS at 5 years in the placebo arm of this trial were respectively compared with predicted RFS, DMFS, and OS at 5 years in the routine surveillance arm of the model. (Predicted DMFS is a function of transition probabilities starting from the recurrence-free and loco-regional recurrence states, while predicted OS is a function of all transition probabilities in the model.)

Company's predicted RFS over the modelled time horizon

- The resulting predictions of RFS based on the modelled cause-specific hazards in each treatment arm using the parametric models given in the previous slide



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Source:
Company submission: Section B.3.3.1 (page 67)

Company's modelling of transitions from LR → DM and LR → death

LR → DM

- Real-world data from Flatiron database → company conducted a retrospective database analysis including adults with newly diagnosed Stage III, IIIA, IIIB or IIIC melanoma after complete resection, n = 1,166. LR experienced by n = 147
- Company developed a K-M curve using data for the LR population → event of interest = further progression to DM
- The company reported that median survival (survival meaning reaching the DM health state) was 66 weeks → an exponential parametric function was fitted to the observed data
- Assumed that the LR to DM cause-specific hazard from the Flatiron database is the same for both treatment arms

LR → death

- No direct transitions from LR → death in the Flatiron sample → the cause-specific hazard for this transition approximated based on the exponential model of RF → death in the pembrolizumab arm of KEYNOTE-054
  - people with LR will be at a higher risk of death than those in RFS because of the higher likelihood of developing DM and higher associated mortality risk for DM

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Source:

Company submission: Section B3.3.1 (pages 75 to 76)

ERG report: Section 5.2.7 (pages 64 to 65)

Company FAC response performa: issue 19

Please see ERG report: Section 5.2.7 (Figure 3, page 65) for the exponential model fitted to the observed LR to DM data from the Flatiron database

Company's modelling of transitions from DM → death

- Transition probability calculated based on the distribution of first-line treatments for advanced melanoma received
- First-line treatment options included pembrolizumab, ipilimumab, nivolumab, nivolumab plus ipilimumab, vemurafenib, dabrafenib, dabrafenib plus trametinib (based on being recommended by NICE, NG14)
- OS & PFS individual patient data (IPD) were used from the KEYNOTE-066 trial for pembrolizumab in the advanced setting
- Extrapolation of the IPD from KEYNOTE-066 was done using the exponential distribution to estimate outcomes for pembrolizumab
- For the other treatment options for advanced melanoma, hazard ratios for OS and PFS vs. pembrolizumab were each obtained from a network meta-analysis conducted by the company including trials conducted in advanced melanoma
- The hazard ratios for each treatment were then applied to the pembrolizumab curves for OS and PFS
- OS for each arm was calculated as the sum of the expected mean overall survival associated with different first-line treatments, weighted by their current market shares → given on next slide

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Source:

Company submission: Section B3.3.1 (pages 76 to 79)

KEYNOTE-006 trial = multicentre, randomised, open-label phase III trial among ipilimumab-naïve unresectable or advanced melanoma patients.

A key clinical question arising from the introduction of adjuvant treatment with pembrolizumab is the role of rechallenge in the advanced setting, where pembrolizumab is the current standard of care. The KEYNOTE-054 trial is expected to answer this question but the data from the part 2 of the study are not yet available. In the company's base case they have taken the conservative assumption of no rechallenge. This is explored in sensitivity analysis.

Company's estimates of advanced treatment market shares

Regimens in advanced setting	Market shares (%)				Reference
	Pembrolizumab (no re-challenge)	Routine surveillance	Pembrolizumab (re-challenge)	Routine surveillance	
Pembroliz-umab	0.0%	27.8%	27.8%	27.8%	Ipsos Oncology Monitor, 2018
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%	

- Market share for pembrolizumab, nivolumab, nivolumab plus ipilimumab was assumed to be 0% in the base case as the company assumed no further treatment with a PD-1 inhibitor

NICE

30

Source:

ERG report: Section 5.2.7 (Table 18, page 66)

Rechallenge = treatment with pembrolizumab given in the advanced melanoma setting when pembrolizumab was given as treatment following surgical resection, stage III melanoma.

Market shares for the advanced treatment regimens assumed to be given in the advanced setting 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%). For patients receiving routine surveillance, no further adjustments are made to the distribution of treatments used.

Company's resource use

- People in the RF health state incur costs of routine surveillance in addition to medication costs
- Assumed that the main treatment choice for people with LR is further surgery followed by routine surveillance → proportion of people and type of surgery aligned with KEYNOTE-054 trial
- Assumed that all individuals in the DM health state are eligible for treatment in the advanced setting
- Distribution of therapies administered in the advanced setting is taken from the most recent market research of current UK treatment patterns → previous slide
- Assumed that all individuals who stop first- or second-line systemic treatment in the advanced setting would receive best supportive care → 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 in the advanced setting, TA366 (information was initially used in TA319, ipilimumab in the first-line setting for melanoma)

ERG comment: No justification was given for the assumption that all patients entering the DM health state were to receive systemic therapies

NICE

31

Source:

ERG report: Section 5.2.9 (pages 71 to 74)

ERG report: Section 3.2 (Table 32, page 82)

Utility values used in the company's model

Health state	Base case utilities		Source
	Value	Standard error	
Recurrence-free (without toxicity)	0.870	0.008	KEYNOTE-054
Loco-regional recurrence	0.830	0.016	
Distant metastases (pre-progression)	0.775	0.012	
Distant metastases (post-progression)	0.590	0.020	Beusterien (2009)
Adverse events (included diarrhea, hyperthyroidism, pneumonitis, fatigue, alainine aminotransferase increased, arthralgia, headache, dyspnoea)	-0.05457	0.0170	KEYNOTE-054

- Utilities were adjusted by UK general population utility where utility decreases with age based on Ara and Brazier study (2010)

NICE

32

Source:

Company submission: Section B3.4.5 (Tables 31 and 33, pages 84 and 86)

Cost effectiveness results

Company's deterministic base case with commercial access agreement discount for pembrolizumab

	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER £/QALY
Pembrolizumab	161,954	7.91	-	-	-
Routine surveillance	165,941	5.18	-3,988	2.73	Dominant

- Total life years gained for pembrolizumab = 9.79 and for routine surveillance = 6.61
- Results using confidential discounts for subsequent therapies presented in part 2

NICE

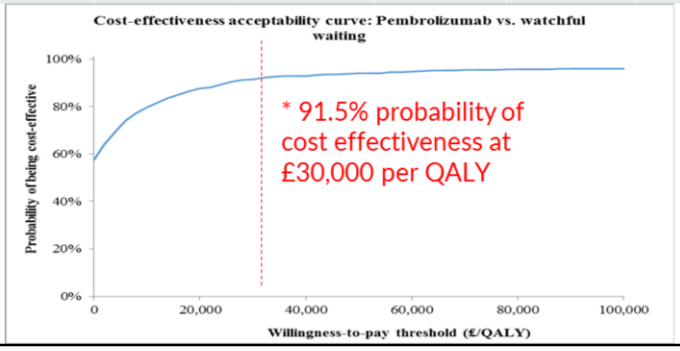
34

Source:

Company submission: Section B3.7.1 (Table 53, page 106)

Company's probabilistic base case with commercial access agreement discount for pembrolizumab

	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER £/QALY
Pembrolizumab	163,093	7.97	-	-	-
Routine surveillance	167,063	5.36	-3,970	2.62	Dominant



NICE

35

Source:

Company submission: Section B3.8.1 (Table 54, page 107)

Company submission: Section B3.8.1 (Figure 21, page 108)

Based on 1,000 PSA iterations

Company's scenario analysis results with commercial access agreement discount for pembrolizumab

Scenario	Scenario detail	Impact on base case ICER (BC = dominant)
Time horizon – 10 years		Dominant
Distributions	RF → LR & RF → DM: both log-normal	Dominant
	RF → LR: generalised gamma & RF → DM: log-normal	Dominant
	RF→ LR: exponential & RF → DM: Gompertz	£6,992
PH model with a constant treatment effect	RF → LR: Weibull RF → DM: Gompertz RF → death: exponential	£6,073
PH model with a time-varying treatment effect	RF → LR: Weibull RF → DM: Gompertz RF → death: exponential	Dominant
Rechallenge with pembrolizumab in advanced setting	People who transition from RF → DM >18 months from start of adjuvant treatment	Dominant

36

Source:

Company submission Part A: Section A16 (page 20)

ERG comments: cost effectiveness analyses

- The company made significant efforts to make best use of the available data from the KEYNOTE-054 trial and other relevant trials to estimate the cost effectiveness of pembrolizumab in this indication
- The immaturity of the trial data means that none of the projections undertaken by the company produces clinically plausible overall survival or distant metastases estimates for the routine surveillance arm
- The currently available data are too immature to be used to estimate the treatment effect of pembrolizumab
- The company's estimated ICERs per QALY gained are unreliable
- No additional or exploratory analyses have been undertaken as the ERG considers that the KEYNOTE-054 trial data are too immature to produce a reliable ICER per QALY gained

NICE 37

Source:

ERG report: Section 5.5 (page 88)

Section 5.3.3 (page 83)

Section 5.4 (page 88)

ERG comments: immaturity of KEYNOTE-054

- Model not populated with RFS data from KEYNOTE-054 trial → company used data on first recurrence event
- Overall survival and distant metastases-free survival data from KEYNOTE-054 have not reached maturity yet → these were indirectly based upon projections of first recurrence events. First recurrence events were not pre-specified outcomes in the KEYNOTE-054 trial statistical analysis plan
- Overall survival and distant metastases-free survival data from KEYNOTE-054 trial are too immature to be analysed and/or presented fully in the company submission and too immature to be included in the economic model
- Previous research identified that immature data can lead to spurious projections of overall survival, especially in cancer studies
- Only 1% (0.03 QALYs) of the company's total discounted QALY gain estimate (2.73 QALYs) is accrued during the first 16 months of the model time horizon, the median period for available follow-up data from KEYNOTE-054

NICE

38

Source:
ERG report: Section 5.3.3 (page 83)

ERG comments: impact of immature data on model OS and DMFS projections

- The company model projects slightly higher 5-year OS and, at the same time, much lower 5-year DMFS for routine surveillance than would be expected based on similar data from the EORTC 18071 trial
  - OS: 55.2% in company model versus 54.4% for patients in the placebo arm of the EORTC 18071 trial
  - DMFS: 30.2% in the company model versus 38.9% for patients in the placebo arm of the EORTC 18071 trial

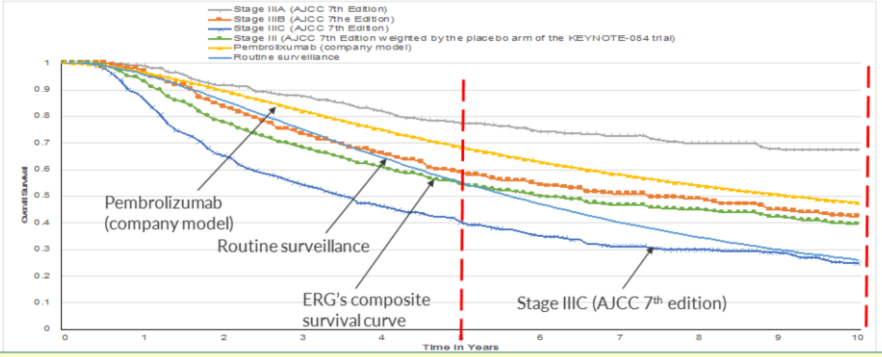
NICE 39

Source:
ERG report: Section 5.3.3 (page 83)

The company compared the estimated 5-year OS and DMFS results generated by their model for patients in the routine surveillance arm against those reported in the EORTC 18071 trial. The EORTC 18071 trial assessed ipilimumab for adjunctive therapy versus placebo for resected Stage III melanoma.

ERG additional work on OS modelling (1)

- The ERG validated the company's OS projections by creating a composite stage III survival curve by combining OS data from the 2010 SEER database for patients with Stage III melanoma by AJCC 7th Edition staging classifications, weighted by the proportions of patients in each of these stages in the KEYNOTE-054 trial
- The composite OS curve provides an approximation of the expected OS for the placebo arm of the KEYNOTE-054 trial



ERG comments: Clinically implausible projections. For the first 5 years, projected OS in the routine surveillance (RS) arm of the company model is better than that demonstrated by the ERG's composite expected OS curve. By 10 years, the company model projected OS curve for RS arm is approximately equal to the 2010 SEER database OS curve for patients with Stage IIIC disease

Source:
ERG report: Section 5.3.3 (pages 86 to 87)

ERG additional work on OS modelling (2)

- The ERG compared the 2018 IMDDP database 5- and 10-year melanoma-specific survival by staging classification in the AJCC 8th Edition and the expected melanoma-specific survival for the population in the KEYNOTE-054 trial to the predictions from the company model

	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%

ERG comments: At 5-years, the company model predicts that 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. This value from the KEYNOTE-054 trial composite is 28%

At 10-year, the company model predicts that 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. This value from the KEYNOTE-054 trial composite is 35%

NICE

41

Source:

ERG report: Section 5.3.3 (Table 33, page 86)

ERG comments: company model projections

- 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, 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) → considered clinically implausible by the ERG
- None of the exhaustive list of parametric curves considered by the company produces results that are sensible for both DFMS and OS

NICE

42

Source:

ERG report: Section 5.3.3 (page 86)

ERG comments: impact of immature data on estimation of treatment effect

- The data are too immature to draw the conclusion that there is a lifetime treatment effect associated with treatment with pembrolizumab
  - The company made this assumption evidenced by the hazard rate of a first recurrence event 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
  - This assumption has a considerable impact on the model outcomes:
    - 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
- These estimates on the model outcomes cannot be considered reliable as the company's underlying projections of first events are not robust → these analyses highlight the sensitivity of the company results to the actual treatment effect which cannot be accurately measured due to the immaturity of the data

NICE

43

Source:
ERG report: Section 5.3.3 (pages 86 to 87)

ERG comments: disease classification

- Patient benefit & resulting cost effectiveness of adjunctive therapy with pembrolizumab versus routine surveillance is likely to vary by disease state → data on 5- and 10-year melanoma specific survival rates for melanoma stages IIIA to IIID (AJCC 8th Edition classifications) indicate that melanoma-specific survival rates differ markedly depending on disease stage
- The ERG have not been able to separately generate estimates of cost effectiveness using Kaplan-Meier data on time to first event for patients in the KEYNOTE-054 trial with stage IIIA, B and C disease as the numbers of events were very small

NICE 44

Source:
ERG report: Section 5.3.3 (page 87)

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

Equality and innovation

Equality

- No equality issues identified by the company or professional organisation (BAD)
- Clinical expert advice to the ERG and a comment received during scoping highlighted that there is inequitable access to sentinel lymph node (SLN) mapping and biopsies across the UK → may limit access to adjuvant treatment

Innovation

- Pembrolizumab has a novel mode of action → can be used as standard adjuvant treatment regardless of tumour BRAF mutation status, PD-L1 status and AJCC stage III classification

NICE 45

Source:

Equality: Company submission: Section B1.4 (page 19)

ERG report: Section 3.7 (page 27)

Consultation comments table: page 5

Innovation: Company submission: Section B2.13 (page 49)

Comment received during scoping: “In order to be fully assessed for stage patients need access to Sentinal node biopies. This is variable across the country. For example if SNB is only available for patients with 1-4mm thick melanoma then patients with >4mm melanoma will be staged as stage 2b or c and will not be able to access the adjuvant treatment. Equality of access to SNB needs to be considered and rasied within this technology appraisal. Current NICE guidance on SNB within NG14 do not recommened SNB for all as, at the time, adjuvant treatments were not available. “

Authors

Emily Eaton Turner
Technical Lead

Victoria Kelly
Technical Adviser

with input from the Lead Team (Jane Adam, Pam Rees and Steve Edwards)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

April, 2018

File name	Version	Contains confidential information	Date
MSD submission Pembolizumab (ID1266) Document B REDACTED	**1**	**Yes**	**25th June 2018**

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Abbreviations

AE	Adverse Event
AIC	Akaike information criterion
AEOSI	Adverse Events of Special Interest
AJCC	American Joint Committee Cancer
APaT	All patients as treated
ASaT	All subjects as treated
BIC	Bayesian Information Criterion
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	International Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte-associated protein
DM	Distant metastases
DMFS	Distant Metastasis Free Survival
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EHR	Electronic health records
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
ESMO	The European Society for Medical Oncology
HRG	Health Resource Group
HRQoL	Health related Quality of Life
HR	Hazard ratio
HTA	Health technology appraisal
IA1	Interim analyses 1
IARC	International Agency for Research on Cancer
ICER	Incremental cost effectiveness ratio
IPD	Individual patient data
ITT	Intention to treat
LR	Locoregional recurrence
MIMS	Monthly Index of Medical Specialities

MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme
MSE	Mean squared error
N/A	Not applicable
NCCN	The National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached
ONS	Office of National Statistics
OS	Overall survival
PAS	Patient access scheme
PbR	Payment-by-results
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
QoL	Quality of life
RCT	Randomised Controlled Trial
RF	Recurrence free
RFS	Recurrence free survival
RSD	Reference study dataset
SAE	Serious Adverse Events
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TNM	Tumour, Node, Metastases
ToT	Time on treatment
TSD	Technical Support Document
TTO	Time trade off

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full marketing authorisation for this indication. [redacted] Table 1 summarises the decision problem.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with completely resected melanoma at high risk of recurrence.	Adults with completely resected melanoma at high risk of recurrence.	In line with NICE final scope.
Intervention	Pembrolizumab 200mg IV Q3W	Pembrolizumab 200mg IV Q3W	In line with the anticipated licence and with the final NICE scope.
Comparator(s)	Routine surveillance	Routine surveillance	In line with the final NICE scope.
Outcomes	The outcome measures to be considered include: • Overall survival • Recurrence free survival • Distant metastases free survival • Adverse effects of treatment • Health related quality of life	The outcome measures to be considered include: • Recurrence free survival • Distant metastases free survival • Adverse effects of treatment • Health related quality of life	OS data is immature, therefore RFS data will be used to assess the efficacy of pembrolizumab, as an adjuvant treatment in patients with completely resected stage III melanoma, at high risk of recurrence. This is an acceptable clinical surrogate marker as described in Section 2.3.1, Section 2.4.2 and Section 2.13.

B.1.2 Description of the technology being appraised

Refer to Appendix C for the draft summary of product characteristics (SmPC) for the use of pembrolizumab in this indication.

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAB) of the IgG4/kappa isotype designed to exert a dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its associated ligands, PD-L1 and PD-L2 which appear on the antigen-presenting or tumour cells. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour inactivity.[1]
Marketing authorisation/CE mark status	Pembrolizumab currently has a marketing authorisation covering the following indications: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. • KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and

	brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Indication to which this submission relates: • [redacted]
Method of administration and dosage	200mg every three weeks (Q3W); intravenous (IV) infusion for 1 year.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	£2,630 per 100mg vial . The average treatment cost is £[redacted] (at list price).
Patient access scheme (if applicable)	A Commercial Access Agreement has been arranged with NHS England which is a discount of [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

B1.3.1 Brief overview of the disease/ condition for which this technology is being used.

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.

Malignant melanoma is one of the most aggressive types of skin cancer, contributing to over 90% of all cutaneous tumour deaths globally.[2] Melanoma has also been identified as the most commonly diagnosed cancer among adolescents and young adults globally.[3] UK specific estimates suggest that melanoma is the 5th most common cancer in the UK and accounts for 2.7 deaths per 100,000, ranking 32nd out of 172 globally for mortality secondary to skin cancer.[4] [5] Furthermore demonstrate that melanoma has an incidence of 4% of all new cancer

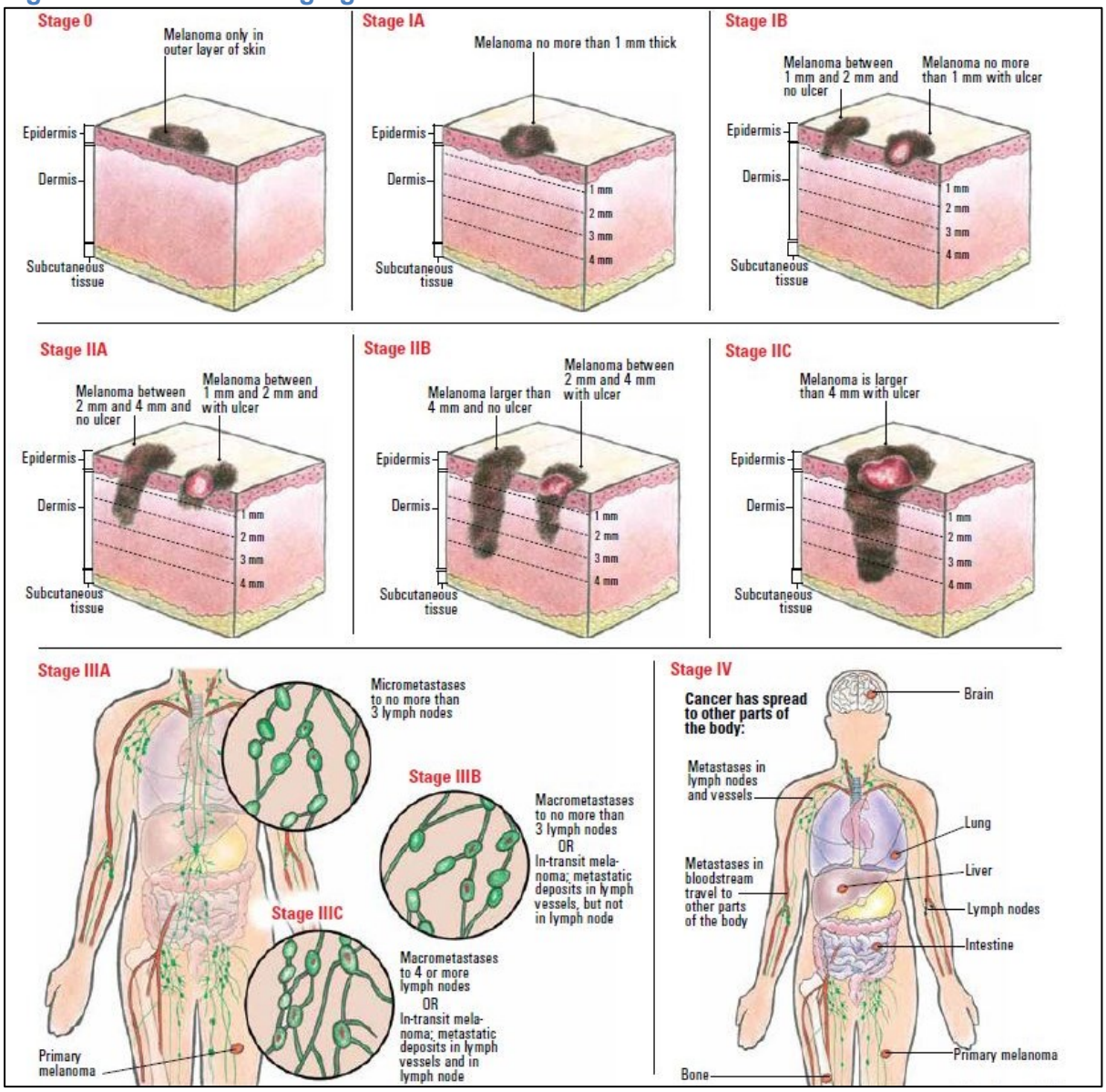
diagnosis in the UK.[4, 6] The rates of melanoma diagnosis increased by 128% in the UK between 1993-1995 and 2013-2015, with the increase greater in males than in females.[6]

A comprehensive review undertaken by the International Agency for Research on Cancer (IARC) identified that the main risk factors associated with the development of melanoma, include a familial history of melanoma, fair skin type and hair colour, high density of moles, previous history of melanoma, and additional environmental factors such as intense or chronic exposure to ultraviolet light. [7-9]

Melanoma is classified using the American Joint Committee Cancer (AJCC) Tumour, Node, Metastases (TNM) classification as summarised in Figure 1. This submission is focused on patients with stage III melanoma, which is typically characterised by regional nodal involvement and primary tumour ulceration. Stage III melanoma is further sub-categorised to IIIA, IIIB, and IIIC dependent on the presence of micro-, macro- or satellite-metastases.

KEYNOTE-054 enrolled patients with stage IIIA (lymph node metastasis >1mm), stage IIIB, stage IIIC based on the 7th edition of the AJCC criteria. Patients with stage IIIA (lymph node metastasis >1mm) were included within this study as these groups of patients have a significantly higher risk of relapse and mortality compared to patients with ≤1mm nodal metastasis.[10]

Figure 1: Melanoma staging classification.[11]



As of February 2018, the AJCC 8th edition TNM classification criterion for stage III melanoma was released. However, at the time of KEYNOTE-054 protocol development and initiation of patient enrolment, the AJCC 7th edition was used. Comparisons of the 7th and 8th editions are provided in Table 3. The recent changes of the AJCC TNM classification do not impact the clinical relevance of the KEYNOTE-054 population. Throughout this submission the AJCC 7th edition TNM classification criterion are cited.

Table 3: Comparison of the 7th and 8th AJCC TNM classification

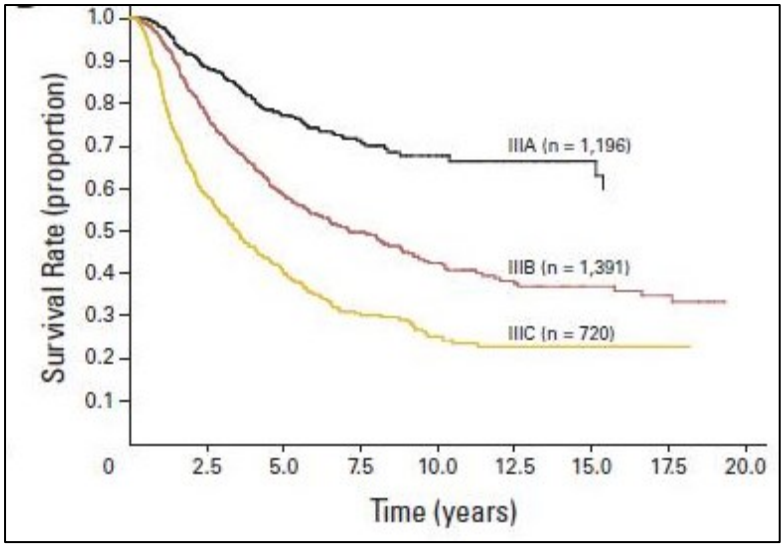
*The 5-year overall survival rates according to the current AJCC 8th edition Staging Guidelines are 93%, 83%, 69% and 32% for Stage IIIA, Stage IIIB, Stage IIIC and Stage IIID, respectively. [12]

Stage III Category	AJCC Edition 7 (2009)	AJCC Edition 8 (2017)*
IIIA	T1-4a/ N1a/ M0 T1-4a/ N2a/ M0	T1a/b-T2a/ N1a or N2a/ M0
IIIB	T1-4b/ N1a/ M0 T1-4b/ N2a/ M0 T1-4a/ N1b/ M0 T1-4a/ N2b/ M0 T1-4a/ N2c/ M0	T0/ N1b or N1c/ M0 T1a/b-T2a/ N1b/c or N2b/ M0 T2b/T3a/ N1a-N2b/ M0
IIIC	T1-4b/ N1b/ M0 T1-4b/ N2b/ M0 T1-4b/ N2c/ M0 Any T/ N3/ M0	T0/ N2b, N2c, N3b or N3c/ M0 T1a-T3a/ N2c or N3a/b/c/ M0 T3b/T4a/ Any N _N1/ M0 T4b/ N1a-N2c/ M0
IIID	-	T4b/ N3a/b/c/ M0

At the time of protocol development (KEYNOTE-054), 5-year Overall Survival (OS) rates as reported by the AJCC 7th edition, for patients with stage IIIA, IIIB, IIIC melanoma were 78%, 59%, and 40%, respectively (Recurrence at 5 years has been reported to be 37% in patients with stage IIIA disease, 68% for IIIB disease, and 89% for patients with stage IIIC disease[33] and therefore there is an unmet medical need for effective therapies to be given in the adjuvant setting to minimise the recurrence of this aggressive malignancy.

Figure 2).[3] Recurrence of melanoma is associated with substantial patient morbidity and mortality. Recurrence at 5 years has been reported to be 37% in patients with stage IIIA disease, 68% for IIIB disease, and 89% for patients with stage IIIC disease[33] and therefore there is an unmet medical need for effective therapies to be given in the adjuvant setting to minimise the recurrence of this aggressive malignancy.

Figure 2: Stage III melanoma survival curves based on the AJCC 7th edition TNM staging system.[3]



B1.3.2: Summarise the clinical pathway in a diagram showing the context and the proposed placement of the technology within the pathway

There are a number of relevant clinical guidelines for stage III melanoma available within the UK and Europe, and are summarised in Table 4. Of relevance to this submission is the NICE NG14. At present, NICE does not recommend the use of adjuvant therapies in patients with surgically resected stage III melanoma at high risk of recurrence.[13] In comparison the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommends the use of adjuvant therapies including the use of immunotherapies.[14, 15]

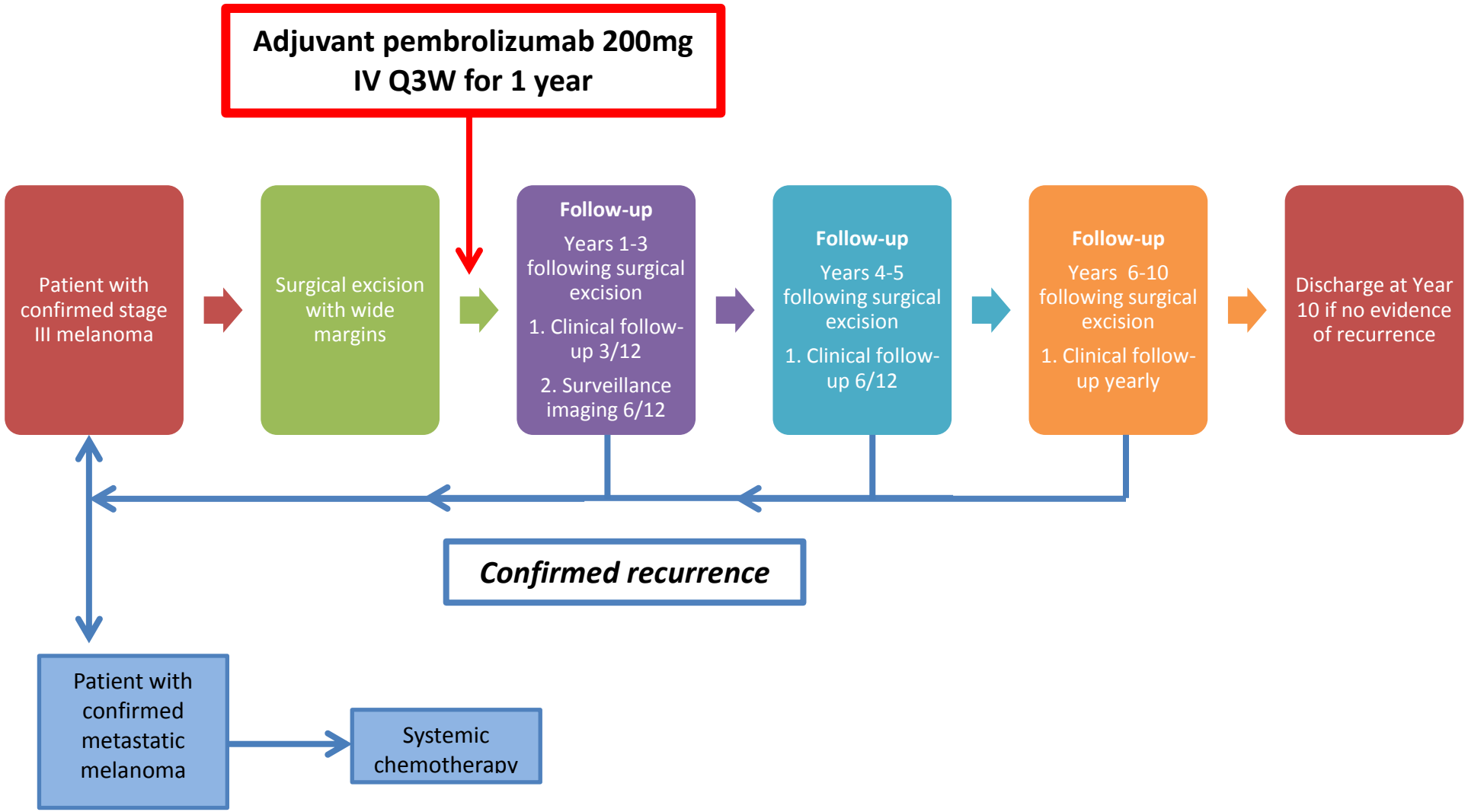
Table 4: Treatment guidelines for patients with stage III melanoma, at high risk of recurrence following complete surgical resection.

Organisation	Recommendations for Stage III melanoma
NICE (NG14), 2015[13]	• Surgical: wide-excision with therapeutic lymph node dissection in patients with palpable stage IIIB-IIIC. • Routine surveillance: follow-up every 3 months for the first 3 years following surgical excision and then every 6 months for the subsequent 2 years, and discharging at the end of 5 years. • Imaging, either MRI or CT is recommended 6 monthly for the first 3 years post-surgical excision.
The European Society for Medical Oncology (ESMO), 2015[15]	• Surgical: wide-excision of primary tumour with margin. • There is no consensus on the optimal schedule or frequency of follow-up visits, or on the clinical utility of imaging in patients with resected melanoma. • High risk patients (i.e. stage IIIB-IIIC), ultrasound of lymph nodes, CT or whole-body PET/PET-CT are recommended. • Following surgical resection, patients should be evaluated for adjuvant interferon therapy.

The National Comprehensive Cancer Network (NCCN), 2018[14]	• Surgical: Active lymph node basin surveillance +/- complete lymph dissection. Patients with clinical stage III, wide exicision of primary tumour + complete therapeutic lymph node dissection is recommended. • Routine surveillance: Clinical examination every 3-6 months for 2 years then, every 3-12 months for subsequent 3 years then, annually. Imaging is recommended every 3-12 months to screen for recurrence. • Adjuvant therapies are recommended for patients athigh risk of recurrence or malignancy spreading further into the lymph nodes. Adjuvant therapies include nivolumab (stage IIIB/C), dbrefenib/trametinib, high dose ipilimumab, interferon alfa. • Radiation therapy to lymph node basin for a specific group of patients at high risk of recurrence.

The recommendation of a NICE NG14 is summarised in Figure 3 below.

Figure 3: Current clinical pathway of care showing the context of the proposed use of the technology.



Diagnosis and Management

In summary, 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. 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 (refer to Table 4).

Recurrence Management

As the risk of melanoma recurrence is at its highest within 5 years of the primary diagnosis, NICE clinical guidelines recommend a period of observation for 3-5 years.[13] Based on a position paper reporting the consensus view of the majority of UK clinicans recommends additional follow-up of 10 years following surgical exicision of stage III melanoma.[16] The economic model developed for this submission, takes into account the additional period of follow-up. Patients are followed-up in a tertiary setting every 3 months for the first 3 years following completion of treatment, then every 6 months for the next 2 years and then discharging them at the end of the 5 years. Current UK guidelines recommend follow-up within a shared model of care under a medical oncologist in combination with a dermatologist and/or plastic surgeon.[13]

The risk of melanoma recurrence is the highest in the first 3 years post-surgical resection; patients undergo surveillance imaging on a 6-monthly basis. This usually entails a CT chest, abdomen and pelvis, but can also include CT brain, PET scan or MRI. UK specific evidence has suggested that approximately 60% of recurrences were asymptomatic at presentation and detected by scheduled surveillance imaging.[17]

Surgery alone has been shown to be insufficient to achieve a cure in most patients with high risk stage III melanoma.[2, 18] Adjuvant (postoperative) systemic therapy targets residual micro-metastatic disease with the goal of improving recurrence free survival (RFS) and subsequently overall survival (OS).[18] Until recently, adjuvant therapy has been limited by a lack of options that significantly improve OS together with risks from treatment associated toxicities.[19-21]

With this submission, pembrolizumab (PD-L1 inhibitor) is proposed to be used as an adjuvant therapy for surgically resected stage III melanoma at high risk of recurrence in adult patients. The proposed positioning of pembrolizumab as an adjuvant therapy is anticipated to prevent

recurrences and subsequently provide greater benefit and value to both patients and the healthcare system.

B.1.4 Equality considerations

We do not anticipate any equity or equality considerations.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

To identify and select relevant studies, a systematic literature review (SLR) search was carried out in accordance with NICE guidance [22], according to a previously prepared protocol to identify relevant studies to inform indirect comparisons between pembrolizumab and placebo. The clinical trial searches and screening were conducted in two parts. The first search for RCTs was executed on February 7, 2018 and shown in Appendix D Tables 1-3. The second search for systematic literature reviews and meta-analyses was also executed on February 7, 2018 are shown in Appendix D Tables 4-6.

Refer to Appendix D for full details of the process and methods undertaken.

B.2.2 List of relevant clinical effectiveness evidence

A SLR was performed to identify all relevant published and unpublished randomised controlled trials (RCTs) and non-randomised clinical trials (non-RCTs) relating to pembrolizumab and routine surveillance (as the relevant comparator) as per the final scope in Table 5. As the manufacturer, Merck Sharpe & Dohme (MSD) is aware of all relevant clinical trial data for pembrolizumab.

A single citation was identified from the SLR; this represented the use of pembrolizumab as an adjuvant treatment for high-risk stage III melanoma following surgical resection in adult patients and forms the evidence base for this submission.[23] At the time of SLR search, unpublished evidence from KEYNOTE-054 was available, howeverat the time of this submission, it has now been published.[24]

KEYNOTE-054 is a randomised, double-blind, ongoing Phase III trial assessing adjuvant immunotherapy with anti-PD-1 monoclonal Pembrolizumab (MK-3475) versus placebo, in patients who have undergone complete surgical resection of stage III melanoma. This submission utilises data from the first interim analyses (IA1) with a data cut off 2nd October

2017, and is available within the clinical study report (CSR). [redacted] Further information on methods, trials outcomes including assessment and participant baseline characteristics can be found in Sections 2.3.1, 2.3.2, 2.3.4 respectively.

Table 5: Clinical effectiveness evidence

Study	Study of Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk stage III melanoma (MK-3475-054/ KEYNOTE-054).				
Study design	Randomized, double blinded clinical trial				
Population	KEYNOTE-054 included adult patients with stage III melanoma having undergone complete surgical resection				
Intervention(s)	Pembrolizumab 200mg every 3 weeks (Q3W) for 1 year.				
Comparator(s)	Placebo/ Routine surveillance				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	KEYNOTE-054 is the only available data for pembrolizumab in this indication.				
Reported outcomes specified in the decision problem	**Recurrence free survival** **Safety and Tolerability** Health related quality of life Distant metastases free survival Overall survival **Those in bold are included in the health economic model.*				
All other reported outcomes	**Time on treatment** **Those in bold are included in the health economic model.*				

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B2.3.1 Trial overview: KEYNOTE-054

Eligibility Criteria (Inclusion criteria)

Patients were eligible for inclusion if the following criteria were met;

- Provided written consent and are at least 18 years of age
- Had complete resection of stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as stage IIIA (>1mm lymph node metastasis), any stage IIIB, or stage IIIC. No past of current in-transit metastases or satellitosis.
- Had tumour sample evaluable for PD-LI expression.

- Resection of stage III lymph nodes must have been performed in complete compliance with the criteria for adequate surgical procedures for CLND.
- Had disease status for the post-surgery baseline assessment documented by full chest/abdomen/ pelvis CT and/or MRI with neck CT and/or MRI (for head and neck primaries) and complete clinical examination after informed consent and prior enrolment.
- Post-lymph node dissection radiotherapy must have been completed within the 13 week post-surgery period and prior to treatment start.
- Had ECOG performance status of 0 or 1
- Patients had an interval from surgery to first study drug treatment ≤13 weeks.
- Had adequate organ function as defined in Table 6 below. All screening labs should be performed within 14 days (+/- 3 days) prior to treatment initiation.

Additional exclusion criteria are listed in Section 9.3.2 of the company CSR. This includes but not limited to; presence of mucosal or ocular melanoma, adequate surgical and pathological procedures undertaken, participation/ receiving investigation agent or used an investigation agent in the 4 weeks prior to first dose of pembrolizumab.

Table 6: Adequate organ function laboratory values

System	Laboratory value
Haematological	
Absolute neutrophil count (ANC)	≥1,500/mcl
Platelets	≥100,000/mcl
Haemoglobin	≥9 g/dl or ≥5.6 mmol/L
Renal	
Creatinine or Measured or calculated creatinine clearance (GFR	≤ 1.5 xULN or ≥ 60 ml/min for patients with creatinine levels >1.5 x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN or Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN
Coagulation	
International normalised ratio (INR) or Prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤ 1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants. ≤ 1.5xULN unless patients are receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

Trial design

KEYNOTE-054 (NCT02362594) is an international, double blind, placebo-controlled phase III study of the EORTC Melanoma Group, evaluating adjuvant therapy with pembrolizumab (KEYTRUDA) versus placebo after complete resection of stage IIIA (>1mm lymph node metastasis), IIIB and IIIC melanoma (classified using the AJCC 7th edition)[3]. Placebo was the

comparator of choice for this study based on the limited treatment options for this group of patients at the time of protocol development.

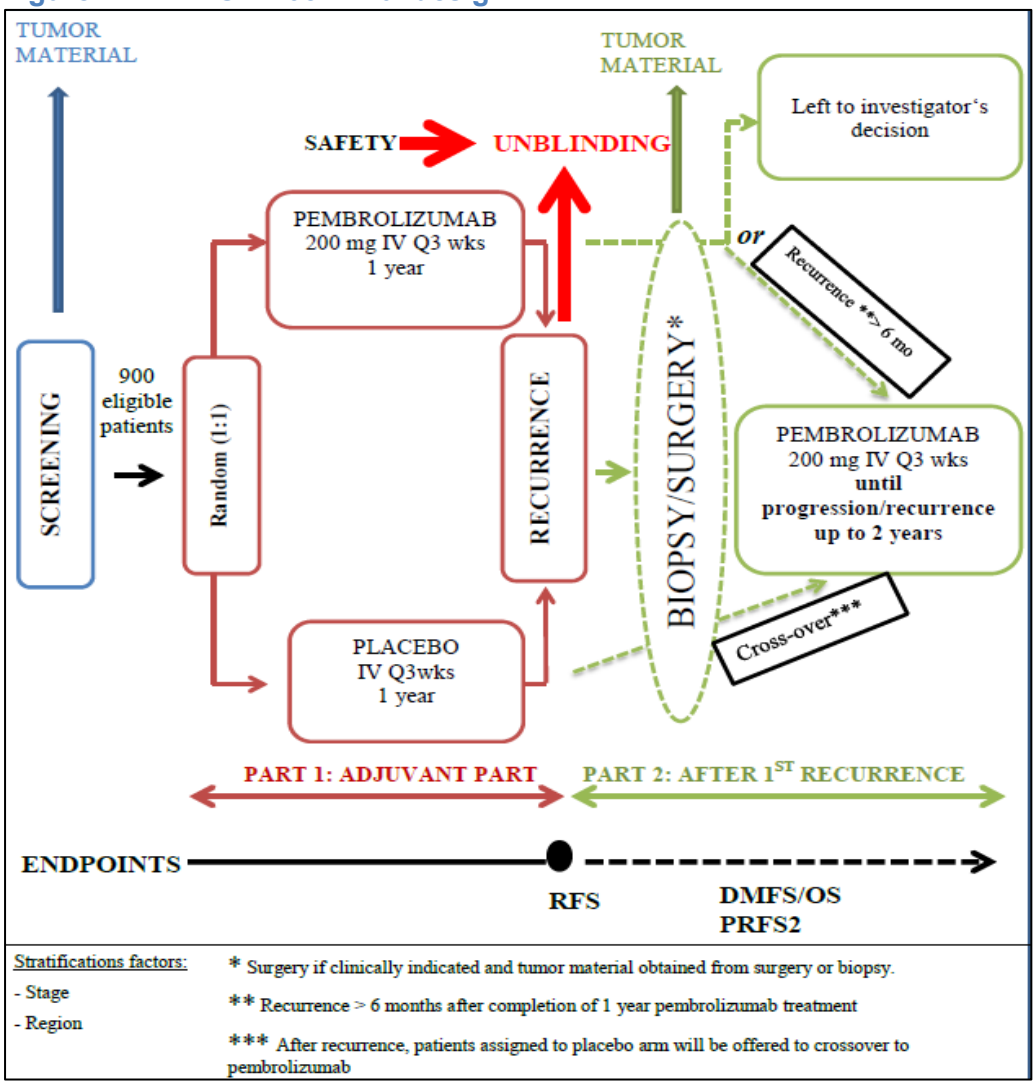
The trial design for KEYNOTE-054 is summarised in Figure 4. The treatment phase of the study consists of 2 parts:

1. Part 1 (Adjuvant therapy): Pembrolizumab or placebo was administered Q3W for a total of 18 administrations or until disease recurrence or unacceptable toxicity.

2. Part 2 (Crossover or Re-Challenge with pembrolizumab treatment) following disease recurrence following adjuvant treatment.

Relevant to this submission is Part 1; this includes efficacy data as per data cut off 2nd October 2017. Part 2 is ongoing and not included within this submission.

Figure 4: KEYNOTE-054 Trial design



Randomisation

Randomisation was performed centrally via an Interactive Voice Response System and patients were stratified by;

1. Stage (IIIA (>1mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes)
2. Region (North America, European countries, Australia and other countries as designated.

Patients were randomised to receive either pembrolizumab 200mg IV or placebo Q3W for one year duration or a total of 18 administrations. As this was a double-blinded study, neither the treatment group nor its description were provided to the investigator, the sponsor, EORTC staff, CRO, patients or site staff.

In this trial, patients could discontinue from treatment but continue to participate in the scheduled clinical activities, as long as consent was not withdrawn. Patients were categorised as "discontinuation due to recurrence" or "treatment discontinuation in the absence of recurrence". Patient discontinuation was also required from study treatment for the following conditions;

1. Completed 1 year of adjuvant treatment with pembrolizumab
2. Unacceptable adverse events
3. Intercurrent illness that prevented further administration of treatment
4. Investigator decision to withdraw the patient
5. Non-compliance with trial treatment or procedure requirements including lost to-follow up
6. Patients with a confirmed positive serum pregnancy test
7. Administrative reasons
8. Patient or legal representative withdraws consent for treatment
9. Occurrence of new malignancy

Patients who discontinued treatment were followed up for 30 days for adverse event (AE) monitoring. If patients suffered from an AE at the time of discontinuation, follow-up continued until resolution or determination that the event was stable or irreversible. Any treatment related deaths occurring beyond this time frame were reported to the EORTC. In the occurrence of treatment discontinuation in absence of recurrence, patients underwent clinical examinations and imaging every 12 weeks for the first two years, every 6 months for the next 3 years, and on a yearly basis thereafter.

With KEYNOTE-054, patients in the placebo arm who have a confirmed disease recurrence were un-blinded. Similarly, patients in the intervention arms with a confirmed disease recurrence were un-blinded.

Settings and locations where data was collected

This was a global study undertaken in 23 countries; Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Serbia, Spain, Sweden, Switzerland, United Kingdom and United States. Approximately two-thirds of patients (n=677) were enrolled across Europe, of which 52 were enrolled from UK centres. Patients were enrolled and underwent randomisation from August 2015 to November 2016.

Trial drugs and concomitant medication

Patients were randomised to receive either pembrolizumab or placebo, in a double-blinded process as summarized in Table 7. Placebo was normal saline solution prepared by the local pharmacist, dosed and administered in the same manner as the investigational product.

Table 7: Study treatments

Drug	Dose	Dose frequency	Route of administration	Treatment period	Use
Pembrolizumab	200mg	Q3W	IV infusion	Day 1 of each 3 week cycle for a total of 18 administrations (~ 1 year)	Experimental
Placebo	0mg	Q3W	IV infusion	Day 1 of each 3 week cycle for a total of 18 administrations (~1 year)	Control

All concomitant medications received within 30 days prior to the first dose of study drug through 30 days after the last dose of study drug were recorded including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. The final decision on any supportive therapy or vaccination rested with the investigator and/or the patient's physician.

Prohibited medications include but not limited too;

- Anti-cancer treatments expect those permitted within this trial (pembrolizumab and surgery).
- Any investigational agents other than study drug
- Immunosuppressive agents

- Chronic systemic corticosteroids (expect for patients which developed endocrinopathies requiring stable doses of hormone replacement therapy)
- Live vaccines within 30 days prior to the first dose if study drug and whilst participating in the study.
- Medication or vaccination specified within the exclusion criteria of the study protocol were not permitted during the trial.

Further prohibited medications can be found in the study protocol in Section 5.6.

Outcomes used in the economic model and primary study outcome

The primary outcome was RFS in the overall intention-to-treat population (ITT) and in the subgroup of patients with PD-L1 positive tumours. The outcomes RFS, patient HRQoL, safety and tolerability as per the NICE final scope were included within the health economic model as reported in Section B.3. Full details for RFS, PROs, safety and tolerability data are described below.

Primary outcome

Recurrence free survival

To evaluate the anti-tumor activity of pembrolizumab in the adjuvant setting, the primary outcome of the KEYNOTE-054 was;

1. Recurrence free survival (RFS)
2. RFS for patients with PD-L1 positive expression

RFS has been established as a reliable surrogate efficacy marker for patients with complete resection of stage III melanoma at high risk of recurrence, in the adjuvant setting.[25] RFS for the purpose of this study was defined as the time between date of randomisation and the date of first recurrence (local, regional, distant metastasis) or death, whichever occurs first. RFS was based on disease assessment or date of death provided by the local investigator (Further details are provided in Section 2.3.2). For patients, who remain alive and whose disease has not recurred RFS will be censored on the date of the last visit/contact.

Secondary outcomes

As previously described data presented are based on IA1 DATE 2nd October 2017. As a result data relating to the primary and AE secondary endpoints only were available. The minimum number of events required to analyse the endpoints of DMFS and OS had not been achieved at the time of data cut-off. The following secondary objectives/ outcomes were specified and will be subject to a later report:

1. Distant metastasis free survival (DMFS) [redacted]
2. DMFS in patients with PD-L1 positive tumour expression [redacted]
3. OS [redacted]

4. OS in patients with PD-L1 positive tumour expression [redacted]

Adverse events (AEs) & Serious Adverse events (SAEs)

All adverse events were recorded based upon investigator assessment as to whether those events were drug related (reasonable possibility, no reasonable possibility). This assessment was recorded for all AEs and all AEs were followed until resolution or stabilisation.

Exploratory outcomes

Exploratory outcomes include quality of life (QoL) and health outcome evaluation. The main objective of Health Related Quality of Life (HRQoL) within KEYNOTE-054 was to determine the impact of adjuvant immunotherapy versus placebo. The primary HRQoL endpoint will be overall health/ QoL.

B2.3.2 Outcome assessment

Primary outcome: RFS

Within KEYNOTE-054 recurrence was defined as appearance of one of more new melanoma lesions local, regional or distant defined as;

1. *Local cutaneous recurrence*- occurring within 2cm of tumour bed with neoplastic nature confirmed with either histology/ cytology. Local recurrence following adequate surgical excision of the primary melanoma is associated with aggressive tumour biologic features and is frequently a harbinger of metastases.

2. *Regional lymphatic and nodal recurrences*- can be sub-classified into in-transit metastases and regional nodal recurrences. The neoplastic nature of regional recurrences should be confirmed by histology/ cytology.

    i. In transit metastases: defined by the AJCC as any skin or subcutaneous metastases that are more than 2cm from the primary lesion but are not beyond the regional nodal basin.
    ii. Regional nodal recurrences: regional nodal failure usually occurs within a previously dissected basin and found at the periphery of the prior surgical procedure.

3. Distant metastases
    i. Patterns of metastases- the most common initial sites are non-visceral (including skin, subcutaneous tissue and lymph nodes). Visceral metastases occur in 25% of patients and include lung, brain, liver, gastrointestinal tract and bone.
    ii. Measurable disease- the presence of at least one measurable disease. Single lesions should measure ≥ 10mm in two dimensions. If the

measurable disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by either cytology/ histology.

iii. Non-measurable lesions- including small lesions defined as <10mm using spiral CT and unmeasurable lesions.

Note: Cutaneous relapses occurring beyond the periphery of the previous surgical bed (≥ 2cm) were considered distant metastases. Node relapses occurred beyond the anatomical compartment of the dissected basins was considered distant metastases. Node relapses in the nodal basins situated within different anatomical compartments or beyond the previously dissected basins or in two nodal basins were also considered distant metastases.

Methods of assessments for recurrence in KEYNOTE-054 were undertaken as follows;

1. During the adjuvant treatment period, patients underwent clinical examination and assessment of adverse events every 6 weeks and imaging (CT/MRI) every 12 weeks. On completion of adjuvant therapy, patients underwent clinical examination and imaging every 12 weeks.
2. CT and MRI were mandatory to establish recurrence. Conventional CT with IV contrast and MRI gadolinium was performed with contiguous cuts of 10mm or less slice thickness. Spiral CT was recommended using a 3 or 5 mm contiguous reconstruction algorithm. PET alone was not considered for disease assessment and complementary CT/MRI or biopsy was performed for all cases.
3. Cytology and/ or histology were mandatory to confirm recurrence in solitary, doubtful lesions, cutaneous, subcutaneous, or lymph node lesions. Histological or cytological evidence of recurrence was required in all cases with the exception of brain metastases.
4. Clinically detected new lesions including superficial lesions were confirmed by cytology/ histology. Deep subcutaneous lesions and lymph node lesions were documented by ultrasound with histological/ cytological evidence.

Date of recurrence was defined as the first date when recurrence was observed and was taken into account regardless of the method of assessment. Recurrence was declared for any lesions when;

1. Imaging was performed and progression confirmed.
2. Only pathology was undertaken and malignancy was confirmed.
3. Both pathology and imaging was undertaken with malignancy/ progression confirmed.

Secondary outcomes: AE & SAEs

Adverse events were assessed using the International Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse reporting. Haematological toxicity was assessed on the basis of regular blood tests, with the nadir count computed with each study administration. The nadir count was calculated at each study medication administration and

was graded according to the CTCAE. Non-haematological acute side effects were also assessed and reported separately for each study medication and graded accordingly. SAEs were defined by the Good Clinical Practice Guideline. Toxic deaths were defined as death due to toxicity and the evaluation of toxic deaths is independent of the overall evaluation of response.

Exploratory outcomes: Quality of life and PROs

As the patient's subjective perspective is an inherent component of the HRQoL, a subjective assessment was undertaken. At present, there are no validated immune-specific questionnaires for use in oncology trials. QoL was therefore assessed using the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. All scales and single items met standards for reliability. Further information regarding the instrument can be found in the company protocol. The EQ-5D-3L was also administered and has been used extensively in oncology studies and published results from these studies support its validity and reliability. [26]

Patient reported outcomes were administered by trained site personnel in accordance to the EORTC "Guidelines for administration of questionnaires". Questionnaires (EORTC QLQ-C30 version 3a and EQ-5D-3L) at baseline (defined as within 6 weeks prior to randomisation) were completed with subsequent questionnaires completed every 12 weeks for the first two years, every 6 months for the next 3 years (years 3 to 5) and on a yearly basis thereafter (summarized in Table 8). HRQoL data was collected regardless of the patient's recurrence/ progression status. In order to optimise compliance and completeness of the data, a key person was responsible for the questionnaire data collection. Compliance of the HRQoL assessments was reviewed twice a year.

Table 8: HRQoL Schedule

Assessment	Time window
Baseline	Completed before or one the day of randomisation
Every 12 weeks (during year 1 and 2 after randomisation)	At week 12, 24, 36, 48, 60, 72, 84, 96, 108. Completed 2 weeks before or after intended date.
Every 6 months (during year 3 and 4 after randomisation)	At month 30, 36, 42 and 48. Completed up to 6 weeks before or after intended visit date.

EQ-5D was analysed and included within the economic model, however at the time of the submission, the QLQ-C30 was not analysed. It be available at a later date.

B2.3.3 Comparative summary of trial methodology

A single trial, KEYNOTE-054, forms the evidence base for this submission. Full details relating to trial methodology can be found in Section 2.3.1.

B2.3.4 Participant baseline characteristics

Baseline characteristics of the ITT population are reported in Table 9. In summary, 1,019 patients were randomised and included within the ITT population; 514 to pembrolizumab and 505 to placebo. Treatment groups were generally well-balanced. Across treatment groups there was a majority male population (61.6%) with a mean age of 53.8 (SD 13.9) years. 83.7% and 49.8% of patients had a PD-L1 positive tumour and BRAF mutation detected, respectively (Table 9). A total of 1,011 patients received at least one dose of study treatment; 509 in the pembrolizumab group and 502 in the placebo group. In total, 445 patients were enrolled but not randomised primarily due to meeting the exclusion criteria at randomisation (63.1%) (Table 10). Follow-up was defined as the time from randomisation to the date of death or database cutoff date (2nd October 2017), if the patient was still alive. The median follow-up duration of patients in KEYNOTE-054 was 16.0 months as per data cutoff date (2nd October 2017).

The KEYNOTE-054 publication reported a median follow-up duration of 15 months.[24] The difference in median follow-up between the company CSR and publication arouse due to two different methods utilized to estimate the endpoint as below (refer to Section 2.3.2):

1. EORTC publication: Estimation utilising a Kaplan-Meier approach. Patients were censored from the analysis when they discontinued the study. In patients who were censored, information was only collected on whether they recurred/ death at the time of discontinuation and do not know if/when they would have had an RFS event if they continued the study.

2. Company CSR: Follow-up was defined as the time from randomisation to the date of death or the database cut-off date (2nd October 2017), if the patient was alive. Estimated the median follow-up duration using a similar procedure as the EORTC expect that the event was discontinuation and patients were censored when they had an RFS event. Therefore, the events used in this presented analysis (discontinuation and RFS events) were defined the same way that they were defined for the primary efficacy RFS analysis.

We will use CSR report as the base and Merck stand behind the results reported in the CSR.

Overall, 51.4% and 55.4% patients treated with either pembrolizumab or placebo, respectively completed 18 administrations (as per protocol) of treatment (Table 17). The most common reason for discontinuation in both groups was recurrence/ relapse/ death due to progressive disease (21.4% versus 35.6% in the pembrolizumab and placebo groups, respectively) (Table 17).

Table 9: Participant's baseline characteristics; ITT population.

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	514		505		1,019	
Gender						
Male	324	(63.0)	304	(60.2)	628	(61.6)
Female	190	(37.0)	201	(39.8)	391	(38.4)
Age (Years)						
< 50	193	(37.5)	186	(36.8)	379	(37.2)
50 to 64	196	(38.1)	193	(38.2)	389	(38.2)
65 to 74	97	(18.9)	98	(19.4)	195	(19.1)
>= 75	28	(5.4)	28	(5.5)	56	(5.5)
Mean	53.9		53.7		53.8	
SD	13.6		14.2		13.9	
Median	54.0		54.0		54.0	
Range	19 to 88		19 to 83		19 to 88	
Region						
North America	38	(7.4)	37	(7.3)	75	(7.4)
Europe	341	(66.3)	336	(66.5)	677	(66.4)
Australia/New Zealand	111	(21.6)	112	(22.2)	223	(21.9)
Other	24	(4.7)	20	(4.0)	44	(4.3)
PD-L1 Status						
PD-L1 Positive	428	(83.3)	425	(84.2)	853	(83.7)
PD-L1 Negative	59	(11.5)	57	(11.3)	116	(11.4)
Unknown	27	(5.3)	23	(4.6)	50	(4.9)
BRAF-Mutation Status						
Mutation Detected	245	(47.7)	262	(51.9)	507	(49.8)
Mutation Not Detected	233	(45.3)	214	(42.4)	447	(43.9)
Unknown	36	(7.0)	29	(5.7)	65	(6.4)
ECOG						
0	485	(94.4)	475	(94.1)	960	(94.2)
1	29	(5.6)	30	(5.9)	59	(5.8)
Primary Cutaneous Melanoma						
Cutaneous	455	(88.5)	460	(91.1)	915	(89.8)

Table 10: Reasons for participants not being randomised.

	n (%)

Not Randomized	445
Central Confirmation Of Pd-L1 Expression Was Non-Eligible	19 (4.3)
Patient Could Not Be Randomized Within 12 Weeks After Clinic	42 (9.4)
Patient Was Ineligible For Another Reason	281 (63.1)
Patient's Refusal	103 (23.1)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

This section reports the relevant statistical methodology of KEYNOTE-054.

B2.4.1 Analysis populations

1. *Efficacy analysis population.* The primary efficacy analyses were based on the ITT population; patients were analysed in the treatment group allocated at randomisation and no patients were excluded from the analyses. The ITT population included a total of 1,019 patients for the primary endpoint; RFS as defined in Section 2.3.1.

2. *Safety analysis population.* This was based on the all patients treated (APaT) population, which included all 1,011 randomized patients who received at least 1 dose of study treatment. For the avoidance of doubt, the safety population was defined as, all patients who have started their allocated treatment (at least one dose of the study drug).

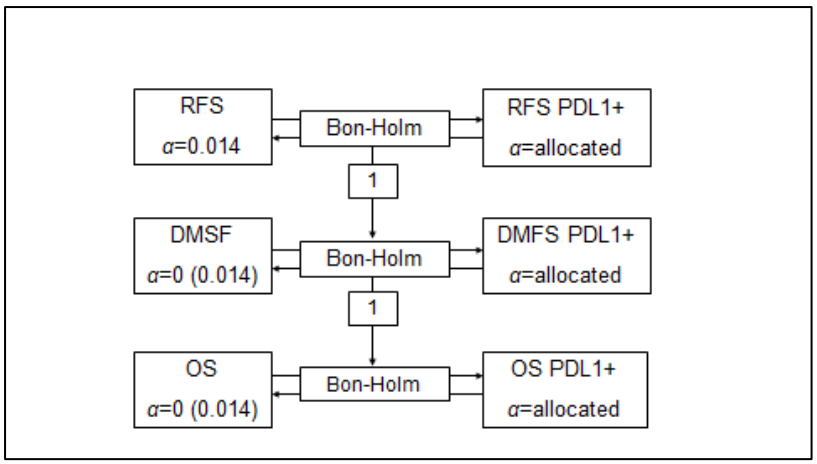
B2.4.2 Sample size, Statistical Methods and Missing Data Methods

Primary and secondary objectives

Sample size

To test the hypotheses, that pembrolizumab and placebo groups differ with regards to the primary endpoint; RFS and in the PD-L1 subgroups, a graphical approach was utilised as shown in Figure 5.[27, 28]

Figure 5: Graphical approach to sample calculation



The study is powered for RFS; the primary endpoint of KEYNOTE-054. The sample size calculation assumed RFS hazard rates for placebo of 0.54 pre-1 year and 0.25 post-1 year from randomisation, a total of 409 events (local/ regional/ distant metastasis/death) for RFS were needed to provide 95% power to detect a pembrolizumab:placebo hazard ratio (HR) of 0.70 (1-sided logrank test, alpha=2.5%) or an increase of the median RFS from 1.64 to 2.87 years (median ratio=1.75). Therefore, the study planned to randomise 900 eligible patients (approximately 450 patients per arm), with a further 2.5% additional patients enrolled to compensate for the ineligible patients and early consent withdrawal.

RFS for PD-L1+ subgroup is the other primary endpoint of this study. The power is presented for PD-L1+ subgroup where the events in the subgroup range from 30-60% of the 409 overall RFS events, the subgroup HR=0.55, 0.6, 0.65 or 0.7, with α=0.025. Under these scenarios, the power for rejecting at least 1 RFS hypothesis is at least 93%.

Interim analysis

Results reported in this submission are based upon a planned interim analysis after 330 RFS events. A protocol amendment was finalised on 2nd October 2017, to account for an interim analyses following 330 RFS events, to assess the efficacy of pembrolizumab with respect to RFS. Additional clarifications were made in Amendment 02 which did not impact the conduct of the study.

As previously described, due to a lack of follow-up data, DMFS and OS were not assessed in IA1 and are expected subject to sufficient DMFS and OS events. However, MSD note that within a meta-analysis of randomised controlled trials among patients with surgically resected stage II-III melanoma, RFS was demonstrated as a valid surrogate marker of OS.[25] Furthermore the authors suggest that a HR of ≤0.77 is an accurate predictive marker of OS benefit within this target population.[25]

Statistical analysis

Primary objective

The following methods were undertaken to address the primary objectives;

1. To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves RFS, as compared to placebo in high-risk patients with complete resection of stage IIIA (>1mm metastasis), IIIB, IIIC melanoma.

2. To prospectively assess whether in the subgroup of patients with PD-L1-positive tumour expression, pembrolizumab improves RFS as compared to placebo.

Assessment of RFS was performed using the ITT population. The Kaplan-Meier technique was used to obtain estimates of the survival-type distributions (RFS), and the standard error of the estimates were computed using the Greenwood formula.[29] Medians were presented with a 95% confidence interval based on the non-parametric method of Brookmeyer and Crowley.[30] The comparison of the time-to-event distributions between the two treatment arms was assessed using the log-rank test stratified by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes), as indicated at randomisation. The HR, and its (1-2xα)*100% confidence interval, of Pembrolizumab:Placebo, was estimated using a Cox proportional hazards (PH) model (using Efron's tie-handling method), stratified by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 nodes vs. IIIC ≥4 nodes) as indicated at randomisation, with treatment as the single covariate.

Based on the number of RFS events at the time of the interim analysis (n=351) and the spending function that was used (Lan-DeMets alpha spending function with O'Brien-Fleming stopping rules), alpha = 0.008 (one-sided) was used to test the hypothesis in the overall population, corresponding to a 98.4% (two-sided) confidence interval.[31, 32] Since pembrolizumab was shown to be superior to placebo in the overall population, the alpha (0.025, one-sided) was subsequently used to test the hypothesis in the PD-L1+ population. This corresponds to a 95% (two-sided) confidence interval. As a result, a 98.4% confidence interval was used for the overall population, but a 95% confidence interval was used for the PD-L1+ population.

To evaluate the robustness of the RFS endpoint, two sensitivity analyses with differing censoring rules were performed as shown in Table 11.

Table 11: Sensitivity analyses accounting for varying censoring rules.

Situation	Primary analysis	Sensitivity analysis 1	Sensitivity analyses 2
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment	Recurrence at date of new anticancer treatment
Recurrence of death documented after ≤1 missed disease assessment	Recurrence at date of documented recurrence or death	Recurrence at date of documented recurrence or death.	Recurrence at date of documented recurrence or death
Recurrence or death after ≥ 2 missed disease assessments	Recurrence at date of documented recurrence or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Recurrence at date of documented recurrence or death

Secondary objectives

The following methods were undertaken to address the secondary objectives:

1. To compare adverse event profiles (AE & SAE) between patients receiving pembrolizumab versus patients in the placebo arm.

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests and clinical examination. The ASaT population is the primary safety analysis population presented in this submission which includes all enrolled patients who received at least 1 dose of pembrolizumab in KEYNOTE-054. Summary statistics (counts, percentages etc.) were provided for safety endpoints as appropriate. No formal toxicity treatment comparisons with reported p-values were undertaken, as per trial's protocol.

Results reported in this submission are based upon planned interim analyses following ~300 RFS events as described in Section B2.4.1. Analyses of efficacy (assessed as RFS) and safety in patients with stage III melanoma are the primary focus of this submission.

KEYNOTE-054 will continue to the next endpoint, DMFS, followed by OS. [redacted] and have not been addressed in the submission as detailed in Section B2.3.2.

Exploratory objectives

As discussed in Section B2.3.2, only EQ-5D-3L was analysed and used for the economic model presented in this submission. QoL measures will be available at a later date and were not used for the economic model.

Sample size

The primary HRQoL endpoint was the global health/ QoL scale. A difference of 10 points on the 100-point QLQ-C30 scale between the two arms was considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With a 2-sided alpha set at 5% and a power of 80% to detect a difference of 10 points (effect size 0.5), a minimum of 128 patients (64 per treatment arm) was required. For an effect size of 0.75 (difference of 15 points), 56 patients (28 per treatment arm) were required. Therefore this study was sufficiently powered to detect differences in HRQoL.

Statistical analysis

This submission will also focus on the following exploratory objectives:

1. To compare quality of life between the two treatment groups (pembrolizumab versus placebo).

Data was scored according to the algorithm described in the EORTC scoring manual. The QoL scores between the two arms were compared using summary statistics. Non-parametric rank-order tests were performed using a two-sided significant level of 5% to detect for significant differences between the treatment arms. An overall effect of treatment on the QoL scores was determined primarily on the basis of the primary analysis. Differences were only considered clinically relevant if they exceeded the 10-point threshold. Mechanisms of compliance were investigated prior to undertaking the main analyses. Compliance by instrument, visit and treatment arm was described by absolute number and relative percentage. Missing values were imputed via linear regression models and were analysed similar to the main method as a sensitivity analyses to address the stability of the main results.

Further details on sample size and statistical analysis plan for EQ-5D-3L are discussed in Section 3.4.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality of the included RCT was assessed using the Cochrane Risk of Bias tool; the results of this assessment are provided in Table 12.

Table 12: Cochrane Risk of Bias assessment for included RCT.

Trial	Entry	Judgement	Support for judgement
KEYNOTE 054	Random sequence generation (selection bias)	Low risk	Randomization was conducted by a centralized voice-response system; minimization technique was used for sequence generalization.
	Allocation concealment (selection bias)	Low risk	Randomization was conducted by a centralized voice-response system
	Blinding of participants and personnel (performance bias)	Low risk	Both patients and investigators were blind to treatment allocation
	Blinding of outcome assessment (detection bias)	Unclear risk	RFS was assessed by local investigators, not an independent review committee
	Incomplete outcome data addressed (attrition bias)	Low risk	Number of discontinued patients and reasons were specified and accounted for.
	Selective reporting (reporting bias)	Low risk	Primary outcome (RFS) was reported; secondary endpoints (OS, DMFS, HRQoL) not yet reported.
	Other sources of bias	Low risk	No other potential sources of bias were identified.

Consideration of evidence

KEYNOTE-054 was found to be truly representative of the average patient following a complete surgical resection of stage III melanoma at high risk of recurrence. The population was drawn from the same community as the exposed cohort. Ascertainment was recorded securely and the outcome of interest was not present at the start of the study. Randomisation stratified by melanoma staging and geographic region, allowing for comparability of cohorts on the basis of trial design. Outcomes were performed by independent assessment with length of follow-up sufficient to allow evaluation of the primary outcome; median follow-up was 16.0

months. KEYNOTE-054 undertook a complete follow-up, accounting for all patients. Further information regarding trial design and methods can be found in section 2.3.

KEYNOTE-054 is a double blinded, international randomised controlled trial. The study has been adequately powered to assess the efficacy of pembrolizumab in patients with surgically resected stage III melanoma utilising RFS as its primary outcome, in comparison to placebo. As described previously, the enrolled population is representative of patients expected to receive treatment in current UK clinical practice. Furthermore the use of a placebo as the control arm accurately represents UK clinical practice; given current NICE clinical guidelines recommend watchful waiting following surgical resection of stage III melanoma.

Consideration of UK clinical practice

Patients with stage III melanoma in the UK, currently have no treatment options in the adjuvant setting. As the risk of recurrence is considerably high within this target population due to the associated patient morbidity and mortality, there is a considerable unmet need. Pembrolizumab is a remarkably promising adjuvant treatment option, having shown efficacy including a significant improvement in RFS, with a good tolerability profile as demonstrated in KEYNOTE-054.

As reported in the patient baseline characteristics (Table 9), with approximately two-thirds of patients below 64 years of age with an ECOG score of 0 (94.2%). As the patient population exposed were young, the lifetime risk associated with subsequent recurrences is therefore accompanied with considerable patient morbidity and mortality.

B.2.6 Clinical effectiveness results of the relevant trials

B2.6.1 KEYNOTE-054, clinical effectiveness results

All data reported are based on the interim analysis 1, cut-off 2nd October 2017. As stated above, results are provided for RFS, PRO, and safety only. A total of 1,019 patients were randomised and included within the ITT population;. The median duration of follow-up for patients in the ITT population was 16.0 months (range 2.5-25.3 months). 97.2% of patients commenced adjuvant treatment with pembrolizumab or placebo ≤13 weeks from date of surgery.

Primary outcome

The primary objective was to prospectively assess whether adjuvant therapy with pembrolizumab improved RFS in the whole population as well as a sub-group of patients with PD-L1 positive tumour expression, versus placebo and is described below as a key clinical measure of the economic model.

Clinical outcome measures included within the health economic model

RFS

Pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in RFS in comparison to placebo in patients with lymph node-positive stage III melanoma following complete resection (HR-0.57; 98.4% CI 0.43 to 0.74; p<0.0001). Table 13 and Figure 6 demonstrate that RFS improves over time in the pembrolizumab arm. Median RFS was not reached in the pembrolizumab arm compared with 20.4 months in the placebo arm. The 1 year RFS rate was 75.4% (95% CI 71.3 to 78.9) in the pembrolizumab arm compared with 61.0% (95% CI 56.5 to 65.1) in the placebo group (Table 14). The 18 month RFS rate was 71.4% (95% CI 66.8 to 75.4) in the pembrolizumab group compared with 53.2% (95% CI 47.9 to 58.2) in the placebo group; beyond 18 months there were a limited number of patients (Table 14). The KM curves show separation of RFS rates after 3 months and these remain separated throughout the remainder of the evaluation period (Figure 6).

Fewer distant metastases developed in the pembrolizumab arm, 13.4% than in the placebo arm, 22.6%. Locoregional recurrences occurred in 15.2% of patients in the placebo group and in 10.7% of the patients in the pembrolizumab arm (Table 15). Three deaths contributed to the RFS events; 2 in the pembrolizumab arm and 1 in the placebo arm (Table 15).

For the dual primary endpoint of RFS in patients with PD-L1 positive tumours, results were comparable to those of the overall ITT population. Median RFS was not yet reached in either treatment group. Treatment with pembrolizumab resulted a statistically significantly increased/ longer RFS compared with placebo (HR=0.54; 95% CI 0.42 to 0.69; p<0.0001) (Table 16). The KM curves for PD-L1 positive patients were similar to the overall ITT population; that is the demonstration of separate RFS rates (curves) after 3 months, which was maintained throughout the remainder of the evaluation period (Figure 7).

Table 13: Analysis of Recurrence Free Survival; ITT population.

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio‡ (98.4% CI)‡	p-Value§
Pembrolizumab	514	135 (26.3)	6246.3	2.2	Not Reached (-, -)	82.2 (78.6, 85.3)	0.57 (0.43, 0.74)	<0.0001
Placebo	505	216 (42.8)	5566.3	3.9	20.4 (16.2, -)	73.3 (69.2, 77.0)	---	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.

§One-sided p-value based on log-rank test.

(Database Cutoff Date: 02OCT2017)

Table 14: Recurrence Free Survival Rate Over Time; ITT population.

	Pembrolizumab (N=514)	Placebo (N=505)
RFS rate at 6 Months in % (95% CI)†	82.2 (78.6, 85.3)	73.3 (69.2, 77.0)
RFS rate at 12 Months in % (95% CI)†	75.4 (71.3, 78.9)	61.0 (56.5, 65.1)
RFS rate at 18 Months in % (95% CI)†	71.4 (66.8, 75.4)	53.2 (47.9, 58.2)

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first.

† From the product-limit (Kaplan-Meier) method for censored data.

(Database Cutoff Date: 02OCT2017).

Figure 6: Kaplan-Meier Estimates of Recurrence-Free Survival; ITT population

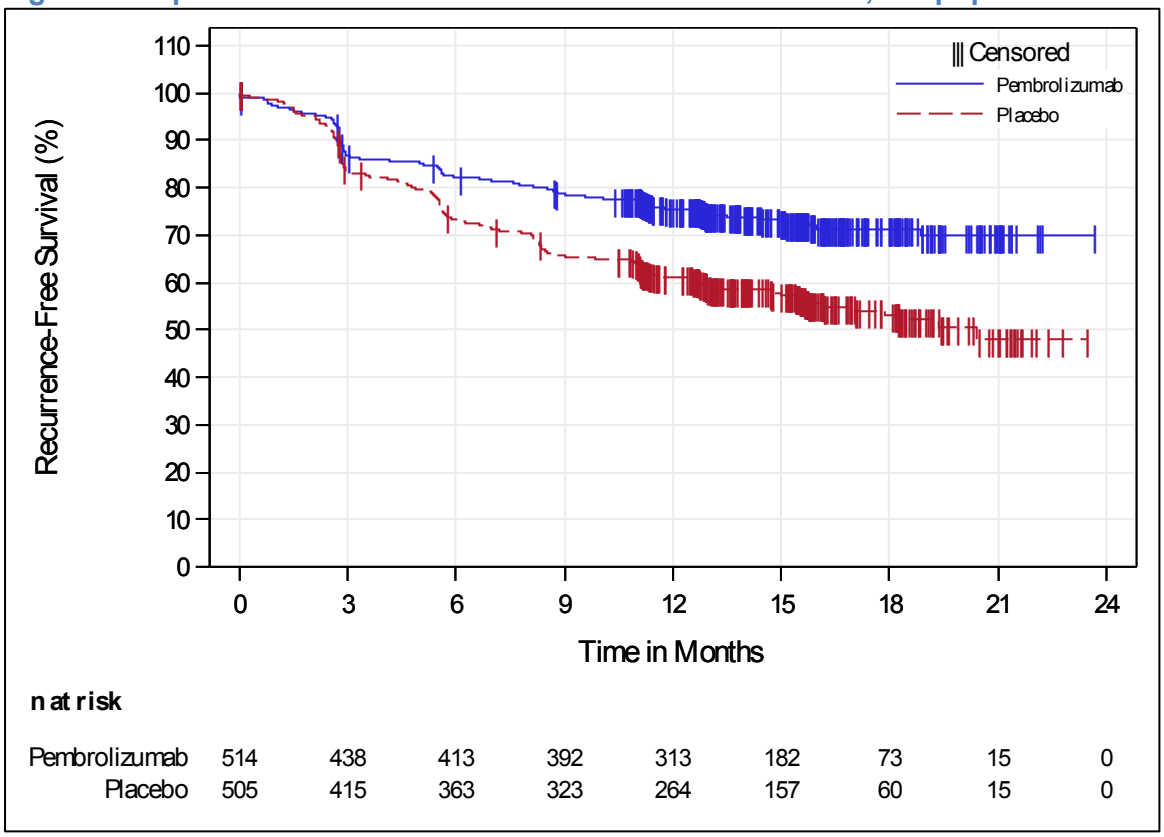


Table 15: Disease status; ITT population

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	514	505
Type of First Event in RFS Analysis		
No event	379 (73.7)	289 (57.2)
Event	135 (26.3)	216 (42.8)
Locoregional recurrence	55 (10.7)	77 (15.2)
Distant metastasis	69 (13.4)	114 (22.6)
Both diagnosed within 30 days from each other	9 (1.8)	24 (4.8)
Death	2 (0.4)	1 (0.2)
DMFS Status		
No event	416 (80.9)	340 (67.3)
Event	98 (19.1)	165 (32.7)
Survival Status		
Alive	489 (95.1)	470 (93.1)
Dead	25 (4.9)	35 (6.9)
Database Cutoff Date: 02OCT2017		

Table 16: Analysis of recurrence free survival; ITT population in patients with PD-L1 positive tumours.

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median RFS† (Months) (95% CI)	RFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Placebo	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab	428	102 (23.8)	5287.4	1.9	Not Reached (-, -)	83.8 (80.0, 87.0)	0.54 (0.42, 0.69)	<0.0001
Placebo	425	176 (41.4)	4830.1	3.6	Not Reached (17.1, -)	75.4 (71.0, 79.2)	---	---

Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. Analysis of recurrence free surivival; ITT population in patients with PD-L1 positive tumours was not utilised in the economic model presented in this submission.

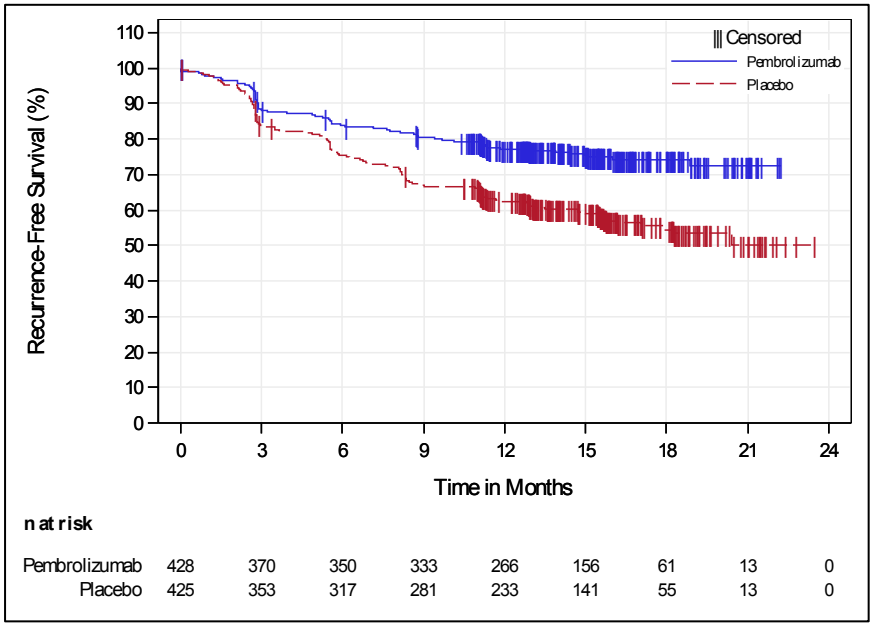
† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization.

§One-sided p-value based on log-rank test.

(Database Cutoff Date: 02OCT2017)

Figure 7: Kaplan Meier estimates of recurrence free survival; ITT population in patients with PD-L1 positive tumours.



Time on treatment.

The median number of days on therapy and median number of administrations was identical in both pembrolizumab and placebo groups (Table 17). Duration of exposure was slightly longer in the pembrolizumab arm compared with the placebo arm (382 vs. 364 person years for an exposure ≥ 3 months and 364 vs. 344 person years for an exposure ≥6 months, respectively) (Table 17).

Table 17: Exposure by drug duration; ASaT population

	Pembrolizumab (N=509)		Placebo (N=502)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	509	393	502	378
>= 1 m	489	392	489	378
>= 3 m	434	382	414	364
>= 6 m	387	364	363	344
>= 12 m	66	70	72	75
Each subject is counted once on each applicable duration category row. Duration of exposure is the time from the first dose date to the last dose date. Database Cutoff Date: 02OCT2017				

Adverse events

Refer to Sections B2.10 and B3.3.

Secondary outcomes

As previously described in Section 2.3.1, secondary endpoint data is not available for IA1. [redacted]

B.2.7 Subgroup analysis

RFS was similar across all protocol-specified subgroups evaluated and was consistent with the overall ITT population. Improved RFS was observed across all subgroups including AJCC cancer stages, including stage IIIA (>1mm lymph node metastasis), PD-L1 positive and negative subgroups, and he BRAF mutation positive and negative subgroups (Appendix E Table 1).

B.2.8 Meta-analysis

Not applicable, as only one trial reported outcomes for pembrolizumab, please see section B2.9.

B.2.9 Indirect and mixed treatment comparisons

Direct evidence comparing pembrolizumab versus placebo is available (KEYNOTE-054); therefore, indirect treatment comparison was not required/ conducted.

B 2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Not applicable

B.2.10 Adverse reactions

The cost utility model reported in section B.3.3 reports specific grade 3-5 AE data occurring at an incidence of >5% among the APaT population reported from KEYNOTE-054. The following data are reported as per the KEYNOTE-054 CSR and are supported by data tables in Section B.3.3

2.10.1. Evidence of Adverse Events

Summary of Adverse Events

Of the 1,011 patients in the APaT population, 475 patients (93.3%) in the pembrolizumab arm and 453 patients (90.2%) in the placebo arm reported at least 1 adverse event (AE) (Table 18). As expected for the comparison of an active treatment versus placebo, a higher proportion

of patients reported drug-related AEs, Grade 3 to 5 AEs (including those considered to be drug related), SAEs (including those considered to be drug related) and AEs leading to the discontinuation in the pembrolizumab group. However, treatment with pembrolizumab was well tolerated as reflected by the low frequency of AEs leading to treatment discontinuation (13.8%), with the most frequently reported AEs leading to discontinuation (≥1 incidence) in the pembrolizumab group were pneumonitis, colitis and diarrhoea. Overall 12.2% and 1.6% of AEs associated with treatment discontinuation were considered drug-related, as assessed by the investigator, in the pembrolizumab and placebo group respectively (Table 18).

The incidence of the most frequent report AEs was consistent between the two treatment groups, with the exception of a higher proportion of patients treated with the pembrolizumab with hypothyroidism, hyperthyroidism and pruritus, which are adverse drug reactions associated with pembrolizumab. The majority of AEs were Grade 1 or 2 in severity in both treatment groups. A full list of AEs can be found in the company CSR in section 12.1.

Table 18: Adverse event summary; ASaT population

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Subjects in population	509		502	
with one or more adverse events	475	(93.3)	453	(90.2)
with no adverse event	34	(6.7)	49	(9.8)
with drug-related[†] adverse events	396	(77.8)	332	(66.1)
with toxicity grade 3-5 adverse events	158	(31.0)	96	(19.1)
with toxicity grade 3-5 drug-related adverse events	74	(14.5)	17	(3.4)
with serious adverse events	128	(25.1)	82	(16.3)
with serious drug-related adverse events	66	(13.0)	6	(1.2)
who died	1	(0.2)	0	(0.0)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)
discontinued drug due to an adverse event	70	(13.8)	18	(3.6)
discontinued drug due to a drug-related adverse event	62	(12.2)	8	(1.6)
discontinued drug due to a serious adverse event	29	(5.7)	11	(2.2)
discontinued drug due to a serious drug-related adverse event	22	(4.3)	2	(0.4)

[†] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment in Part 1; SAEs were followed 90 days after last dose of study treatment in Part 1.
(Database cutoff date: 02OCT2017).

Drug related AEs

The proportion of patients in the KEYNOTE-054 study who had at least one drug-related AE was 77.8% (Appendix F Table 1). Drug related AEs were more frequently reported in the pembrolizumab group compared with the placebo group. The most frequently reported (incidence >10%) drug-related AEs in the trial was fatigue, diarrhoea, pruritus, hypothyroidism and nausea. The majority of drug-related events were Grade 2 in severity in both treatment groups. Hypothyroidism (14.3% vs. 2.6%), hyperthyroidism (9.6& vs. 0.8%) and pruritus (16.7% vs. 9.8%) were adverse drug reactions associated with pembrolizumab in comparison to placebo, respectively (Appendix F Table 1).

Grade 3-5 AEs

Grade 3-5 AEs were more frequently reported in the pembrolizumab groups (31.0% vs. 19.1% in the placebo group)(Table 18). The most frequently reported Grade 3-5 AEs in both treatment groups were hypertension, diarrhoea, colitis, blood creatinine phosphokinase increase and lipase increase. Of note, the frequencies of Grade 3-5 events of hypertension were consistent across both pembrolizumab and placebo arms, with all events being Grade 3.

Drug Related Grade 3-5 AEs

Drug-related Grade 3 to 5 AEs were more frequently reported in the pembrolizumab group (14.5% compared with 3.4% in the placebo group) (Table 18). The most frequently reported drug related Grade 3 to 5 AEs were colitis and Type 1 diabetes mellitus (≥1% incidence) in the pembrolizumab arm. Colitis and Type 1 diabetes mellitus are adverse reactions associated with pembrolizumab. None of these events were fatal. All other drug-related Grade 3 to 5 AEs were reported in <1% of participating patients.

Serious Adverse Events (SAE)

SAEs were reported in 25.1% of patients treated with pembrolizumab, in comparison to 16.3% of patients treated with placebo (Table 18). The most frequently reported SAE in both treatment groups was basal cell carcinoma (pembrolizumab 3.3% vs. placebo 5.0%) (Appendix F Table 2). In addition SAE in the pembrolizumab arm included squamous cell carcinoma and in patients treated with placebo, included cellulitis and malignant melanoma in-situ (Appendix F Table 2). The frequencies of basal cell carcinoma and squamous cell carcinoma were comparable in the two treatment groups.

Drug related SAEs

Drug related SAEs were reported in 13.0% of patients treated with pembrolizumab and 1.2% of placebo treated patients (Table 18). In the pembrolizumab group, the most commonly reported drug-related SAEs was colitis and pneumonitis (Appendix F Table 3). These SAEs are known adverse drug reactions associated with pembrolizumab treatment and their nature and severity is consistent with the established safety profile for pembrolizumab.

Summary of Deaths

Within the pembrolizumab treatment arm two deaths were reported, and were considered by the investigator to be study drug related (Table 18). One patient died within 90 days after the last administered dose of pembrolizumab of a drug reaction with eosinophilia and systemic symptoms (DRESS). The event occurred 23 days following discontinuation of pembrolizumab and was confounded by initiation of other co-suspect drugs, vemurafenib plus cobimetinib, prior to the onset of the event. This AE was considered to be drug related by the investigator, however follow database lock the investigator changed the causality assessement of the event of DRESS to be unrelated to pembrolizumab and related to vemurafenib and cobimetinib.

The second patient experienced an AE leading to death 90 days after receiving the last dose of pembrolizumab. This patient had an AE of autoimmune myositis involving respiratory muscles. The investigator stated that this event was confounded by metastatic progression of the underlying disease. Myositis is a known adverse drug reaction associated with pembrolizumab.

Adverse events of Special Interest (AEOSI)

There was a higher frequency of Adverse Events of Special Interest (AEOSI) observed the pembrolizumab arm of KEYNOTE-054 vs. placebo (34.0% vs. 7.6%) respectively (Appendix F Table 4 to Table 22). Most AEOSI were Grade 1 or 2 in severity, were manageable with treatment interruption, treatment discontinuation, and/or corticosteroid therapy and therefore consistent in nature with characteristics previously reported for pembrolizumab. Patient receiving pembrolizumab most commonly suffered hypothyroidism, hyperthyroidism, pneumonitis, colitis and thyroiditis. The main difference between the pembrolizumab and placebo group was the increased frequency of hypothyroidism and hyperthyroidism; however, these two events were the most commonly reported events in the placebo group of KEYNOTE-054.

2.10.2 Summary of KEYNOTE-054 Adverse Events

Please refer to Table 17 & Table 18.

2.10.3 Adverse Events Conclusions

The results of KEYNOTE-054 demonstrate a favourable safety and tolerability profile for patients treated with pembrolizumab in the adjuvant setting for completely resected, lymph node positive, stage III melanoma. The safety profile of pembrolizumab in KEYNOTE-054 was found to be generally consistent with the established safety profile of pembrolizumab and no new indication-specific immune-related AEs and no new safety signals were identified. As a result, no changes to the current warnings and precautions section of the SPC and prescribing information specific to this indication are indicated.

B.2.11 Ongoing studies

2.11.1 KEYNOTE-054 (NCT02362594)

Refer to Section B2.3. This study has completed recruitment and its estimated study completion date is July 2025. [redacted]

2.11.2 KEYNOTE-053 (NCT02506153)

KEYNOTE-053 is a Phase III RCT comparing physician/ patient choice of either high dose interferon or ipilimumab to pembrolizumab in patients with high risk resected melanoma. There are three primary objectives of the study: (1) to test whether OS is improved with pembrolizumab compared to a control arm of physician/patient choice of high dose interferon (HDI) or ipilimumab in this patient population, (2) to test whether among patients who are PD-L1 positive OS is improved with pembrolizumab compared to this control arm in this patient population, (3) to test whether RFS is improved with pembrolizumab compared to the control arm in this patient population.

For the purpose of this study, patients with surgically resected Stage III or IV cutaneous or mucosal melanoma were eligible for inclusion. The study seeks to recruit 1,240 eligible patients on the assumption of 1:1 randomisation, 2.5 years of accrual and 2.5 years of follow-up after accrual completes. The primary analysis will be intention to treat with all testing stratified by randomisation stratification factors. The OS endpoint will be assessed at 5 years from the date of initial randomisation. One formal interim analyses of the overall population has been scheduled at approximately 75% of RFS events (402 RFS events calculated across

both arms under the alternative). It is anticipated that accrual will be take less than 2.5 years for this study. KEYNOTE-053 will also collect quality of life data, AE data and undertake pharmacokinetic/ pharmacodynamics evaluation.

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity. This novel mode of action confirmed that pembrolizumab can be used as standard adjuvant treatment regardless of tumour BRAF mutation status, PD-L1 status and AJCC stage III classification. As evident by clinical and safety data presented pembrolizumab offers a durable and well tolerated treatment option for patients considered within this submission.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Patients with lymph node positive, stage III melanoma, having undergone complete resection of their primary tumour and involved lymph nodes remain at significant risk of recurrence within 5 years of diagnosis.[2] However, until recently there have been no significant developments in the treatment of this patient population in current UK clinical practice.[13]

Patients within KEYNOTE-054 are considered broadly representative of those seeking treatment in the UK. The choice of RFS as the primary endpoint of KEYNOTE-054 is based on the fact that RFS is a well-established outcome in melanoma and is an appropriate endpoint to assess the impact and safety profile of pembrolizumab in the adjuvant setting.[25] In a recent meta-analysis of 13 clinical studies (n>5,000 patients) involving adjuvant IFN in stage II-III melanoma, RFS was shown to be a valid surrogate endpoint for OS.[25] For the EORTC 18071 ipilimumab study, a validated model predicted an OS benefit based on RFS.[33] Furthermore, the study predicted that adjuvant studies with an HR ≤0.77 for RFS would demonstrate a treatment benefit on OS. In KEYNOTE-054, the HR for RFS (0.57) is therefore expected to predict an OS benefit.[24] The placebo arm in KEYNOTE-054 performed similarly in regards to the rate of RFS over time to the ipilimumab control arm in CHECKMATE-238, supporting the magnitude of the RFS HR in KEYNOTE-054 of pembrolizumab vs. placebo.[24, 34]

The choice of comparator group is representative of current UK clinical practice, where only a period of observation following surgical resection is recommended by NICE.[22] KEYNOTE-054, a double blinded study provides robust evidence of a statistically significant and clinically meaningful improvement in RFS versus placebo (HR=0.57; 98.4% CI: 0.43 to 0.74; p<0.0001).

The treatment effect was consistent in all subgroups analysed and within the overall population, pembrolizumab decreased the risk of death or recurrence by 43% compared to placebo. The safety profile for pembrolizumab remains unchanged and has been shown to be well tolerated in this treatment setting. The safety profile of pembrolizumab was found to be consistent with the established safety profile of pembrolizumab in the Reference Safety Dataset (RSD). AEs were reported in association with pembrolizumab treatment in KEYNOTE-054 which included nausea, fatigue, diarrhoea, pruritus and hypothyroidism, but were not severe, serious or treatment limiting.

Pembrolizumab has a well-established efficacy and clinical benefit in patients with metastatic melanoma, with demonstrated improvement in OS compared with ipilimumab, and is a standard first line treatment in the UK, for this patient population. KEYNOTE-054 now confirms a statistically significant and clinically meaningful benefit in RFS. It also establishes PD-L1 inhibition as active adjuvant therapy for patients with resected lymph node positive, stage III melanoma regardless of stage, PD-L1 tumour expression of BRAF mutation status and can be used more broadly compared to BRAF-directed targeted therapies.[24]

Pembrolizumab has the potential to lengthen the RFS in patients with lymph node-positive stage III melanoma, whilst remaining well-tolerated amongst patients. This therefore demonstrates a favourable and clinically manageable safety profile, which is as anticipated given the mechanism of action of pembrolizumab. The favourable benefit: risk profile and robust data for pembrolizumab in the adjuvant setting addresses a significant unmet need amongst patients with stage III melanoma at high risk of recurrence. This proposed technology has the potential to improve OS based on RFS data presented in this submission and therefore establishes this therapy as a potential standard of care for patients in this indication.

B 2.13.1 End-of-life criteria

End of life criteria: Not applicable.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was undertaken on 27th February 2018 to identify relevant cost-effectiveness studies from the published literature. No cost-effectiveness studies meeting all the inclusion criteria were identified. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

B.3.2 Economic analysis

No cost-effectiveness study meeting the relevant inclusion criteria to this submission was identified, indicating that a de novo cost-effectiveness model was required to assess the cost-effectiveness of pembrolizumab compared with routine surveillance.

B 3.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with high-risk stage III melanoma following complete resection. This is in line with the expected licensed indication and with the NICE final scope.[35] The patient characteristics were based on the KEYNOTE-054 trial[36] and the KEYNOTE-006 trial, for patients in the advance setting.[37]

Table 19: Baseline characteristics of the population in the cost-effectiveness model

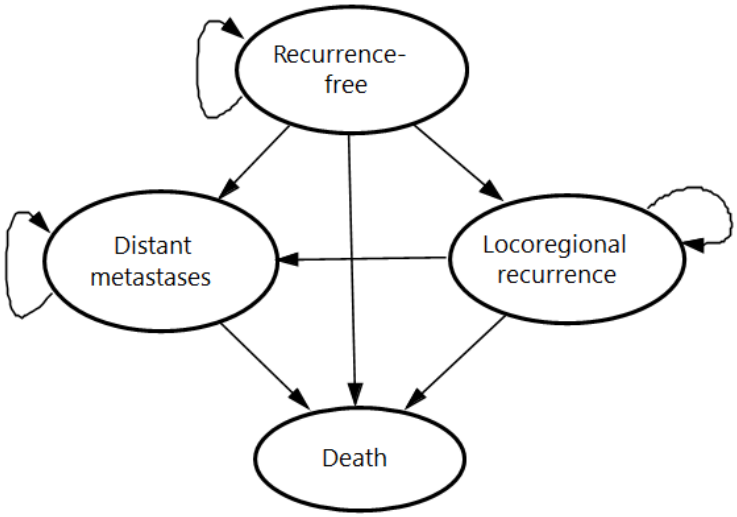
Patient characteristics	Mean Value	Source
Patient Age	53.8	KEYNOTE-054[36]
Proportion male	61.6%	
Percent BRAF+	49.8%	
Average patient weight (kg)	85.1kg (male) 70.6kg (female)	KEYNOTE-006 (European patients)[37]
Weight, standard deviations	15.5 (male) 14.9 (female)	

B 3.2.2 Model structure

A Markov cohort model was developed to estimate health outcomes and costs for pembrolizumab and routine surveillance for patients with high-risk stage III melanoma following complete resection. The state transition diagram in Figure 8 illustrates the health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states; recurrence-free (RF), locoregional recurrence (LR), distant

metastases (DM), and death. This model structure differentiates health states by type of recurrence (either locoregional recurrence or distant metastasis) because the type of recurrence experienced by patients is one of the most significant prognostic factors in stage III melanoma.[38, 39] Therefore, these different types of recurrence are expected to result in different health outcomes and costs.

Figure 8: Model structure



Recurrence-free state

All patients enter the model in the recurrence-free health state, following complete surgical resection of their melanoma. Three transitions are estimated from the recurrence-free state: RF → LR, RF → DM, and RF → death. These transition probabilities were estimated using data from the randomise controlled trial, KEYNOTE-054[36]. Data was used to estimate recurrence-free survival (RFS), with RFS as defined in the KEYNOTE-054 trial; i.e. as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death (whatever the cause), whichever occurred first.[10]

The use of RFS to drive the longer-term projections in the cost-effectiveness model is supported by a recently published study evaluating RFS as a surrogate endpoint. This study concluded that RFS appears to be a valid surrogate end point for OS for adjuvant randomized studies assessing both interferon and a checkpoint inhibitor.[25]

Locoregional recurrence state

Recurrent disease was defined and documented in KEYNOTE-054 as either locoregional or metastatic recurrence (or both). Patients who experienced LR could either remain in this health state or progress to DM and/or death. To estimate transitions starting from the LR health state,

real-world evidence was used, with the same transition probabilities being used for either the pembrolizumab or routine surveillance arm. This assumption is made because data is not yet available from part 2 of the KEYNOTE-054 study, due to lack of follow-up. Given the mechanism of action of pembrolizumab and potential for immune memory, it is considered a conservative assumption to assume no potential for treatment benefit once patients have experienced LR. A proportion of patients with LR are assumed to receive further salvage surgery, as per KEYNOTE-054, which is in keeping with UK clinical practice[17], and all receive continued clinical surveillance. Further details are provided in section 3.5.

Distant metastases state

To estimate the transition from the distant metastases to death state, data from published literature was used. Patients recurring with distant metastatic or advanced disease (from any prior health state) could be eligible for treatment with a targeted therapy or immunotherapy in line with current clinical practice in the metastatic setting. Again it was assumed that, once patients experience distant metastases, there would be no ongoing benefit from adjuvant pembrolizumab for patients. One of the key clinical questions arising from the introduction of adjuvant treatment with pembrolizumab is the role of rechallenge in the advanced setting, where pembrolizumab is the current standard of care. The KEYNOTE-054 trial is expected to answer this question but the data from part 2 of the study are not yet available. In the base case the conservative assumption of no rechallenge is assumed. Therefore, base-case transition probabilities from distant metastases to death differ between treatment arms due to differences in treatments received in the advanced melanoma setting. Alternative assumptions are also explored in the sensitivity analyses.

Death state

Death is an absorbing health state in which no costs or benefits are accrued.

For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period for calculating the cumulative costs and cumulative quality adjusted life years (QALYs) over the modelled time horizon. A lifetime horizon was used in the base case. Costs and QALYs are discounted with an annual rate of 3.5% in line with NICE reference case.[22]

Table 20: Features of economic analyses

	Previous appraisals	Current appraisal	
Factor	Please note, there are no prior technology appraisals conducted in the adjuvant melanoma setting	Chosen values	Justification
Time horizon		46 years	Consistent with NICE reference case
Cycle length		One week	
Half cycle correction		Yes	
Treatment waning effect?		No	Differential treatment benefit is only assumed for patients in the RF health state.
Source of utilities		Utility values collected in KEYNOTE-054 trial	Consistent with NICE reference case
Source of costs		NICE TAs, NHS reference costs, eMit, PSSRU and published literature	Resource use was based on previous HTAs in metastatic melanoma (TA319/357/366)[40-42] clinical input and published literature. Unit costs were taken from recognised national databases

Abbreviations: eMIT - electronic market information tool; HTA – health technology appraisal; PSSRU – personal social services research unit; TA – technology appraisals

B 3.2.3 Intervention technology and comparators

The intervention (i.e. pembrolizumab) was applied in the model as per the anticipated licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]).

It is anticipated that pembrolizumab will be considered for the adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection. The NICE final scope specifies the only relevant comparator is routine surveillance.[35]

Discontinuation rules

The KEYNOTE-054 protocol established that adjuvant treatment should continue until disease recurrence, toxicities leading to discontinuation, physician's decision or 12 months of uninterrupted treatment (whichever occurs first) with pembrolizumab/placebo.

B.3.3 Clinical parameters and variables

B 3.3.1 Modelling Transitions from Recurrence Free Survival

Transition probabilities starting from the recurrence-free state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-054 trial, following the parametric multistate modelling approach described by Williams et al. (2017a & 2017b)[43, 44]. Parametric models were used to estimate the cause-specific hazards of the following transitions over time within the adjuvant pembrolizumab and routine surveillance arms:

Recurrence-free (RF) → Local-recurrence (LR)

RF → Distant metastases (DM)

RF → Death

Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any RFS failure event) is calculated as a function of all three cause-specific hazards.

Estimation of cause-specific hazards for each individual transition

In the base case, cause-specific hazards of each transition in the pembrolizumab and routine surveillance arms were estimated based on parametric models that were separately fitted to data from the pembrolizumab and placebo arms of KEYNOTE-054. In order to fit parametric models to each individual health state transition, standard survival analysis methods were used with one modification to account for competing risks: When analysing time to each specific type of RFS failure, the two competing failure types were treated as censoring events.[45, 46] For example, to model the transition from recurrence-free to distant metastases, patients who experienced a locoregional recurrence or death prior to distant metastases were censored and thus treated as lost to follow-up at the time of the earlier competing event. After these additional censoring criteria were applied to the patient-level time-to-event data for each transition, parametric curve fitting was performed using the survival analysis package flexsurvreg in R software[47], similar to the process for fitting parametric functions for a partitioned survival model.

Six different parametric functions were considered to model transitions from recurrence-free to locoregional recurrence and from recurrence-free to distant metastases in each treatment arm, including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized

gamma distributions. Exponential models were fitted to the transition from recurrence-free to death in each treatment arm due to the small number of direct transitions from recurrence-free to death observed in the KEYNOTE-054 trial (i.e., two in the pembrolizumab arm, one in the placebo arm).[36] Parameter estimates associated with all parametric models are presented in Appendix M

As described below, for each of the two treatment arms, probabilities of each transition from the recurrence-free state were calculated based on all three cause-specific hazard functions. The predicted RFS curve over time in each treatment arm similarly, is estimated based upon all three cause-specific hazard functions. Therefore, in order to select base-case parametric functions, all 36 possible combinations of parametric functions for RF → LR and RF → DM were considered. As mentioned, the cause-specific hazard of RF → death was based on a constant exponential rate in each arm given the small number of events. Criteria for the selection of base-case parametric functions are described below.

Calculation of transition probabilities based on cause-specific hazards

For each individual transition starting from the recurrence-free state, transition probabilities in each weekly cycle were calculated within the model as a function of the cause-specific hazards for all three types of RFS failure. The following calculation steps were performed:

For each cause of RFS failure k (i.e., locoregional recurrence, distant metastases, or death), the average cause-specific hazard within the cycle from week (t-1) to t was calculated as:

$$\overline{h}_k(\mathrm{t}) = H_k(\mathrm{t}) - H_k(\mathrm{t}-1),$$

where $H_k(.)$ is the cause-specific cumulative hazard of cause k (based on the parametric function selected to model cause k).

The average hazard of any RFS failure within the cycle from week (t-1) to t, denoted $\overline{h}_{RFS}(\mathrm{t})$, was calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard was converted into a probability using the formula:

$$1 - e^{-\overline{h}_{RFS}(\mathrm{t})}$$

In each cycle, the relative contribution of each cause k to the overall hazard of RFS failure was derived as:

$$\frac{\overline{h}_k(\mathrm{t})}{\overline{h}_{RFS}(\mathrm{t})}$$

This represents the probability of having had an RFS failure of type k given that an RFS failure has occurred within the cycle.[48] The relative contribution of cause k was then multiplied by the probability of any RFS failure within the cycle to obtain the transition probability corresponding to cause k.

Within each cycle, the transition probability from recurrence-free → death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in the UK were from the Office for National Statistics (ONS).[49]

Selection of base-case parametric functions

As noted by the NICE Decision Support Unit (DSU), assessing model fit is more challenging in the context of multistate models than partitioned survival models, as the target outcomes of interest (e.g., the proportions of individuals experiencing the composite endpoint) are determined by a combination of survival models rather than by a single survival model.[46]

Therefore, to select base-case parametric functions, all 36 possible combinations of parametric functions for recurrence-free → locoregional recurrence and recurrence-free → distant metastases were considered. In accordance with recommendations in the NICE DSU Technical Support Document (TSD) 14 [50], base-case parametric functions were selected such that the same functional form was used to model each health state transition in both the pembrolizumab and routine surveillance arms. The rationale for this approach was to prevent the extrapolated portion of the RFS curves from following drastically different trajectories between the two model arms. Base-case parametric functions were chosen based on the following criteria:

1. **Fit based on mean squared error (MSE):** Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks.[44] MSE was therefore used as an alternative diagnostic test to assess fit of the predicted RFS curve vs. the observed Kaplan-Meier curve during the within-trial period in each treatment arm.

2. **Visual assessment of fit:** Predictions generated by different combinations of parametric functions were also visually verified against the observed data in each treatment arm, following the approach used by William et al. (2017).[44] Specifically, predicted vs. observed cumulative incidence curves were plotted for both recurrence-free → locoregional recurrence and recurrence-free → distant metastases.

3. **Plausibility of long-term extrapolations:** External data from the European Organization for Research and Treatment of Cancer (EORTC) 18071 trial [19] were used to assess the appropriateness of different possible combinations of parametric functions in the routine surveillance arm. EORTC 18071 was a phase 3 trial comparing adjuvant ipilimumab vs. placebo in patients with resected stage III melanoma. Observed RFS, distant metastases free survival (DMFS), and OS at 5 years in the placebo arm of this trial were respectively compared with predicted RFS, DMFS, and OS at 5 years in the routine surveillance arm of the model. (Predicted DMFS is a function of transition probabilities starting from the recurrence-free and locoregional recurrence states, while predicted OS is a function of all transition probabilities in the model.)

Table 21 and Table 22 present the ranking of all 36 combinations of parametric functions from smallest to largest MSE in each treatment arm. Long-term predictions of RFS, DMFS, and OS are also reported for each these different scenarios. Based on these results, the Gompertz function for recurrence-free → locoregional recurrence and generalized gamma function for recurrence-free → distant metastases appeared to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each treatment arm. Among all 36 possible combinations of parametric functions, this combination was ranked fifth in the pembrolizumab arm and first in the routine surveillance arm in terms of MSE. The resulting predictions of RFS, DMFS, and OS at 5 years in the routine surveillance arm (i.e., 27.2%, 30.2%, and 55.2%, respectively) were comparable to reported RFS, DMFS, and OS at 5 years in the placebo arm of the EORTC 18071 trial (i.e., 30.3%, 38.9%, and 54.4%).[19] Although using Gompertz functions for both recurrence-free → locoregional recurrence and recurrence-free → distant metastases resulted in a closer fit with observed data in the pembrolizumab arm, long-term predictions from this scenario were considered higher than plausible.

Table 21: Comparison of different parametric functions used to model RFS in the pembrolizumab arm: Fit with observed data and long-term extrapolations

Rank by MSE	Parametric functions		MSE	Predicted RFS				Predicted DMFS				Predicted OS			
	RF → LR	RF → DM		5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs
1	Gompertz	Gompertz	0.000128	65%	62%	54%	34%	67%	62%	54%	34%	74%	64%	54%	34%
2	Gompertz	Log-normal	0.000144	56%	45%	32%	18%	58%	45%	32%	18%	69%	50%	33%	18%
3	Log-normal	Gompertz	0.000151	58%	50%	37%	22%	63%	52%	38%	22%	72%	56%	40%	23%
4	Generalized gamma	Gompertz	0.000152	58%	50%	37%	22%	63%	52%	38%	22%	72%	56%	39%	23%
5	Gompertz	Generalized gamma	0.000158	54%	42%	27%	14%	56%	42%	27%	14%	68%	48%	29%	15%
6	Log-logistic	Gompertz	0.000174	55%	45%	31%	17%	62%	48%	32%	17%	72%	53%	34%	18%
7	Weibull	Gompertz	0.000180	54%	42%	25%	12%	61%	46%	27%	13%	72%	52%	30%	14%
8	Gompertz	Log-logistic	0.000180	51%	38%	24%	12%	53%	38%	24%	12%	67%	45%	25%	13%
9	Log-normal	Log-normal	0.000187	50%	36%	22%	11%	55%	38%	23%	11%	68%	45%	25%	12%
10	Generalized gamma	Log-normal	0.000188	49%	36%	22%	11%	55%	38%	22%	11%	68%	45%	24%	12%
11	Gompertz	Weibull	0.000195	49%	32%	14%	5%	51%	32%	14%	5%	66%	40%	17%	6%
12	Log-normal	Generalized gamma	0.000210	48%	33%	19%	9%	53%	35%	19%	9%	67%	42%	21%	10%
13	Generalized gamma	Generalized gamma	0.000211	48%	33%	19%	9%	53%	35%	19%	9%	67%	42%	21%	10%
14	Log-logistic	Log-normal	0.000219	47%	33%	18%	9%	53%	35%	19%	9%	68%	43%	21%	10%
15	Weibull	Log-normal	0.000228	46%	30%	15%	6%	53%	34%	16%	7%	68%	42%	19%	7%
16	Log-normal	Log-logistic	0.000241	46%	31%	16%	8%	51%	32%	17%	8%	66%	40%	19%	8%
17	Generalized gamma	Log-logistic	0.000243	46%	30%	16%	8%	51%	32%	17%	8%	66%	40%	19%	8%
18	Log-logistic	Generalized gamma	0.000248	46%	30%	15%	7%	52%	33%	16%	7%	67%	41%	18%	8%
19	Weibull	Generalized gamma	0.000258	45%	28%	13%	5%	51%	31%	14%	5%	67%	40%	16%	6%
20	Log-normal	Weibull	0.000262	44%	26%	10%	3%	48%	27%	10%	3%	65%	36%	13%	4%
21	Generalized gamma	Weibull	0.000263	43%	26%	10%	3%	48%	27%	10%	3%	65%	36%	13%	4%
22	Log-logistic	Log-logistic	0.000285	44%	28%	13%	6%	50%	30%	14%	6%	66%	38%	16%	7%
23	Weibull	Log-logistic	0.000296	43%	26%	11%	4%	49%	29%	12%	5%	66%	37%	14%	5%
24	Log-logistic	Weibull	0.000308	42%	23%	8%	3%	47%	25%	9%	3%	65%	35%	11%	3%
25	Weibull	Weibull	0.000321	41%	22%	7%	2%	47%	24%	7%	2%	65%	34%	10%	3%
26	Exponential	Gompertz	0.000348	45%	25%	8%	2%	56%	33%	10%	2%	70%	43%	13%	3%
27	Gompertz	Exponential	0.000400	40%	18%	3%	0%	41%	18%	3%	0%	61%	28%	5%	1%

28	Exponential	Log-normal	0.000430	38%	18%	4%	1%	49%	24%	6%	1%	66%	35%	8%	2%
29	Exponential	Generalized gamma	0.000486	37%	17%	4%	1%	48%	23%	5%	1%	65%	33%	7%	1%
30	Log-normal	Exponential	0.000513	35%	14%	2%	0%	40%	16%	3%	0%	60%	26%	4%	1%
31	Generalized gamma	Exponential	0.000516	35%	14%	2%	0%	40%	16%	3%	0%	60%	26%	4%	1%
32	Exponential	Log-logistic	0.000549	36%	16%	3%	1%	46%	21%	4%	1%	64%	31%	7%	1%
33	Exponential	Weibull	0.000585	34%	13%	2%	0%	44%	18%	3%	0%	63%	29%	5%	1%
34	Log-logistic	Exponential	0.000594	34%	13%	2%	0%	39%	15%	2%	0%	60%	25%	4%	0%
35	Weibull	Exponential	0.000613	33%	12%	2%	0%	39%	14%	2%	0%	60%	24%	3%	0%
36	Exponential	Exponential	0.001051	27%	7%	0%	0%	37%	11%	1%	0%	59%	21%	2%	0%

Table 22: Comparison of different parametric functions used to model RFS in the routine surveillance arm: Fit with observed data and long-term extrapolations

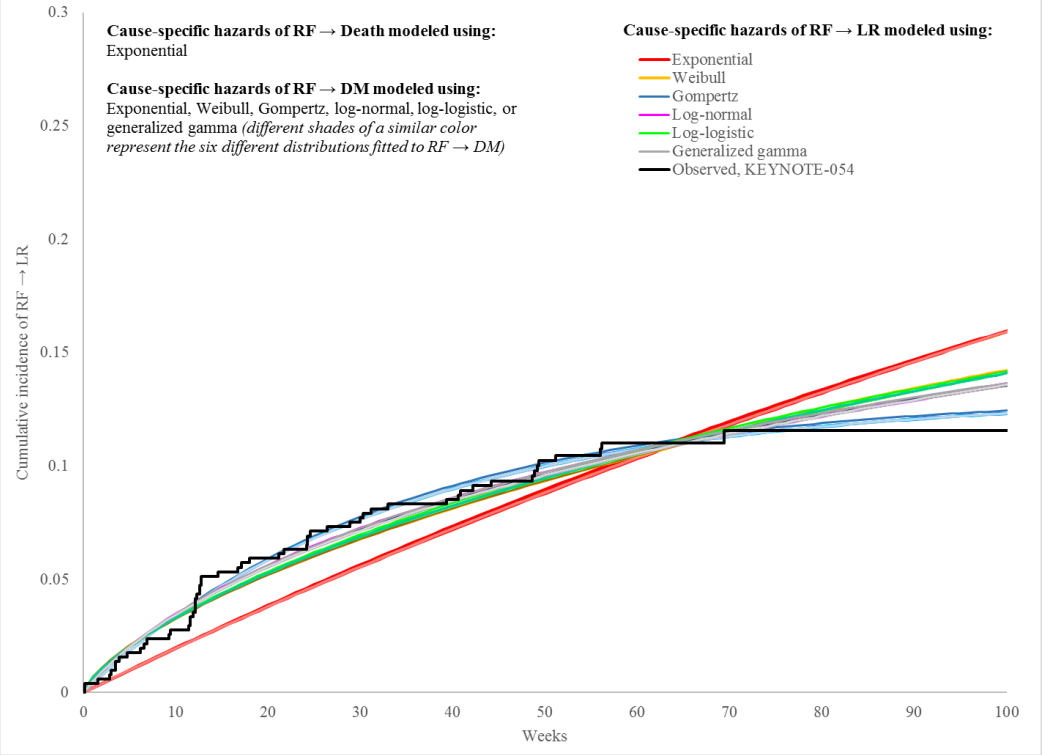
Rank by MSE	Parametric functions		MSE	Predicted RFS				Predicted DMFS				Predicted OS			
	RF → LR	RF → DM		5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs
1	Gompertz	Generalized gamma	0.000273	27%	16%	8%	3%	30%	16%	8%	3%	55%	26%	9%	4%
2	Gompertz	Log-normal	0.000288	27%	15%	7%	3%	30%	16%	7%	3%	55%	26%	9%	3%
3	Gompertz	Gompertz	0.000296	32%	26%	22%	14%	35%	27%	22%	14%	57%	33%	22%	14%
4	Log-normal	Gompertz	0.000341	26%	18%	12%	6%	32%	20%	12%	7%	56%	29%	14%	7%
5	Log-normal	Generalized gamma	0.000349	23%	11%	4%	1%	28%	13%	4%	2%	55%	24%	6%	2%
6	Generalized gamma	Gompertz	0.000356	26%	17%	10%	5%	32%	19%	11%	6%	56%	28%	13%	6%
7	Log-normal	Log-normal	0.000369	22%	10%	4%	1%	28%	12%	4%	1%	54%	23%	6%	2%
8	Generalized gamma	Generalized gamma	0.000375	22%	10%	4%	1%	28%	12%	4%	1%	54%	23%	6%	2%
9	Generalized gamma	Log-normal	0.000395	22%	10%	3%	1%	28%	12%	4%	1%	54%	23%	5%	1%
10	Log-logistic	Gompertz	0.000407	24%	15%	8%	4%	31%	17%	9%	4%	56%	27%	11%	5%
11	Gompertz	Log-logistic	0.000425	23%	12%	5%	2%	26%	12%	5%	2%	53%	22%	7%	3%
12	Weibull	Gompertz	0.000431	22%	12%	4%	1%	31%	15%	5%	1%	56%	26%	7%	2%
13	Log-logistic	Generalized gamma	0.000444	21%	9%	3%	1%	27%	11%	3%	1%	54%	22%	5%	1%
14	Log-logistic	Log-normal	0.000468	20%	9%	3%	1%	27%	11%	3%	1%	54%	22%	4%	1%
15	Weibull	Generalized gamma	0.000469	19%	7%	1%	0%	27%	10%	2%	0%	54%	21%	3%	1%
16	Gompertz	Exponential	0.000473	17%	4%	0%	0%	20%	4%	0%	0%	50%	15%	1%	0%

17	Weibull	Log-normal	0.000493	19%	7%	1%	0%	26%	9%	2%	0%	54%	21%	3%	1%
18	Gompertz	Weibull	0.000506	16%	3%	0%	0%	19%	3%	0%	0%	50%	15%	1%	0%
19	Log-normal	Log-logistic	0.000536	19%	8%	3%	1%	25%	10%	3%	1%	52%	20%	4%	1%
20	Generalized gamma	Log-logistic	0.000571	19%	8%	2%	1%	24%	9%	3%	1%	52%	20%	4%	1%
21	Exponential	Gompertz	0.000587	18%	7%	1%	0%	29%	11%	2%	0%	55%	23%	4%	0%
22	Log-normal	Exponential	0.000595	14%	2%	0%	0%	19%	3%	0%	0%	50%	15%	1%	0%
23	Generalized gamma	Exponential	0.000630	14%	2%	0%	0%	19%	3%	0%	0%	50%	15%	1%	0%
24	Log-normal	Weibull	0.000637	13%	2%	0%	0%	18%	3%	0%	0%	50%	14%	1%	0%
25	Log-logistic	Log-logistic	0.000663	17%	7%	2%	1%	24%	8%	2%	1%	52%	20%	4%	1%
26	Generalized gamma	Weibull	0.000675	13%	2%	0%	0%	18%	3%	0%	0%	50%	14%	1%	0%
27	Weibull	Log-logistic	0.000694	16%	5%	1%	0%	23%	7%	1%	0%	52%	19%	3%	0%
28	Exponential	Generalized gamma	0.000715	16%	4%	0%	0%	25%	7%	1%	0%	54%	19%	2%	0%
29	Log-logistic	Exponential	0.000724	13%	2%	0%	0%	19%	3%	0%	0%	50%	15%	1%	0%
30	Exponential	Log-normal	0.000748	15%	4%	0%	0%	25%	7%	1%	0%	53%	19%	2%	0%
31	Weibull	Exponential	0.000763	12%	2%	0%	0%	18%	3%	0%	0%	50%	14%	1%	0%
32	Log-logistic	Weibull	0.000775	12%	2%	0%	0%	18%	3%	0%	0%	50%	14%	1%	0%
33	Weibull	Weibull	0.000814	11%	1%	0%	0%	18%	3%	0%	0%	50%	14%	1%	0%
34	Exponential	Log-logistic	0.000994	13%	3%	0%	0%	22%	6%	0%	0%	52%	17%	2%	0%
35	Exponential	Exponential	0.001066	10%	1%	0%	0%	18%	3%	0%	0%	50%	14%	1%	0%
36	Exponential	Weibull	0.001138	9%	1%	0%	0%	17%	2%	0%	0%	49%	14%	1%	0%

Visual assessment also supported the choice of Gompertz and generalized gamma as the base-case parametric functions for RF → LR and RF → DM, respectively. For the trial period, Figure 9 and Figure 10 show the observed cumulative incidence of transitions from RF → LR in the pembrolizumab and routine surveillance arms, respectively, alongside the predicted cumulative incidence from the 36 different combinations of parametric functions. In both the pembrolizumab and routine surveillance arms, combinations of parametric functions that used Gompertz for RF → LR appeared to achieve the best fit with the observed cumulative incidence of RF → LR.

Analogous figures are presented for the cumulative incidence of RF → DM in each treatment arm (Figure 11 and Figure 12). In the pembrolizumab arm, combinations of parametric functions that used Gompertz for RF → DM appeared to produce the best fit (as expected based on MSE results), but close fits were also achieved when using log-normal or generalized gamma for RF → DM. In the routine surveillance arm, combinations of parametric functions that used generalized gamma, log-normal, or Gompertz for RF → DM resulted in similarly closest fit with the observed cumulative incidence of RF → DM.

Figure 9: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence in the pembrolizumab arm



In Figure 9 and Figure 10, each colour family represents one of the six different distributions fitted to the cause-specific hazards of RF → LR. The different shades within a particular colour family represent the six different distributions fitted to the cause-specific hazards of RF → DM. As shown, the predicted cumulative incidence of RF → LR was largely driven by the choice of parametric function for the cause-specific hazards of RF → LR, but varied slightly based on the parametric function used to model the cause-specific hazards of RF → DM.

Figure 10: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence in the routine surveillance arm

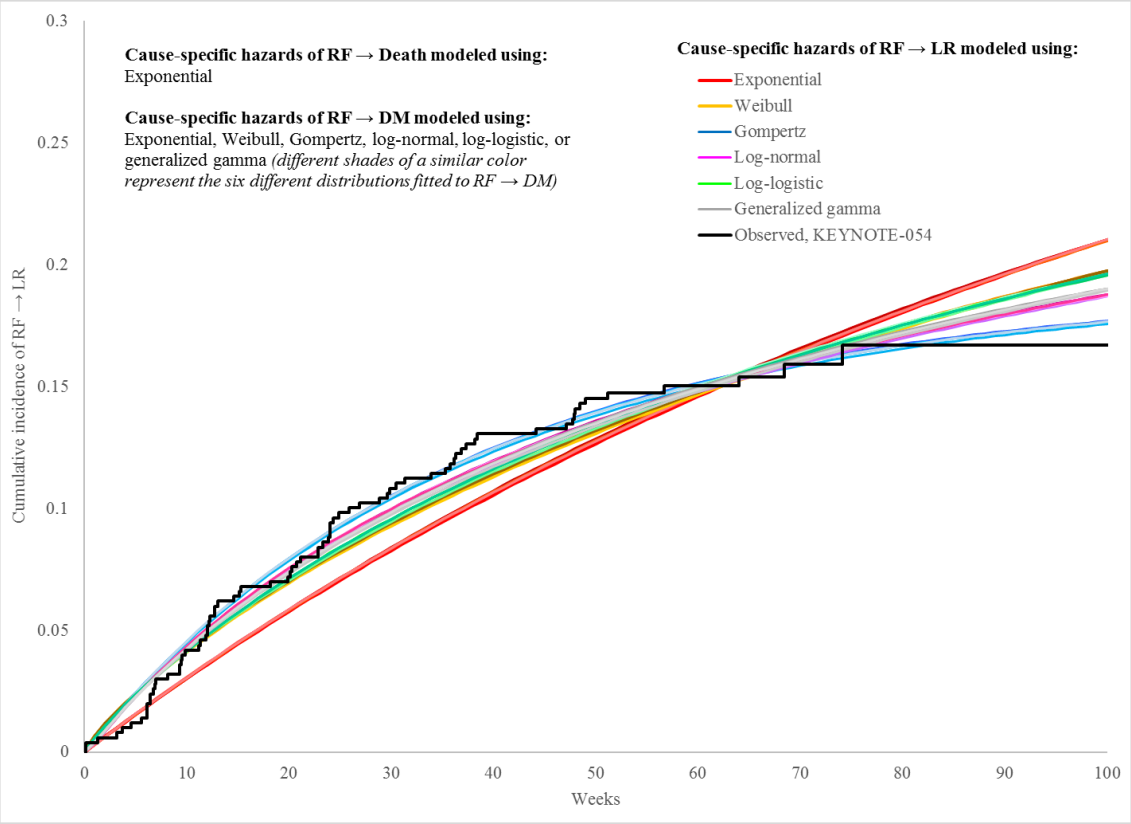


Figure 11: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in the pembrolizumab arm

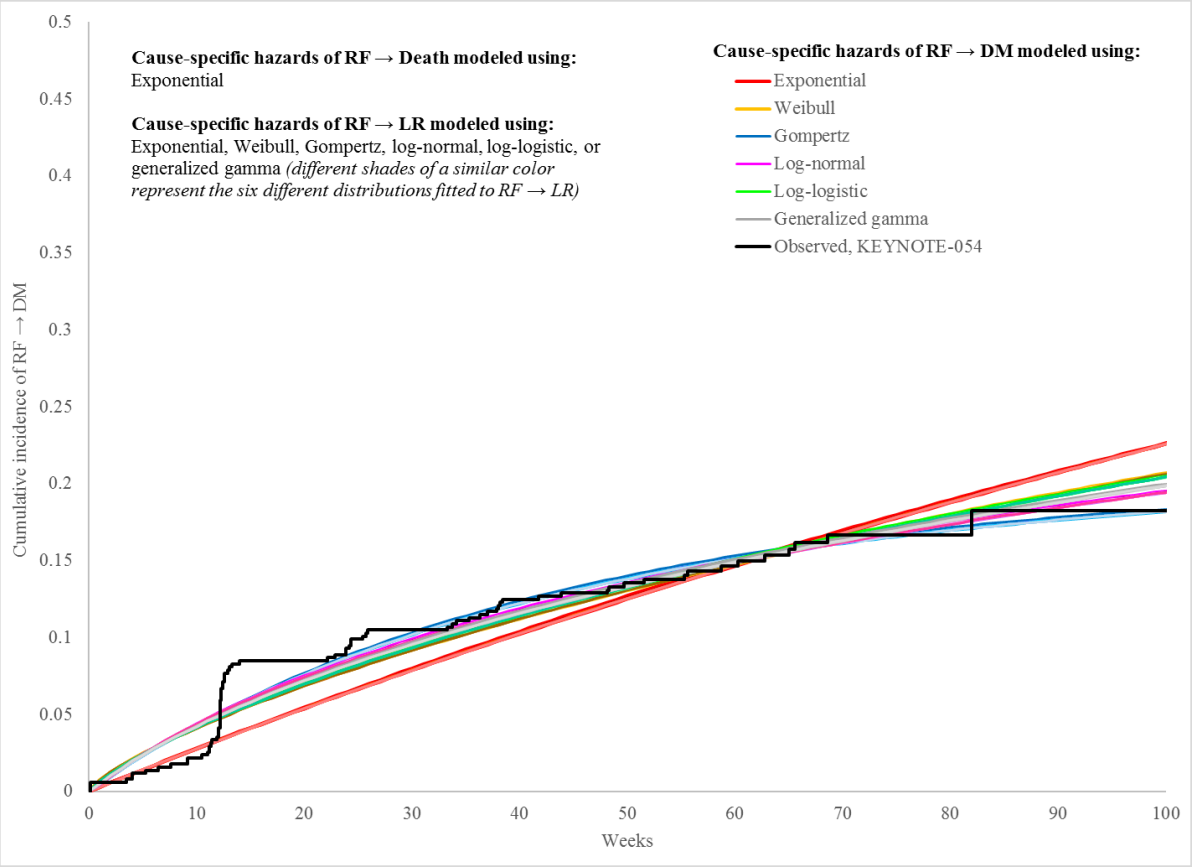
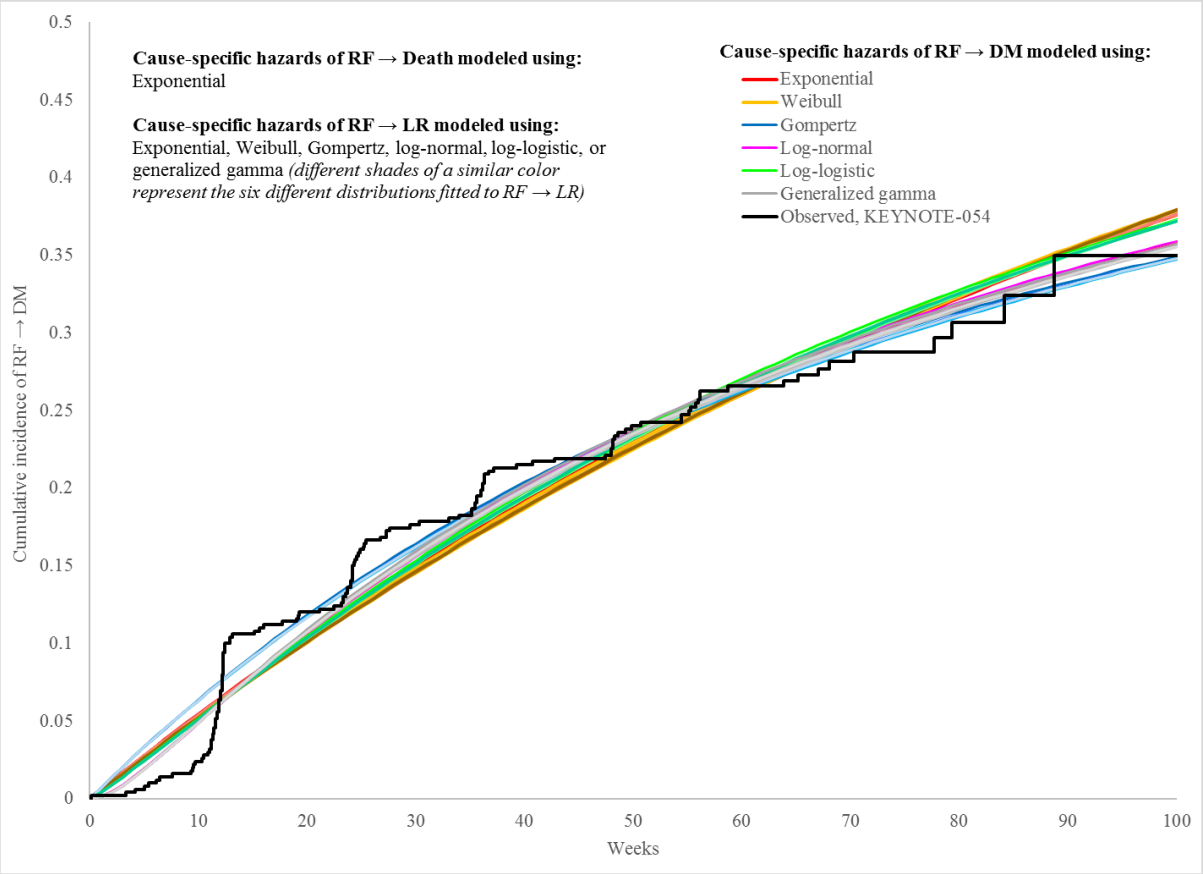


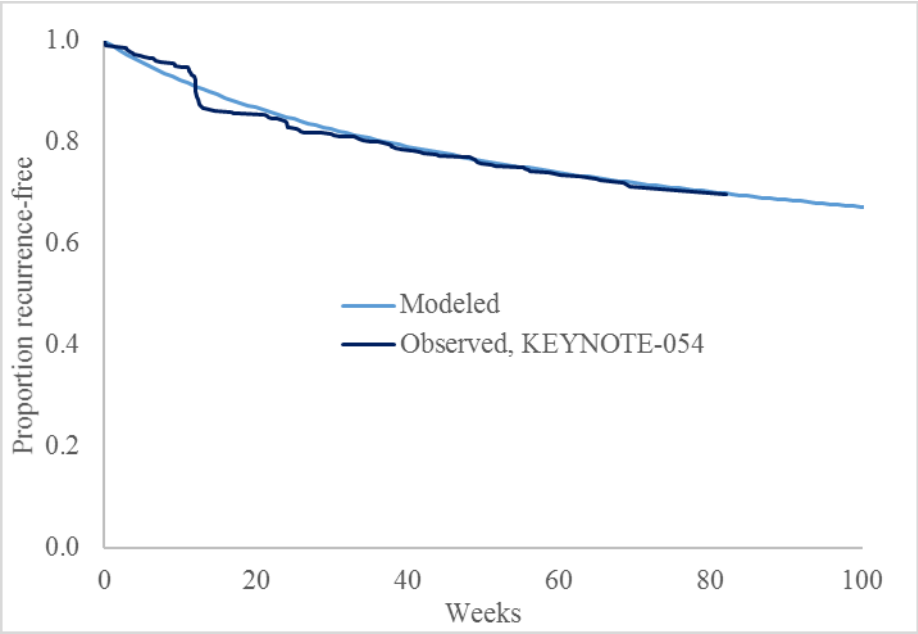
Figure 12: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in the routine surveillance arm



The base-case analysis therefore modelled the cause-specific hazards in each treatment arm using: Gompertz for recurrence-free → locoregional recurrence; generalized gamma for recurrence-free → distant metastases; and exponential for recurrence-free → death. Resulting predictions of RFS during the trial period and over the entire modelled time horizon are presented in Figure 13 and Figure 14, respectively. In the sensitivity analyses, alternative combinations of parametric functions, from amongst those that were best fitting, are explored.

Figure 13: Validation of predicted vs. observed RFS within the trial period under the base-case parametric distributions

a. Pembrolizumab



b. Routine surveillance

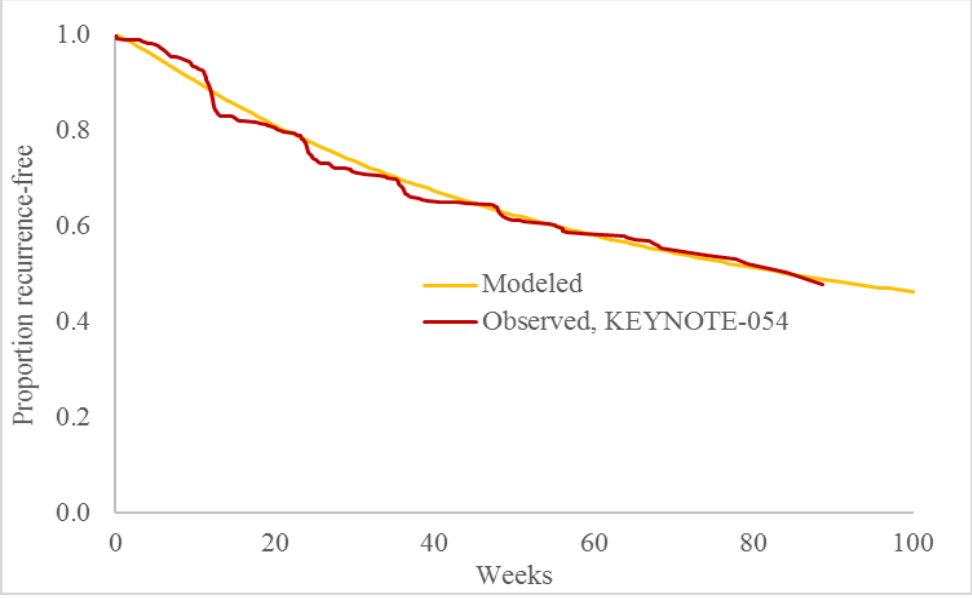
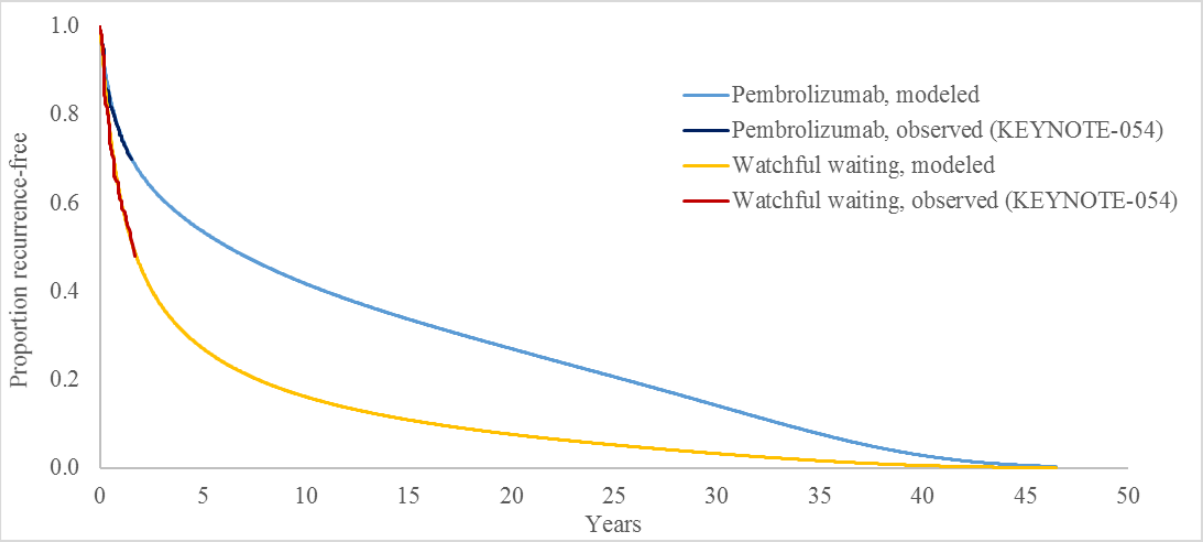


Figure 14: Predicted RFS over the modelled time horizon under the base-case parametric distributions



Alternative scenarios to modelling RFS

In scenario analyses, alternative parametric distributions were tested for the cause-specific hazards of recurrence-free → locoregional recurrence and recurrence-free → distant metastases. These are outlined in Section B.3.8.

Additionally, the following two proportional hazards modelling approaches were tested as scenario analyses to further explore uncertainty in the estimation of transition probabilities starting from the recurrence-free state:

Proportional hazards models with a time-constant treatment effect: Under this alternative approach, cause-specific hazards were estimated based on proportional hazards parametric models (i.e., exponential, Weibull, or Gompertz) that incorporated a time-constant hazard ratio for pembrolizumab vs. routine surveillance.

Proportional hazards (PH) models with a time-varying treatment effect: Under this alternative approach, cause-specific hazards were estimated based on proportional hazards parametric models that incorporated a time-varying hazard ratio for pembrolizumab vs. routine surveillance. Specifically, a different treatment effect is assumed during vs. after the first year following initiation of adjuvant therapy, given the protocol-defined maximum treatment duration of 1 year. Additional potential inflection points in the hazard ratio were not considered due to the limited follow-up time available from KEYNOTE-054 as of the current data cut-off date.

Under both approaches, an exponential model with a time-constant treatment effect was used for transitions from recurrence-free → death given the small number of events observed in KEYNOTE-054.

For each of the above modelling approaches, Table 23 and Table 24 present the ranking of all 9 combinations of proportional hazards parametric functions from smallest to largest MSE in each treatment arm. Long-term predictions of RFS, DMFS, and OS are also reported for each these different combinations. Under both the time-constant and time-varying treatment effect approach, the Weibull function for RF → LR and Gompertz function for RF → DM appeared to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each treatment arm. Among all 9 possible combinations of proportional hazards parametric functions, this combination was ranked second in both treatment arms in terms of MSE. Based on MSE results and visual inspection of Figure 15 - Figure 18, using Gompertz functions for both RF → LR and RF → DM resulted in a closer fit with observed data in both arms; however, long-term predictions from this combination were considered higher than plausible.

Scenario analyses based on these alternative modelling approaches therefore used Weibull for RF → LR, Gompertz for RF → DM, and exponential for RF → death.

Table 23: Comparison of different parametric functions used in scenario analyses to model RFS in the pembrolizumab arm: Fit with observed data and long-term extrapolations

a. Alternative scenario using proportional hazards models with a time-constant treatment effect

Rank by MSE	Parametric functions		MSE	Predicted RFS				Predicted DMFS				Predicted OS			
	RF → LR	RF → DM		5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs
1	Gompertz	Gompertz	0.000212	59%	55%	48%	31%	61%	56%	48%	31%	71%	58%	48%	31%
2	Weibull	Gompertz	0.000341	48%	35%	19%	8%	56%	39%	21%	9%	69%	46%	24%	10%
3	Gompertz	Weibull	0.000363	42%	23%	6%	1%	45%	23%	6%	1%	63%	32%	9%	2%
4	Gompertz	Exponential	0.000467	39%	18%	3%	0%	41%	18%	3%	0%	61%	28%	5%	1%
5	Weibull	Weibull	0.000562	35%	14%	3%	0%	41%	17%	3%	0%	61%	27%	5%	1%
6	Exponential	Gompertz	0.000569	41%	23%	7%	2%	52%	30%	9%	2%	67%	39%	12%	3%
7	Weibull	Exponential	0.000697	32%	11%	1%	0%	38%	13%	2%	0%	60%	24%	3%	0%
8	Exponential	Weibull	0.000870	30%	9%	1%	0%	39%	13%	1%	0%	61%	24%	3%	0%
9	Exponential	Exponential	0.001051	27%	7%	0%	0%	37%	11%	1%	0%	59%	21%	2%	0%

b. Alternative scenario using proportional hazards models with a time-varying treatment effect

Rank by MSE	Parametric functions		MSE	Predicted RFS				Predicted DMFS				Predicted OS			
	RF → LR	RF → DM		5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs
1	Gompertz	Gompertz	0.000186	60%	57%	49%	31%	62%	57%	49%	31%	71%	59%	49%	31%
2	Weibull	Gompertz	0.000232	56%	48%	34%	18%	60%	50%	35%	19%	71%	54%	37%	20%
3	Gompertz	Weibull	0.000249	50%	32%	13%	4%	52%	32%	13%	4%	67%	41%	15%	5%
4	Gompertz	Exponential	0.000286	49%	30%	10%	3%	51%	30%	10%	3%	67%	39%	13%	3%
5	Weibull	Weibull	0.000309	47%	27%	9%	2%	51%	29%	9%	2%	67%	38%	12%	3%
6	Exponential	Gompertz	0.000331	55%	45%	28%	13%	60%	48%	30%	14%	71%	53%	33%	16%
7	Weibull	Exponential	0.000353	46%	25%	7%	2%	50%	27%	8%	2%	66%	36%	10%	2%
8	Exponential	Weibull	0.000436	46%	25%	7%	2%	50%	27%	8%	2%	66%	37%	11%	2%
9	Exponential	Exponential	0.000495	45%	24%	6%	1%	50%	26%	7%	1%	66%	36%	9%	2%

Table 24: Comparison of different parametric functions used in scenario analyses to model RFS in the routine surveillance arm: Fit with observed data and long-term extrapolations

a. Alternative scenario using proportional hazards models with a time-constant treatment effect

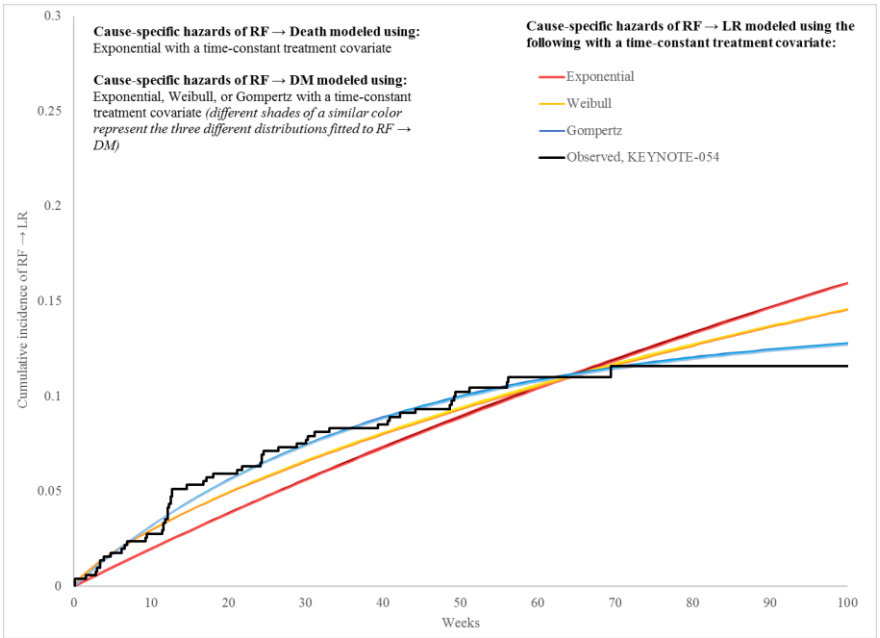
Rank by MSE	Parametric functions		MSE	Predicted RFS				Predicted DMFS				Predicted OS			
	RF → LR	RF → DM		5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs
1	Gompertz	Gompertz	0.000318	39%	36%	31%	20%	42%	36%	31%	20%	60%	41%	31%	20%
2	Weibull	Gompertz	0.000348	28%	17%	7%	3%	36%	21%	9%	3%	58%	31%	11%	4%
3	Gompertz	Weibull	0.000360	20%	6%	1%	0%	23%	6%	1%	0%	52%	18%	2%	0%
4	Exponential	Gompertz	0.000413	22%	9%	1%	0%	33%	14%	2%	0%	57%	26%	5%	1%
5	Gompertz	Exponential	0.000430	17%	4%	0%	0%	20%	4%	0%	0%	50%	15%	1%	0%
6	Weibull	Weibull	0.000557	15%	3%	0%	0%	21%	4%	0%	0%	51%	16%	1%	0%
7	Weibull	Exponential	0.000701	12%	2%	0%	0%	19%	3%	0%	0%	50%	14%	1%	0%
8	Exponential	Weibull	0.000814	12%	2%	0%	0%	20%	3%	0%	0%	51%	15%	1%	0%
9	Exponential	Exponential	0.001066	10%	1%	0%	0%	18%	3%	0%	0%	49%	14%	1%	0%

b. Alternative scenario using proportional hazards models with a time-varying treatment effect

Rank by MSE	Parametric functions		MSE	Predicted RFS				Predicted DMFS				Predicted OS			
	RF → LR	RF → DM		5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs	5 yrs	10 yrs	20 yrs	30 yrs
1	Gompertz	Gompertz	0.000297	37%	34%	29%	19%	40%	35%	29%	19%	60%	40%	30%	19%
2	Weibull	Gompertz	0.000350	27%	16%	6%	2%	35%	20%	7%	2%	58%	30%	10%	3%
3	Gompertz	Weibull	0.000392	19%	5%	0%	0%	22%	6%	0%	0%	51%	17%	1%	0%
4	Exponential	Gompertz	0.000434	22%	9%	1%	0%	33%	14%	2%	0%	57%	26%	4%	1%
5	Gompertz	Exponential	0.000462	17%	4%	0%	0%	20%	4%	0%	0%	50%	15%	1%	0%
6	Weibull	Weibull	0.000618	14%	2%	0%	0%	20%	4%	0%	0%	51%	15%	1%	0%
7	Weibull	Exponential	0.000742	12%	2%	0%	0%	19%	3%	0%	0%	50%	14%	1%	0%
8	Exponential	Weibull	0.000877	11%	1%	0%	0%	20%	3%	0%	0%	50%	15%	1%	0%
9	Exponential	Exponential	0.001066	10%	1%	0%	0%	18%	3%	0%	0%	49%	14%	1%	0%

Figure 15: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence in the pembrolizumab arm: Alternative scenarios using proportional hazards models

a. Alternative scenario using proportional hazards models with a time-constant treatment effect



b. Alternative scenario using proportional hazards models with a time-varying treatment effect

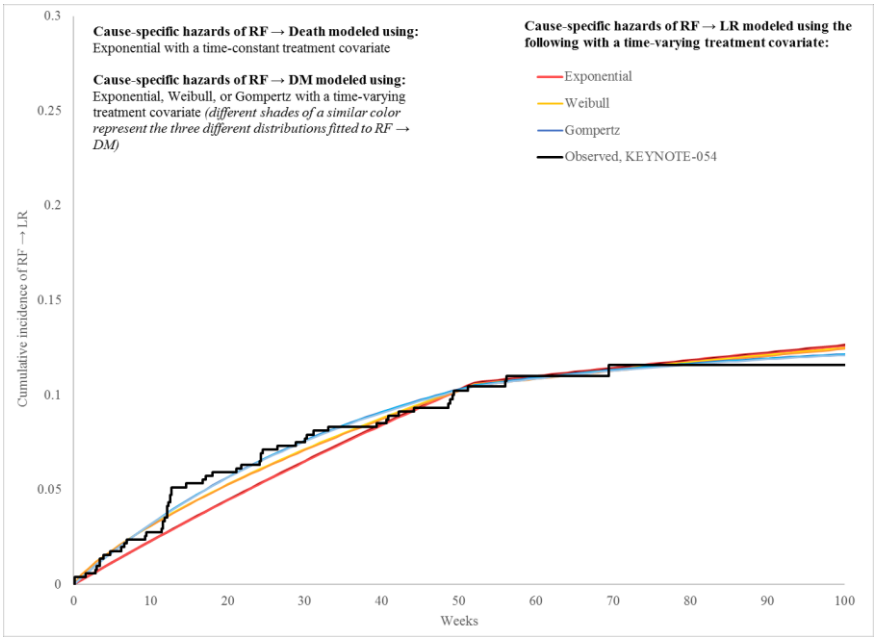
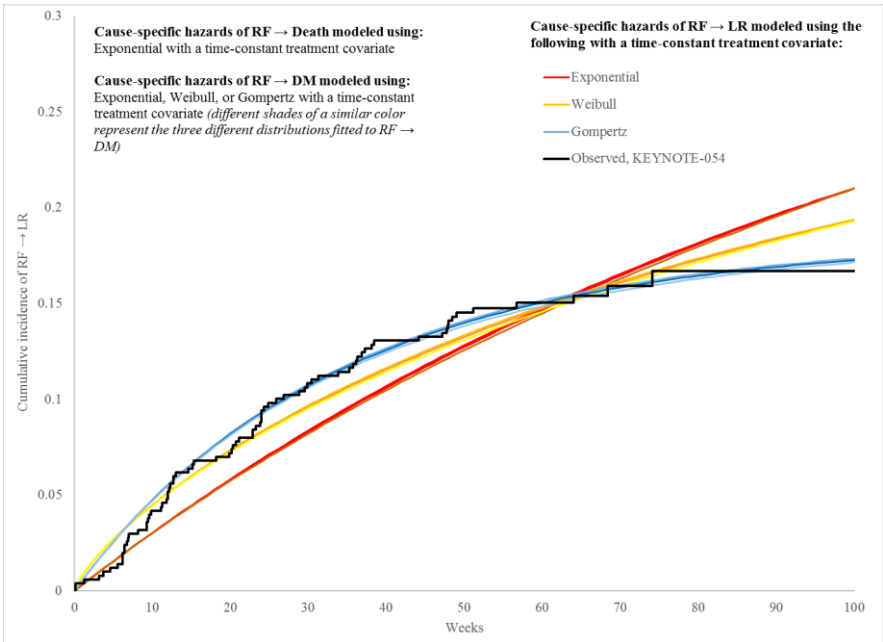


Figure 16: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence in the routine surveillance arm: Alternative scenarios using proportional hazards models

a. Alternative scenario using proportional hazards models with a time-constant treatment effect



b. Alternative scenario using proportional hazards models with a time-varying treatment effect

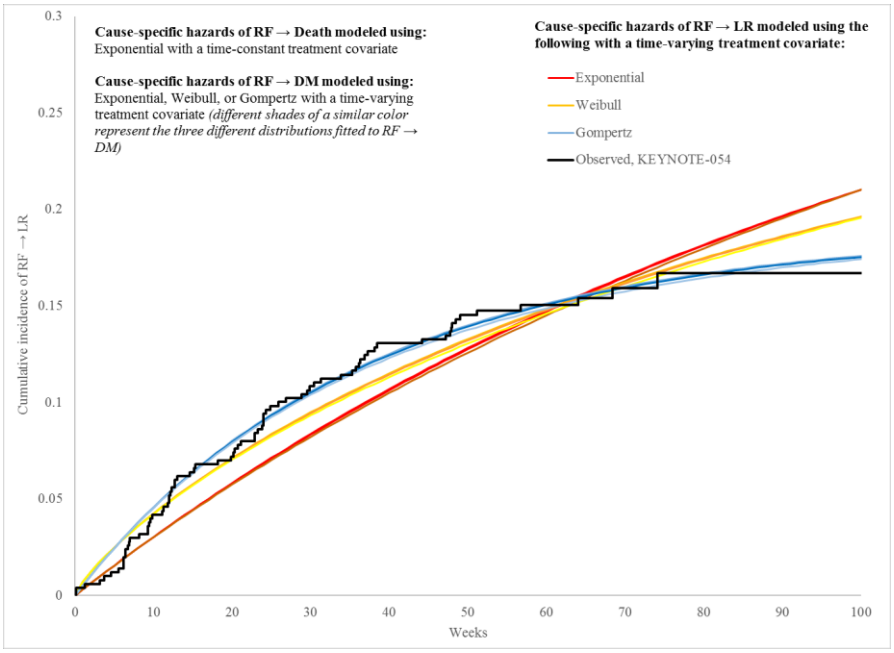
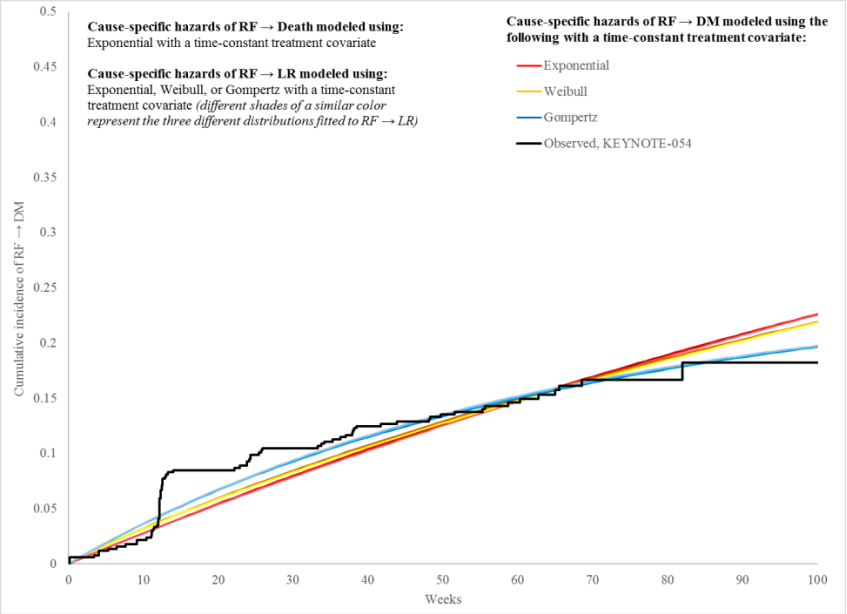


Figure 17: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in the pembrolizumab arm: Alternative scenarios using proportional hazards models

a. Alternative scenario using proportional hazards models with a time-constant treatment effect



b. Alternative scenario using proportional hazards models with a time-varying treatment effect

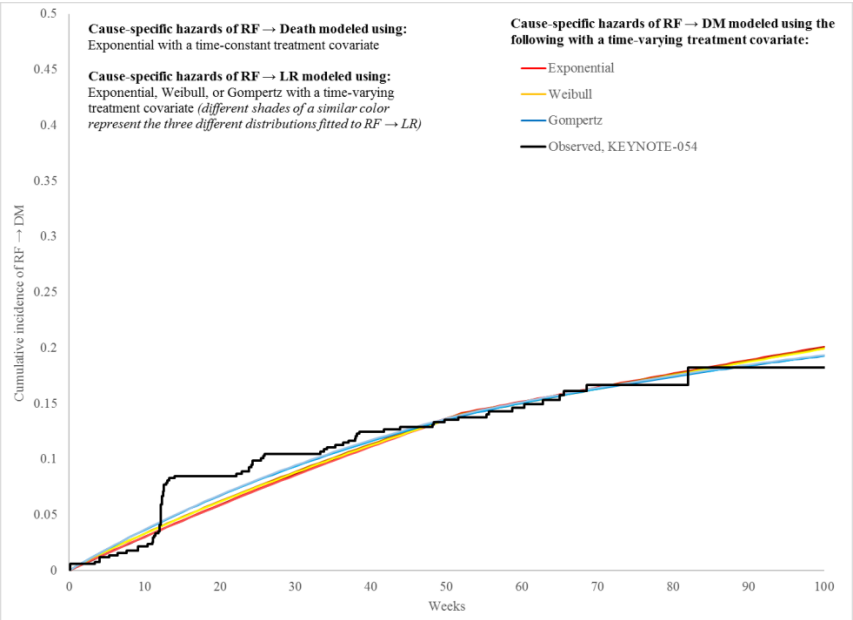
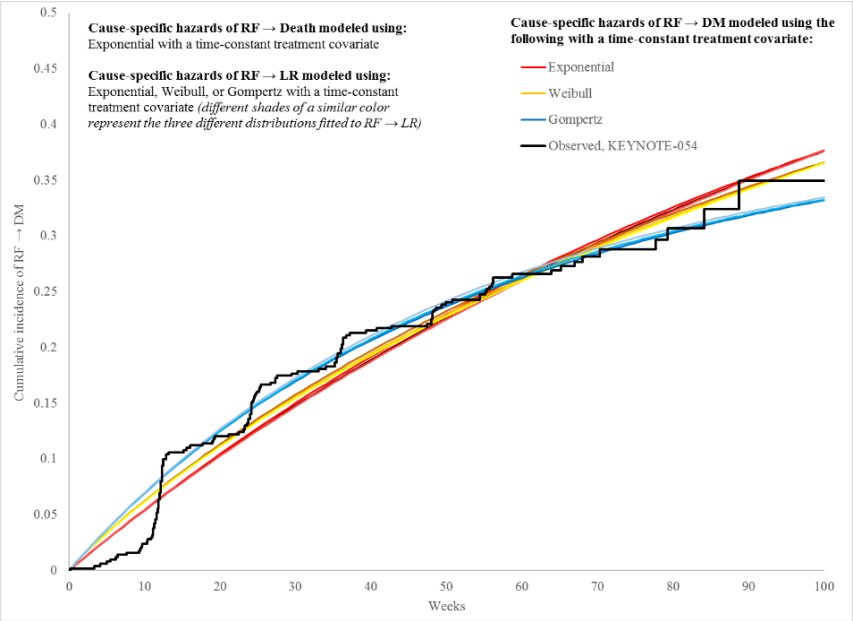


Figure 18: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in the routine surveillance arm: Alternative scenarios using proportional hazards models

a. Alternative scenario using proportional hazards models with a time-constant treatment effect



b. Alternative scenario using proportional hazards models with a time-varying treatment effect

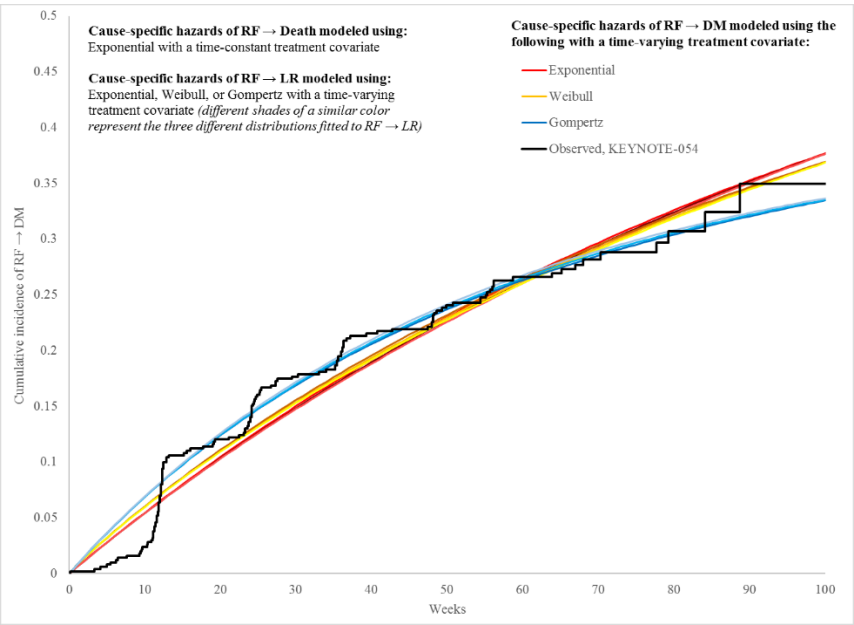


Table 25 provides a summary of the approach used in the base case and the two additional approaches conducted as scenario analysis.

Table 25: Overview of base case modelling approach and scenario analysis for RFS

Estimation approach	Treatment arm	RF→LR	RF→DM	RF→death
Base case	Pembrolizumab	Gompertz	Generalised Gamma	Exponential
Base case	Routine surveillance	Gompertz	Generalised Gamma	Exponential
Scenario 1 – proportional hazards model with time constant treatment effect	Both	Weibull	Gompertz	Exponential
Scenario 2 – proportional hazards model with time varying treatment effect	Both	Weibull	Gompertz	Exponential

Modelling Transitions from Locoregional Recurrence

As highlighted, only data from part 1 of the KEYNOTE-054 trial is available at present. As per the study protocol, as soon as a patient experienced disease recurrence, they entered into part 2 of the study, which has not been analysed as part of this analysis. Therefore, no estimates of the transition probabilities from LR → DM or LR→death could be derived from the available data cut. As an alternative, real-world data were used instead.

The Flatiron database collects real-world clinical data, both structured and unstructured, from electronic health records (EHR) used by cancer care providers in the US. Overall, the database covers 2 million active patients, 2500 clinicians, 265 cancer clinics and 800 unique sites of care. A retrospective database analysis of pre-existing data from the Flatiron database was carried out. EHR data from January 1, 2011 to February 28, 2018 were used and eligible patients included US-based, newly diagnosed adult patients with stage III, IIIA, IIIB or IIIC melanoma after complete resection. All patients considered in the Flatiron database have had their respective patient charts from the EHR available for analysis. This permits a longitudinal view of the data of cancer patients, which can be studied at disease as well as treatment level. Full details of the inclusion / exclusion criteria for this analysis are provided in the analysis report.[51] Eligible patients were followed from the date of locoregional recurrence to distant metastasis, death, the last date of data availability, or February 28, 2018, whichever occurred earliest. An analysis of comparability between patients in KEYNOTE-054 and the Flatiron study has also been conducted and is presented in Appendix L. A fully overview of the analysis is provided in the analysis report.[51]

In the absence of available data from KEYNOTE-054, the transition probability from LR → DM was assumed to be equivalent between the adjuvant pembrolizumab and routine surveillance

arms, and the cause-specific hazard of this transition was estimated. An exponential parametric function was fitted to observed data on time to DM from the time of entry into the LR state. Patients without this transition were censored at the end of follow-up. Within the study sample in the Flatiron data, no direct transitions from LR → death were observed; therefore, there were no censorings due to competing risk events in the sample.

Because no direct transitions from LR → death were observed in the Flatiron sample, the cause-specific hazard for this transition was approximated based on the exponential model of RF → death in the pembrolizumab arm of KEYNOTE-054. Within each cycle, the transition probability from LR → death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality[52], given the age and gender distribution of the cohort by that cycle. It should be noted that patients with LR will still be at higher risk of death than those in RFS because of the higher likelihood of developing DM and the higher associated mortality risk for DM.

Modelling Transitions from Distant Metastases

In each adjuvant treatment arm, the transition probability from DM to death is calculated based on the distribution of first-line treatments for advanced melanoma received in that arm. First-line treatment options were assumed to include the following, based on the set of regimens approved by NICE for the treatment of advanced melanoma and as used in clinical practice: pembrolizumab, ipilimumab, nivolumab, nivolumab plus ipilimumab, vemurafenib, dabrafenib, and dabrafenib plus trametinib.[53] Second-line therapies for advanced melanoma are included in each adjuvant treatment arm but only with respect to their cost. Survival within the distant metastases state was assumed to depend on the choice of first-line therapy.

Estimation of mean survival by first-line treatment for advanced melanoma

For each advanced melanoma treatment option, exponential models of overall survival (OS) and progression-free survival (PFS) were estimated as follows. To estimate pembrolizumab in the advanced melanoma setting, exponential curves were fitted to the individual patient data (IPD) for OS and PFS for pembrolizumab 10mg/kg 3-weekly from the KEYNOTE-006 trial.[54] KEYNOTE-006 was a multicenter, randomised, open-label phase III trial among ipilimumab-naïve unresectable or advanced melanoma patients. The exponential parametric models for PFS and OS are provided in Appendix L, as are the resulting curves.

To estimate outcomes for the other advanced treatment regimens, hazard ratios (HRs) for OS and PFS vs. pembrolizumab were each obtained from a network meta-analysis (NMA) of trials

conducted in advanced melanoma.[55] For ipilimumab, nivolumab, and nivolumab plus ipilimumab, HRs were based on NMA results for the first-line BRAF wildtype population. For vemurafenib, dabrafenib, and dabrefenib plus trametinib, HRs were based on NMA 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. This assumption was made because the treatment effects in subgroup analyses in KEYNOTE 006 were consistent in BRAF wildtype and BRAF mutant positive populations[54]. Further detail is provided in the associated technical report.[55]

Table 26: HRs of OS and PFS failure with other treatment regimens vs. pembrolizumab in the advanced melanoma setting

Advanced regimen	HR of death vs. pembrolizumab		HR of progression or death vs. pembrolizumab		Expected survival in distant metastases state (weeks)	
	HR	*SE of ln(HR)*	*HR*	*SE of ln(HR)*	*OS*	*PFS*
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SE - standard error

Estimation of the hazard rate of death from distant metastases by adjuvant treatment arm

In each adjuvant treatment arm, the hazard rate of DM → death was assumed to depend on the distribution of first-line treatments received for advanced melanoma. The role of rechallenge with pembrolizumab (or another agent targeting the PD-1/PD-L1 pathway) in the advanced setting, following adjuvant therapy, is currently an area of clinical uncertainty. Therefore a number of potential assumptions have been explored.

For patients in each arm, the exponential hazard rate of death from distant metastases was calculated based on: the market shares of different first-line advanced treatments in each adjuvant treatment arm; and the expected survival associated with each advanced treatment regimen.

Specifically, expected OS (in weeks) in each treatment arm was calculated as a weighted average of expected OS associated with different first-line treatments for advanced

melanoma, weighted by their current market shares in the first-line advanced setting[56]. For patients receiving routine surveillance, no further adjustments are made to the distribution of treatments used. For the adjuvant pembrolizumab arm however, the assumption of no further treatment with a PD-1 inhibitor was made, and explored in the sensitivity analysis. The market share for these regimens in the advanced setting 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 + trametinib) cannot exceed the proportion of patients who were BRAF+ in KEYNOTE-054 (i.e., 49.8%)[10]. Table 40 details the distribution of treatments used in the first-line advanced setting in the base case and sensitivity analysis.

PFS is estimated using the same methodology. The ratio of mean PFS to mean OS was then estimated for each adjuvant treatment arm and is used to calculate utility values and weekly disease management costs (see Section B.3.4 and B.3.5) in the DM health state.

Table 27: Hazards of death from distant metastases by adjuvant treatment arm, base case and sensitivity analysis

Adjuvant regimen	**Expected survival in distant metastases state (weeks):** *Weighted average based on first-line advanced treatment market shares*			**Distant metastases → death**: *Exponential hazard rate based on expected OS*
	OS	*PFS*	*Ratio of PFS to OS*	
Base case with no rechallenge				
Pembrolizumab	119	70	0.59	0.0084
Routine surveillance	153	83	0.55	0.0065
Sensitivity analysis with rechallenge				
Pembrolizumab	168	61	0.36	0.0060
Routine surveillance	n/a	n/a	n/a	n/a

In the rechallenge sensitivity analysis, patients in the adjuvant pembrolizumab arm were assumed to be eligible for rechallenge with pembrolizumab if they transition from recurrence-free to distant metastases at least 18 months after adjuvant treatment initiation. Among these patients, the exponential hazard rate of death from DM was based on the efficacy of pembrolizumab in the KEYNOTE-006 trial (see Appendix L). A further scenario was provided whereby patients in the pembrolizumab arm receive treatment in the advanced setting at the

same distribution as routine surveillance (i.e. the current distribution seen from market share data).

B 3.3.2 Overview of health state transitions considered in the economic model

As a summary, an overview of the approaches used to estimate transitions between health states is provided below. The scenario and sensitivity analyses, used to explore the uncertainty in these parameter estimations, are also outlined. The results are presented in Section B.3.8.

Table 28:Summary of health state transitions considered in the economic model

Transition(s)	Estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
RF → LR RF → DM RF → Death[1]	Based on a parametric multistate modelling approach in which different parametric functions were fitted to each of the three individual transitions starting from RF, accounting for competing risks In the base case, separate parametric models were fitted for each treatment arm of KEYNOTE-054	Patient-level data from KEYNOTE-054 Life tables for England & Wales (2014-2016) - *for transitions to death*	Alternative combinations of parametric distributions Proportional hazards parametric models with a time-constant treatment effect Proportional hazards parametric models with a time-varying treatment effect
LR → DM LR → Death[1]	Transition probabilities starting from LR were assumed to be equivalent between pembrolizumab and routine surveillance An exponential model of LR → DM was fitted using real-world patient-level data from the Flatiron database Because no direct transitions from LR → Death were observed in the Flatiron sample, transition was modelled based on the exponential rate of RF → Death in the pembrolizumab arm of KEYNOTE-054	Patient-level data from the Flatiron database Patient-level data from KEYNOTE-054 Life tables for England & Wales (2014-2016) - *for transitions to death*	Exponential rates of each transition varied +/- 10%
DM → Death[1]	In each adjuvant treatment arm, the transition probability from DM to death was assumed to depend on the distributions of first-line treatments received for advanced melanoma	IPD from KEYNOTE-006 Network meta-analysis comparing treatments for advanced melanoma	Alternative assumptions about subsequent treatments in each model arm (rechallenge scenario) Exponential rates of OS and PFS failure with treatments for advanced

		Life tables for England & Wales (2014-2016)	melanoma varied +/- 10%

[1] Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from national life tables given the age and gender distribution of the cohort at each cycle.

B 3.3.3 Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, with a few exceptions:

- Diarrhoea Grade 2 is also included to be consistent with previous NICE appraisals. [57-59]

- Febrile neutropaenia of any grade is also included as clinicians have suggested that this AE has significant impact on quality of life and costs. The inclusion of febrile neutropaenia is also consistent with recent NICE appraisal[57, 58]. There were however, no cases of febrile neutropenia in either arm of the KEYNOTE-054 trial.

- Pneumonitis of any grade is also included based on Evidence Review Group (ERG) feedback in previous appraisals of immunotherapy agents[60, 61].

The incidence of AEs for pembrolizumab and placebo (representing 'routine surveillance') was taken from the KEYNOTE-054 trial.[10] It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since the 5% cut-off is based on AEs of any grade. Mean durations of the included AEs were also collected from KEYNOTE-054 using pooled data from both treatment arms, and were used within the model to estimate the duration of the disutility impact from each AE. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 29.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm. This was consistent with the methods used in previous oncology submissions and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.[57, 58]

Table 29: Incidence and duration of modelled AEs, as reported in the KEYNOTE-054 trial

Type of AE	Grades	Pembrolizumab n = 509	Routine surveillance (based on placebo arm of KEYNOTE-054) n = 502	Mean duration of AE (weeks)
		n (%)	n (%)	
Diarrhoea	2+	27 (5.30%)	15 (2.99%)	1.8
Hyperthyroidism	3+	1 (0.20%)	0 (0.00%)	4.1
Pneumonitis	1+	15 (2.95%)	3 (0.60%)	20.3
Fatigue	3+	4 (0.79%)	2 (0.40%)	15.2
Alanine aminotransferase increased	3+	3 (0.59%)	1 (0.20%)	1.6
Arthralgia	3+	3 (0.59%)	0 (0.00%)	3.6
Headache	3+	0 (0.00%)	1 (0.20%)	0.7
Dyspnoea	3+	1 (0.20%)	0 (0.00%)	4.7

B.3.4 Measurement and valuation of health effects

B 3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality-of-life (HRQoL) was evaluated in the KEYNOTE-054 trial using the EuroQoL EQ-5D-3L. The estimated utilities were used in the cost-effectiveness model as the evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case. [62]

In KEYNOTE-054, the EQ-5D questionnaire was administered at baseline and every 12 weeks for the first two years and every 6 months up to 4th year (included), regardless of recurrence/progression or treatment status.

The EQ-5D analysis below is based on the all subjects as treated (ASaT) population. UK preference-based scores were used for all patients analysed from the KEYNOTE-054 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique.[63]

B 3.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-054 EQ-5D data.

B 3.4.3 Health-related quality-of-life studies

Please see Appendix H for a list of the studies identified through the SLR.

B 3.4.4 Adverse reactions

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, as outlined in section B.3.3.

Disutility associated with AEs was modelled in each treatment arm as a function of: the frequencies of included AEs; the mean durations of these AEs per affected patient in KEYNOTE-054; and the estimated disutility associated with an active grade 3+ AE based on a repeated measures regression analysis of EQ-5D-3L data from this trial. AE-related disutility was applied as a one-time QALY decrement in the first model cycle. Disutility of grade 3+ AEs represents the estimated difference in utility associated with recurrence-free (without toxicity) vs. recurrence-free (during any grade 3+ AE) in KEYNOTE-054. This is estimated using a separate model for visits at the recurrence-free state only, whereby the presence of AEs at each visit (Grade 3+ AE, other AEs, or no AE) was included as the independent variable to estimate the utility decrements due to AEs during recurrence-free state. The results of this model are presented in Table 30.

Table 30: Mixed effects regression model of utility in the recurrence-free state as a function of AE status, based on KEYNOTE-054 data

Covariate	Estimate	Standard error	P value
Intercept	0.8695	0.00792	0.0001
AE status at visit			
During grade 3+ AE	-0.05457	0.0170	0.0013
During other grade AE	-0.02986	0.0077	0.0001
Without toxicity	(reference)	-	-

B 3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

EQ-5D-3L utility values collected in the relevant patient population to the decision problem are preferred for decision-making.[62] Base-case utility values for the recurrence-free, locoregional recurrence, and pre-progression distant metastases states were therefore derived through repeated measures regression analyses of patient-level EQ-5D-3L data from the KEYNOTE-054 trial (Table 31). At each visit where health state was assessed, the corresponding EQ-5D-3L score were used to characterise utility. Visits with missing EQ-5D-3L scores were excluded. A linear mixed-effects model was used to account for the correlation among repeated measures within an individual. The dependent variable of the model was EQ-5D-3L

utility score, and the independent variable was a categorical variable for health state. The patient effects were included as a random effect to account for unobserved, patient-specific characteristics and multiple observations per patient. The standard error and 95% confidence intervals of utility scores associated with each health state were summarized and used in the sensitivity analysis of the model. Full results and information on compliance of EQ-5D are provided in Appendix N.

Recurrence free and locoregional recurrence

The linear mixed-effects model described above was used to estimate values in the RF and LR states from the KEYNOTE-054 trial data. These were used in the base case and are presented in Table 31. A scenario analysis was also incorporated which uses the utility values estimated in Middleton (2017)[64], one of the studies identified in the systematic literature review. The study looked at societal preferences for health states associated with adjuvant melanoma in respondents in the UK and Australia, from which the UK values have been taken.

Distant metastases

In each treatment arm, utility in the distant metastases state is estimated from two separate utility estimates. The first is a utility value for pre-progression in the metastatic setting, which is estimated based on the utility data collected in KEYNOTE-054 (using the linear mixed model outline above). The second utility value is for post-progression in the metastatic setting, which is taken from a study of societal preference values for advanced melanoma health states in the United Kingdom and Australia (Beusterien et al. 2009).[65] This was a cross-sectional study conducted in the UK (n=63) and Australia (n=77) that used the standard gamble method to elicit utilities for health states of advanced melanoma from members of the general public. There are limitations with the use of this study as the utility values are taken from a healthy population, without melanoma, which is not aligned with the NICE reference case. However values were not available from KEYNOTE-054 (due to study follow-up) or KEYNOTE-006 (due to questionnaires ceasing at the 30 day post-study safety visit), which would have been preferable. This study was used in a previous appraisal of an immunotherapy as a first line treatment for advanced melanoma (TA384).[66] This utility for post-progression distant metastases was therefore used instead of an estimate from KEYNOTE-054, based on the expectation that the available follow-up in KEYNOTE-054 would be too limited to capture average utility over the entire post-progression disease course until death.

A single utility value is then calculated as a weighted average of the two utility values, based on the proportion of time spent progression-free within the distant metastases state. This estimate of mean time spent in PFS vs. OS within the distant metastases state was calculated based on market shares of first-line treatment regimens in the advanced setting (Table 40), and the estimated efficacy of those treatment regimens in the advanced setting (see Section B.3.3). The base case assumes different market shares of advanced treatment regimens within both treatment arms, resulting in a different ratio of PFS: OS for pembrolizumab vs. routine surveillance and different distant metastases utility values.

A scenario is included which uses only the data from KEYNOTE-054 to estimate utility in the distant metastases health state. A scenario is also provided in which all utilities (including for the distant metastases health state) are based on Middleton et al. (2017).[64]

The utility of the death state was set to zero.

Table 31: Health state utilities in the base case and scenario analyses

Health state	Base case: Utilities based on KEYNOTE-054 and Beusterien et al. (2009)		Sensitvity analysis: Utilities based on KEYNOTE-054 for all states		Sensitivity analysis: Utilities based on Middleton et al. (2017) for all states	
	Value	SE	Value	SE	Value	SE
Recurrence-free (without toxicity)	0.870	(0.008)	0.870	(0.008)	0.840	Not reported
Locoregional recurrence	0.830	(0.016)	0.830	(0.016)	0.703	Not reported
Distant metastases (pre-progression)	0.775	(0.012)	0.775	(0.012)		Not reported
Distant metastases (post-progression)	0.590	(0.020)			0.581	Not reported

Age-related disutility

A constant value for HRQoL is applied in each cycle. A study by Ara and Brazier[67] suggests that average utility decreases with age. Therefore, age-adjusted utilities are applied in the model to account for the impact of age on utilities. The selected algorithm from Ara et al. (presented in Table 32) is a linear regression model predicting mean utility values for individuals within the general population, conditional on age (in years), age-squared, and gender. This approach has been used rather than the use of age-related disutilities from Kind

et al. (1999)[68] as was done in TA357 and TA366[41, 42]. This change has been made based on feedback received from the ERG in a previous pembrolizumab appraisal.[69]

Table 32. Regression coefficients used for the estimation of age-related disutility from Ara et al.[67]

Parameter	Coefficient
Age (years)	-0.0002587
Age^2	-0.0000332
Male	0.0212126
Intercept	0.9508566

The utility values chosen for the cost-effectiveness model are presented in Table 33. The applicability of the selected health state utility values was not assessed by clinical experts as these values were consistent with the NICE reference case.

Table 33: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	Utility value: standard error	Reference in submission (section and page number)	Justification
Recurrence-free (without toxicity)	0.870	0.008	B.3.4 [page 85]	KEYNOTE-054[10]
Locoregional recurrence	0.830	0.016	B.3.4 [page 85]	
Distant metastases (pre-progression)	0.775	0.012	B.3.4 [page 85]	
Distant metastases (post-progression)	0.581	Not reported	B.3.4 [page 85]	Beusterien (2009)[65]
Diarrhea	-0.05457	0.0170	B.3.4 [page 83]	KEYNOTE-054[10]
Hyperthyroidism	-0.05457	0.0170	B.3.4 [page 83]	
Pneumonitis	-0.05457	0.0170	B.3.4 [page 83]	
Fatigue	-0.05457	0.0170	B.3.4 [page 83]	
Alanine aminotransferase increased	-0.05457	0.0170	B.3.4 [page 83]	
Arthralgia	-0.05457	0.0170	B.3.4 [page 83]	
Headache	-0.05457	0.0170	B.3.4 [page 83]	
Dyspnoea	-0.05457	0.0170	B.3.4 [page 83]	

B.3.5 Cost and healthcare resource use identification, measurement and valuation

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below.

B 3.5.1 Intervention and comparators' costs and resource use

Pembrolizumab

As per the anticipated licence, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion every three weeks (Q3W).The list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. A commercial access agreement is currently in

place for patients with NSCLC and melanoma. The discount of [redacted] equates to a reduced price per cycle of [redacted]

In the base case, the relative dose intensity (as reflected in the pembrolizumab arm of KEYNOTE-054) was applied to the drug acquisition cost per infusion of adjuvant pembrolizumab to account for any delays or interruptions in administration (e.g., due to AEs).

Table 34: Dosing schedule and relative dose intensity for adjuvant pembrolizumab

Adjuvant regimen	Dosing schedule description	Relative dose intensity (%)
Pembrolizumab	200 mg IV Q3W, up to 1 year	99.7%

Abbreviations: IV, intravenous; Q3W, once every 3 weeks.

Routine surveillance

There is no drug cost associated with routine surveillance, the current standard of care. The cost of regular clinical follow-up and imaging is outlined under the health state cost.

Treatment duration

The proportion of patients remaining on adjuvant pembrolizumab at each scheduled infusion was based on the observed Kaplan-Meier curve for time to treatment discontinuation in the KEYNOTE-054 trial (Figure 19). In the trial, patients randomized to adjuvant pembrolizumab received treatment for up to 1 year or until completion of 18 doses (i.e., the number of scheduled doses over 1 year). Based on this maximum duration, there was sufficient follow-up data from the trial to directly observe time on adjuvant treatment, without the need for extrapolation.

As illustrated in Figure 19, a small percentage of patients in the pembrolizumab arm of KEYNOTE-054 remained on adjuvant therapy beyond 1 year, as the 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 Kaplan-Meier curve beyond the scheduled 1-year treatment period (represented by the dashed line in Figure 19).

Figure 19: Observed Kaplan-Meier curve for time to treatment discontinuation in the pembrolizumab arm of KEYNOTE-054

Administration costs

The time required for the administration of pembrolizumab is 30 minutes. The Health Resource Groups (HRG) code for SB12Z: *Deliver Simple Parenteral Chemotherapy at First Attendance* based on the latest NHS reference costs 2016-2017 was used to reflect administration costs for pembrolizumab. The assumption had been previously agreed with NHS England for previous NICE submissions for pembrolizumab (TA357, TA366).[41, 42]

Table 35: Administration costs of pembrolizumab

Treatment	Type of administration required	NHS reference cost code	Setting	Cost
Pembrolizumab	Simple Chemotherapy, at First Attendance	SB12Z	Total HRG	£241.07

Clinical monitoring of patients being treated with pembrolizumab as adjuvant therapy is expected to follow current clinical practice for routine surveillance. These are outlined under the recurrence-free health state below.

B 3.5.2 Health-state unit costs and resource use

A comprehensive literature search was conducted on 27th February 2018, to identify costs and resource use in the treatment of and on-going management of stage III melanoma. Please see Appendix I for details of the search strategy and literature identified.

There are four health states included in the model – recurrence-free (RF), locoregional recurrence (LR), distant metastases (DM) and death (see section 3.2). Health state resource use and costs for all health states are outlined below.

Recurrence-free health state

In current clinical practice, patients defined as high risk following complete surgical resection will be followed-up accordingly to the surveillance policy outlined in a position paper from UK clinicians.[16] This includes both clinical review and imaging at set intervals. No blood tests are recommended for routine surveillance. Clinical follow-up is assumed to be alternated between the medical oncologist, plastic surgeon and dermatologist, based on clinical expert input.

Table 36:Routine surveillance resource use

Resource use element	RF – monthly resource use up to year 3		RF – monthly resource use, years 3-5		RF – monthly resource use, years 5-10	
	% Patients	Resource use	% Patients	Resource use	% Patients	Resource use
Salvage surgery	N/A	N/A	N/A	N/A	N/A	N/A
Outpatient visits						
Medical oncologist	100%	0.17	100%	0.08	100%	0.04
Radiation oncologist	0%	0.00	0%	0.00	0%	0.00
General practitioner	0%	0.00	0%	0.00	0%	0.00
Plastic surgeon	100%	0.08	100%	0.04	100%	0.02
Dermatologist	100%	0.08	100%	0.04	0%	0.02
Cancer specialist nurse	0%	0.00	0%	0.00	0%	0.00
Radiologic exams						
CT scan of abdomen/pelvis	100%	0.17	100%	0.08	0%	0.00
CT scan of chest	100%	0.17	100%	0.08	0%	0.00
MRI of brain	100%	0.17	100%	0.08	0%	0.00
Totals (£)[1]:	22.44 per week		11.22 per week		2.03 per week	
Source	Larkin et al. (2013)[16]					

Abbreviations: CT- computed tomography; MRI – magnetic resonance imaging

The per cycle cost was estimated using the relevant NHS 2016/17 reference costs for each resource use components (see Table 37). Patients without disease recurrence at ten years were assumed to be discharged from follow-up.

Table 37: NHS Reference costs 2016/17 for routine surveillance

Item	Source	Unit Price
Clinical follow-up		
Medical oncologist visit	NHS Reference Costs 2016/17 - Total outpatient attendances for 370 (medical oncology)	161.13
Dermatologist visit	NHS Reference Costs 2016/17 - Total outpatient attendances for 330 (dermatology)	£103.05
Plastic surgeon visit	NHS Reference Costs 2016/17 - Total outpatient attendances for 160 (plastic surgery)	£100.72
Imaging		
MRI of brain	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z	£142.32
CT scan of abdomen/pelvis	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z	£90.04
CT scan of chest		£90.04

Locoregional recurrence health state

The main treatment of choice for patients with locoregional recurrence will be further surgery, with curative intent. The proportion of patients receiving surgery and the types of surgery performed are taken directly from the KEYNOTE-054 trial and outlined in Table 38. The cost of surgery is taken from the corresponding HRG codes from the NHS Reference Costs 2016/17.

Table 38: Frequency of salvage surgery for patients with local recurrence and distant metastases

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	

Table 39: NHS Reference costs 2016/17 for surgical procedures

Item	Source	Unit Price
In-transit metastases resection or other surgery	JC41Z - Major Skin Procedures (Total HRG)	£2,911.01
Lymphadenectomy	WH54A - Procedures on the Lymphatic System with CC Score 1+ (Total HRG)	£2,076.83 (weighted average)
	WH54B - Procedures on the Lymphatic System with CC Score 0 (Total HRG)	
Skin lesion resection	JC42A - Intermediate skin procedures (Total HRG)	£497.41

This cost is applied as a one-off cost upon entry into the health state. Patients are presumed to receive continued follow-up as outlined in the UK consensus paper.[16]

Distant metastases health state

Systemic treatment for advanced melanoma

The primary treatment option for patients with confirmed advanced disease (i.e. unresectable or metastatic disease) will be 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.[14]

All patients progressing to distant metastases are assumed to be 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.[56]. As highlighted in section 3.2, the use of re-challenge with pembrolizumab after adjuvant therapy is currently an area of clinical uncertainty. 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. This assumption is explored in a sensitivity analysis. Market share distributions for both scenarios are provided in Table 40.

Table 40: Market share assumptions for advanced melanoma therapies (no rechallenge and with no challenge) – first line metastatic

Regimens in advanced setting	Market shares (%)				Reference
	Pembrolizumab (no rechallenge)	Routine surveillance	Pembrolizumab (rechallenge)	Routine surveillance	
Pembrolizumab	0.0%	27.8%	27.8%	27.8%	Ipsos Oncology Monitor, 2018 [56]
Ipilimumab	50.2%	5.8%	5.8%	5.8%	
Nivolumab	0.0%	3.8%	3.8%	3.8%	
Nivolumab plus 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 plus trametinib	33.4%	29.5%	29.5%	29.5%	

B 3.5.3 Advanced melanoma treatment costs and resource use

The dosing schedule for each drug is based on the administration assessed and approved by NICE; summarised in Table 41.

Table 41: Drug doses for each treatment given in the advanced setting

Treatment	Dose	Frequency	Source
Pembrolizumab	2mg/kg	3-weekly	NICE TA366
Nivolumab	3mg/kg	2-weekly	NICE TA384
Nivolumab plus ipilimumab	First four doses Nivolumab: 1mg/kg Ipilimumab: 3mg/kg	3-weekly	NICE TA400
	After four doses Nivolumab: 3mg/kg	2-weekly	
Vemurafenib	960mg	Twice-daily	NICE TA269
Dabrafenib	150mg	Twice-daily	NICE TA321
Dabrafenib plus trametinib	Dabrafenib: 150mg Trametinib: 2mg	Twice-daily Daily	NICE TA394

The unit costs per pack or vial of treatment administered (for pembrolizumab, nivolumab, ipilimumab, vemurafenib, trametinib and dabrafenib) are presented in Table 42. A patient access scheme (PAS) is in place for all therapies. The level of discount presented in the schemes is unknown (except for pembrolizumab) therefore the list prices are presented in Table 42.

Table 42. Treatment cost per pack/vial

Treatment	Pack size/vial volume	Cost per pack/vial	Source
Pembrolizumab	100mg vial 50mg vial	£2,630 £1,315	MIMS 2018: 100mg MIMS 2018: 50mg
Nivolumab	100mg vial 40mg vial	£1097 £439	MIMS 2018: 10mg/ml, 10-ml vial MIMS 2018: 10mg/ml, 4-ml vial
Ipilimumab	5mg/ml vial concentration 10ml (50mg) vial 40ml (200mg) vial	 £3,750 £15,000	 MIMS 2018: 5mg/ml, 10-ml vial MIMS 2018: 5mg/ml, 40-ml vial
Vemurafenib	240mg 56-tab pack	£1,750	MIMS 2018: 240mg 56-tab pack
Dabrafenib	50 mg, 28-cap pack 75 mg, 28-cap pack	£933.33 £1,400	MIMS 2018: 50 mg, 28-cap pack MIMS 2018: 75 mg, 28-cap pack
Trametinib	2mg tablet, 30-tab pack 2mg tablet, 30-tab pack	£4,800 £1,120	MIMS 2018: 2 mg, 30-tab pack MIMS 2018: 2 mg, 7-tab pack

Abbreviations: MIMS – monthly index of medical specialities; mg- milligram; ml - millilitre

To estimate drug cost, the number of vials required per infusion was calculated based on log-normal distributions of male and female patient weight, using the means and standard

deviations reported for European patients in the KEYNOTE-006 trial (see Table 19). This approach calculated the proportion of patients requiring different number of vials based on the estimated percentage of patients who fall into the corresponding weight interval. This calculation is an accurate method of accounting for drug wastage which has been used in prior NICE submissions in the advanced melanoma setting (TA366).[41] As a scenario analysis, the assumption of vial-sharing was also tested.

Treatment duration

Durations of first-line treatment regimens for advanced melanoma were modelled using the exponential rates of PFS failure (as described in section B.3.3) to approximate treatment discontinuation rates. Some regimens or components of regimens were subject to a maximum treatment duration based on the dosing schedules recommended by NICE[53] (Table 43). Dose intensity was assumed to be 100 percent.

Table 43. Treatment duration and dose intensity for treatments in advanced setting

Treatment	Drug component (for combination therapies)	Exponential rate of discontinuation[2]	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 plus trametinib	Dabrafenib (in combination)	0.008	No maximum	100%
	Trametinib (in combination)		No maximum	

Abbreviations: n/a – not applicable; ToT – time on treatment

Treatment administration

Drug administration costs are assumed as outlined in Table 44. Per infusion costs are applied for pembrolizumab, nivolumab and ipilimumab. For the oral agents (vemurafenib, dabrafenib and trametinib) the administration cost "Deliver exclusively Oral Chemotherapy" was applied to the first cycle only. Subsequent doses were assumed to be taken orally at home. Pharmacy costs, to dispense and check a prescription every 28 days, were taken into account in the calculation of the administration costs. An average of 12 minutes of pharmacist time for dispensing each oral medicine was accounted for and applied to the hourly cost of a pharmacist time. This approach is consistent with that used in TA366.[41] The cost of a pharmacist time was derived from the PSSRU 2017.[70]

Table 44. Drug and administration costs used in the model per treatment cycle

Treatment	Type of Administration Required	Unit Cost
Pembrolizumab	Simple Chemotherapy	£241.07
Nivolumab	Simple Chemotherapy	£241.07
Ipilimumab	Complex chemotherapy	£299.68
Vemurafenib	First 28-day cycle: Oral chemotherapy	£170.75

Dabrafenib	Subsequent 28-day cycles: Pharmacy cost	£9.00
Trametinib		

Table 45: NHS reference costs and PSSRU costs – administration of treatments

Type	Source	Unit Price
Deliver simple parenteral chemotherapy at first	NHS Reference Costs 16/17 SB12Z- Total HRG	£241.07
Deliver more complex Parenteral Chemotherapy at first attendance	NHS Reference Costs 16/17 SB13Z – Total HRG	£299.68
Deliver exclusively oral chemotherapy	NHS Reference Costs 16/17 SB11Z- Total HRG	£170.75
Single complete metabolic panel	NHS Reference Costs 2016/17 DAPS04	£1.13
Cost of one hour of pharmacist time	PSSRU (2017); Hospital based scientific and professional staff – Band 6 (Pharmacist)	£45

Key: NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Subsequent therapies in the advanced setting

In line with current treatment practice, a proportion of patients are assumed to receive second-line treatment in the advanced setting. Similarly to the first-line setting, in the adjuvant pembrolizumab arm, the market share of second-line pembrolizumab in the advanced setting was assumed to be 0%. Market shares for the remaining advanced treatment regimens were proportionately increased, subject to the constraint that the total market share of BRAF inhibitors cannot exceed the proportion of patients who were BRAF positive in KEYNOTE-054. No other assumptions regarding treatment sequencing and re-challenge are made for simplicity. The distribution of treatments used in the second-line setting in presented in Table 46. In both adjuvant treatment arms, a proportion of patients were assumed to receive no active second-line treatment due to death, deterioration of performance status or patients and clinician choice after the first-line regimen. Data from the IPSOS market research indicates that the proportion of first line patients going on to receive second line treatment is 32.6%.[56] This figure is supported by the NICE submission for ipilimumab for previously treated unresectable malignant melanoma, which puts the figure at 21% (TA319).[40] The proportion of patients receiving no active treatment is therefore assumed to be 67.4%.

Table 46. Market share assumptions for advanced melanoma therapies – second line metastatic

Regimens in advanced setting	Market shares (%)		Reference
	Pembrolizumab	Routine surveillance	
Pembrolizumab	0.0%	13.3%	Ipsos Oncology Monitor, 2018
Ipilimumab	20.4%	4.5%	
Nivolumab	0.0%	5.2%	
Nivolumab + ipilimumab	0.0%	2.4%	
Vemurafenib	4.4%	2.6%	
Dabrafenib	0.0%	0.0%	
Dabrafenib + trametinib	7.8%	4.6%	
No active treatment	67.4%	67.4%	

Mean time on treatment was assumed to be 21 weeks for all second-line regimens (except ipilimumab as monotherapy or in combination which was capped at the maximum duration of 12 weeks, as per the SmPC[71]). The mean duration of 21 weeks is consistent with the NICE submission for pembrolizumab in ipilimumab-naive patients (TA366)[41], which assumed a fixed duration of 7 cycles at an interval of Q3W for best supportive care. This assumption is also in line with the NICE submission for pembrolizumab in patients previously treated with ipilimumab (TA357)[42], which considered a mean treatment duration of 6.86 cycles (20.57 weeks) based on mean PFS in the pembrolizumab arm of the KEYNOTE-002 trial.[72] Drug and drug administration costs associated with second-line advanced regimens are applied as a one-time cost at the time of entering the distant metastases state. The drug costs, dosing requirements and administration costs used are all the same as those reported for first-line treatment in advanced setting. These are summarised in Table 41 to Table 42 and Table 44 to Table 45.

Best supportive care

It is assumed that, once patients stop first or second line systemic treatment in the advanced setting, all patients would receive supportive care. Therefore, the cost of supportive care was included for patients who enter the distant metastases health state. Data for the components of supportive care are taken from a previous appraisal for pembrolizumab in the advanced setting (TA366)[41], which were initially used in the ipilimumab first-line appraisal (TA319)[40] and taken from the MELODY study. An overview of supportive care components, their frequencies and costs are provided in Table 47 . All resource use costs are taken from the NHS reference costs 2016/17, PSSRU 2017 and the most recent version of MIMS.

Table 47. Detailed frequencies of resource use in the distant metastases state

[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 48. Unit costs of health care resources in the distant metastases state

Resource use element	Unit cost (£)	Sources
Salvage surgery		
Surgical resection	2,911.01	NHS Reference Costs 2016/17 - Total HRG activity for JC41Z (major skin procedures)
Lymphadenectomy	2,076.83	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for WH54A and WH54B
Skin lesion resection	497.41	NHS Reference Costs 2016/17 - Total HRG activity for JC42A (intermediate skin procedures)
Outpatient visits		
Medical oncologist	161.13	NHS Reference Costs 2016/17 - Total outpatient attendances for 370 (medical oncology)
Radiation oncologist	130.85	NHS Reference Costs 2016/17 - Total outpatient attendances for 800 (clinical oncology, previously radiotherapy)
General practitioner	32.00	PSSRU 2017 without qual, inc direct care staff
Palliative care, physician outpatient visit	151.12	NHS Reference Costs 2016/17 - Total HRG activity for SD04A (medical specialist palliative care attendance, 19 years and over)
Psychologist	139.33	PSSRU 2017 per hour client contact, assumes 1 hour - see AG calculations
Plastic surgeon	100.72	NHS Reference Costs 2016/17 - Total outpatient attendances for 160 (plastic surgery)
Dermatologist	103.05	NHS Reference Costs 2016/17 - Total outpatient attendances for 330 (dermatology)
Cancer specialist nurse	82.09	NHS Reference Costs 2016/17 - Total HRG activity for N10AF (specialist nursing, cancer related, face to face)
Inpatient stays		
Oncology/general ward	1,816.32	NHS Reference Costs 2016/17 - Elective inpatients for JC42A (intermediate skin disorders aged 13 and over)
Palliative care unit - inpatient	397.65	NHS Reference Costs 2016/17 - Total HRG activity for SD01A (inpatient specialist palliative care, 19 years and over)
Home care		
Palliative care physician	142.00	PSSRU 2017 medical specialist palliative care attendance
Palliative care nurse	102.00	NHS Reference Costs 2016/17 - Community health services for N21AF (specialist nursing, palliative/respite care, adult, face to face)
Home aide visits	98.00	PSSRU 2017- Outpatient Non-medical Specialist Palliative Care Attendance
Laboratory tests		
Complete blood count	3.00	NHS Reference Costs 2016/17 - Directly accessed pathology services for DAPS05 (haematology)
Complete metabolic panel	1.00	NHS Reference Costs 2016/17 - Directly accessed pathology services for DAPS04 (clinical biochemistry)
Lactate dehydrogenase	1.00	NHS Reference Costs 2016/17 - Directly accessed pathology services for DAPS04 (clinical biochemistry)
Radiologic exams		
CT scan of abdomen/pelvis	90.04	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
CT scan of chest	90.04	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z

MRI of brain	142.32	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z
CT scan of brain	90.04	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
PET/CT scan	142.32	NHS Reference Costs 2016/17 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z
Bone scintigraphy	222.12	NHS Reference Costs 2016/17 - Total HRG activity for RN16A (nuclear bone scan of other phases, 19 years and over)
Echography	70.36	NHS Reference Costs 2016/17 - Total HRG activity for RD51A (simple echocardiogram, 19 years and over)
Chest x-ray	125.26	NHS Reference Costs 2016/17 - Total HRG activity for RD30Z (contrast fluoroscopy procedures with duration of less than 20 minutes)
Pain management		
Morphine - Oral	5.45	MIMS (accessed 12/5/2015) 300 ml (10mg/ml), dose: 10-20mg every 4 hours
Morphine - IV	100.95	MIMS (accessed 12/5/2015) 10 x 1 ml (15mg/ml), dose: 10-20mg every 4 hours
Morphine - Transdermal patch	17.60	MIMS (accessed 23/03/2018) BuTrans 5 microgram/hr square patch, 4
NSAIDs (Ibuprofen)	2.24	MIMS (accessed 23/03/2018) 84 x 400mg, dose: 300-400mg 3 times daily
Other: Paracetamol	1.59	MIMS (accessed 23/03/2018) 100 x 500mg, dose: 500mg-1g every 4 hours

B 3.5.4 Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section B.3.3. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in B.3.4.

Adverse event unit costs were mostly derived from TA 319[40], which used the MELODY study as the main data source. Costs were inflated to 2017[73] or updated to the 2016/17 NHS reference costs where appropriate. Table 49 below presents the unit costs per AE that was applied in the cost-effectiveness model.

Table 49. Adverse event unit costs

Type of adverse event	Cost per event (£)			Source for cost
	Original cost values	Original reporting year	Inflation-adjusted costs (£)[73]	
Diarrhoea	684.01	2013	749.12	Oxford Outcomes data reported in TA319, inflated to 2017 GBP
Pneumonitis	596.85	2017	596.85	Assumption based on TA417[74]
Hyperthyroidism	473.72	2013	518.81	Oxford Outcomes data reported in TA319 (endocrine disorders), inflated to 2017 GBP
Fatigue	173.89	2013	190.44	Oxford Outcomes data reported in TA319, 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 - Consultant-led outpatient attendances for 191 (pain management)
Headache	0	2017	0.00	Assumption based on TA319
Dyspnoea	0	2017	0.00	Assumption based on TA319

B 3.5.5 Miscellaneous unit costs and resource use

Terminal care

Patients who die from recurrent or advanced melanoma were assumed to require a one off cost for palliative/terminal care. This cost was assumed to be incurred only by those who transition to death from the distant metastases state, based on the assumption that all deaths occurring directly from the recurrence-free or locoregional recurrence states are attributable to causes other than melanoma.

This is defined as 'Terminal Care applied On Death' and related to hospital care in the 90 days before dying, based on Georghiou & Bardsley (2014).[75] The costs of terminal care included services such as emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs. In the model this cost was applied as a one off cost at the point of death for relevant patients. An alternative source was also included as a scenario analysis.[76]

Table 50. Supportive and terminal care costs

Terminal care cost	Cost	Source
District nurse	£321.26	Georghiou & Bardsley inflated to 2017 prices[73]
Nursing and residential care	£1,155.63	
Hospice care – inpatient	£635.60	
Hospice care – final 3 months of life	£5,200.33	
Marie Curie nursing service	£577.81	
Total	**£7,890.64**	

Finally, costs for BRAF mutation testing have not been included in the model as it is assumed that this will take place prior to the initiation of adjuvant therapy.

B.3.6 Summary of base-case analysis inputs and assumptions

B 3.6.1 Summary of base-case analysis inputs

An overview of the key base case inputs is provided in Table 51. The full list of variables used in the cost-effectiveness analysis is presented in Appendix M.

Table 51. Overview of base case inputs

Input	Basecase input		
Model settings			
Timehorizon	46 years		
Parametric functions for modelling transitions from recurrence-free state	RFS→LR	LR→DM	DM→Death
	Gompertz	Gen.Gamma	Exponential
Utility			
Utility source for recurrence-free (without toxicity):	KEYNOTE-054		
Utility source for locoregional recurrence:	KEYNOTE-054		
Utility source for distant metastases (pre-progression):	KEYNOTE-054		
Utility source for distant metastases (post-progression):	Beusterien et al. 2009		
Apply age-related disutility?	Yes		
Treatment in the advanced setting			
Use of immunotherapies in the advanced melanoma setting following adjuvant pembrolizumab	No		
Use of rechallenge with pembrolizumab following adjuvant pembrolizumab for patients who transition from recurrence-free to distant metastases ≥18 months from adjuvant treatment initiation	No		
Consideration of subsequent lines of therapy in the advanced melanoma setting	Cost of first and second line advanced regimens		
Drug and Administration Costs			
Use of vial sharing	No		
Application of relative dose intensity	Yes		

B 3.6.2 Assumptions

Table 52 summarises the assumptions used in the economic model.

Table 52. Model assumptions

Assumption	Justification
Patients with high risk melanoma following complete resection are followed-up according to the	This position paper was developed and co-authored by clinicians working in a wide range of hospitals across the UK. A recent audit of three major cancer

surveillance policy outlined in a position paper from UK clinicians.	centres showed that follow-up of patients was being implemented as outlined in the position paper.[17]
Data from the Flatiron database can be used to estimate the transition probabilities for patients progressing from LR→DM or LR→death.	Data from KEYNOTE-054 on the rate of transition from LR→DM or death is not available at this time (study part 2). Therefore real world data from the US Flatiron database was instead used. A comparison of the KEYNOTE-054 and Flatiron patient characteristics shows a good balance in baseline characteristics.
Patients in either the pembrolizumab or routine surveillance arm have the same transition probabilities from LR→DM and LR→Death.	Due to the unavailability of data from part 2 of the KEYNOTE-054 study, the same transition probability in both arms is assumed. This could be considered to be a conservative assumption, give the mechanism of action of pembrolizumab and potential for immune memory.
All patients progressing to advanced disease will receive systemic therapy in the first line setting. A proportion of patients who progress will go on to receive second-line therapies.	Given recent advancements in the treatments available in the advanced setting, it is assumed that all patients will receive at least one of the treatments recommended under NG14.[14] The use and distribution of first and second line therapies are estimated based on current market research data.[56]
Patients receiving pembrolizumab adjuvant therapy will not be treated with a PD-1/PD-L1 inhibitor in the advanced setting. Patients who received routine surveillance will receive treatment in the distant metastases setting as per the current distribution in the UK clinical practice.	This is a key area of clinical uncertainty which is expected to be resolved when further data is available from KEYNOTE-054. This assumption is explored in the sensitivity analyses.
The treatment duration and outcomes expected for treatments in the distant metastases state are identical to those observed in the trials conducted in the advanced setting.	The trials included in the NMA were conducted in patients with unresectable stage III or IV melanoma (excluding ocular melanoma) upon entry into the trial.
Utilities were adjusted by UK general population utility where utility deceases with age.	Based on the Ara and Brazier study suggesting the impact of age on HRQoL.[67]
Pembrolizumab will be administered for a maximum of 18 cycles (12 months).	This assumption is in line with the KEYNOTE-054 clinical trial.
The incidence of AEs from KEYNOTE-054 was assumed to reflect that observed in practice.	Assumption based on the results of the KEYNOTE-054 trial. The same method and criteria were applied in previous NICE appraisals of pembrolizumab for melanoma (TA357, 366).[41, 42]
Terminal care is only applied to people who die from metastatic melanoma.	It is assumed that deaths occurring directly from the recurrence-free or locoregional recurrences states are attributable to causes other than melanoma.

B.3.7 Base-case results

The results of the economic model are presented in

Table 53 below. In the base case analysis, the estimated mean overall survival was 9.79 years with pembrolizumab and 6.61 years with routine surveillance only. Patients treated with pembrolizumab accrued 7.91 QALYs compared to 5.18 among patients in the routine surveillance cohort.

B 3.7.1 Base-case incremental cost-effectiveness analysis results

Table 53 below presents the base case incremental cost-effectiveness results, incorporating the discount of the CAA. The results show pembrolizumab to be a dominant strategy compared to routine surveillance.

Table 53. Base-case results

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	Inc. LYs	ICER (£/QALY)	ICER (£/LY)
Pembrolizumab	161,954	7.91	9.79	-	-	-	-	-
Routine surveillance	165,941	5.18	6.61	-3,988	2.73	3.18	Dominant	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

B.3.8 Sensitivity analyses

B 3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix M.

Table 54. Incremental cost-effectiveness results based on probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Pembrolizumab	163,093	7.97	-	-	
Routine surveillance	167,063	5.36	-3,970	2.62	Dominant

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 54, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 20 and Figure 21. The cost-effectiveness acceptability curve shows that there is an approximately 91.5% probability of pembrolizumab being cost-effective when compared to routine surveillance at the £30,000 per QALY threshold, with the CAA.

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Figure 20: Scatterplot of PSA results

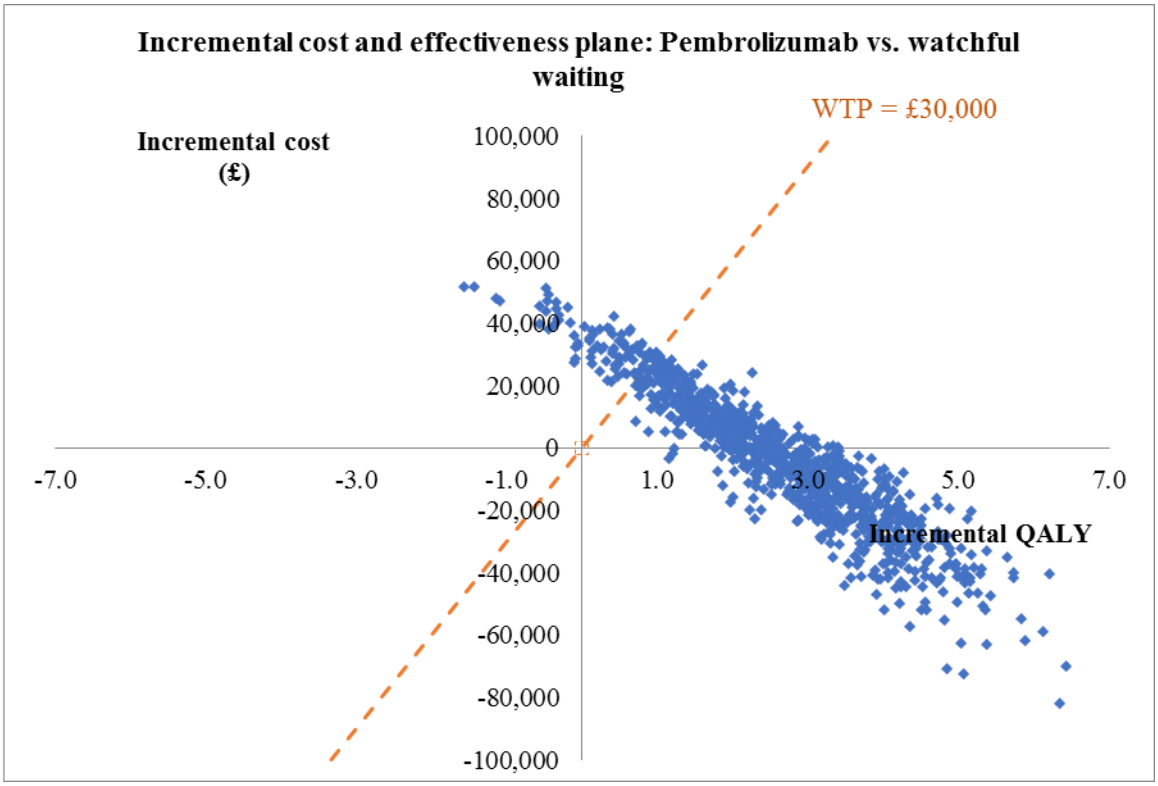
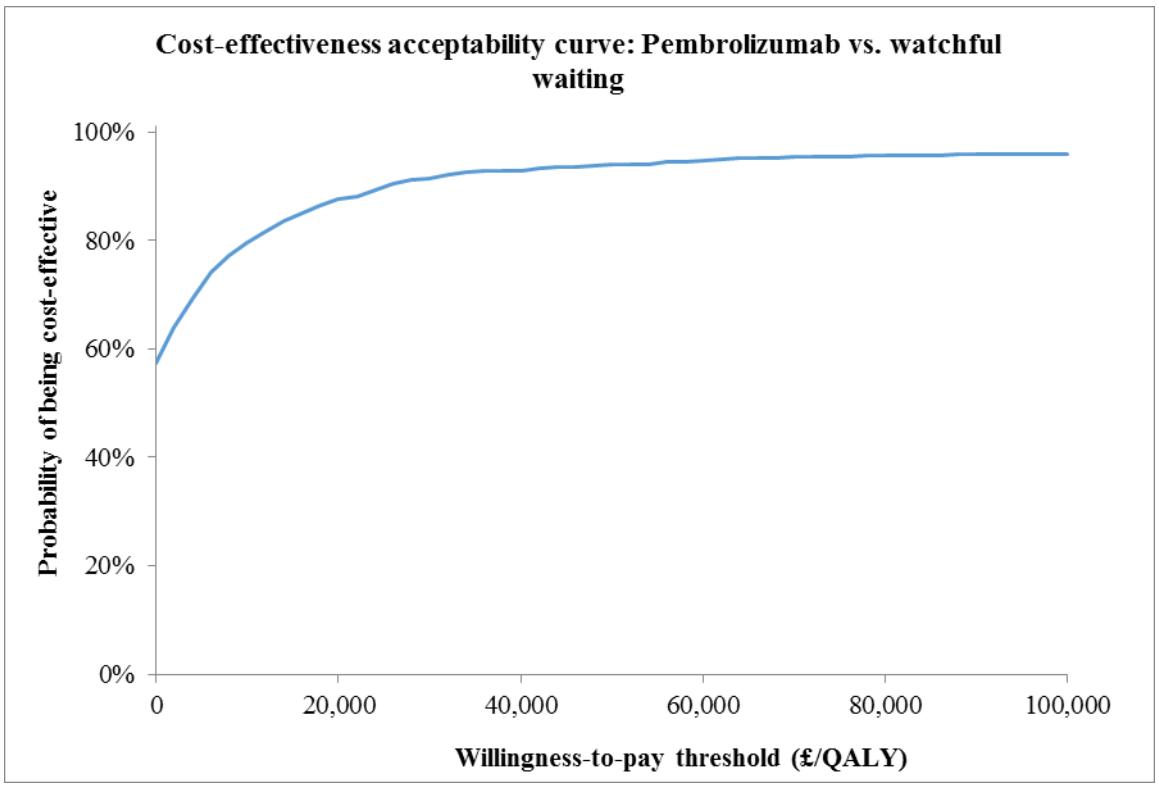


Figure 21: Cost-effectiveness acceptability curve (results discounted)



B 3.8.2 Deterministic sensitivity analysis and scenario analysis

Extensive sensitivity analyses were conducted to explore the uncertainty associated with the estimates of cost-effectiveness. Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions:

The parameters explored are summarized below. The tornado diagram of these deterministic sensitivity analyses (DSA) is presented in Figure 22 and the full table of results are presented in Appendix M.

Model structure

- Time horizon (reduced to 10, 20 years)
- Annual discount rate for costs and benefits (0, 6%)

Efficacy estimates

- Alternative combinations of distributions for estimating transition probabilities from RF→LR and RF→DM were explored. To determine which of the alternative 35 combinations to choose for relevant sensitivity analyses, model selection criteria were applied. Given the 5-year OS reported in the ipilimumab trial for placebo (54.4%) and for ipilimumab (65.4%), which was conducted in a similar patient population (i.e. high risk, stage III melanoma patients)[77], a minimum 5-year OS for the routine surveillance arm of 52% was required in order to be included in the sensitivity anaylsis. A minimum 5-year OS for the pembrolizumab arm of 68% was also stipulated, given the ipilimumab result of 65.4%. Given the efficacy results in the advanced setting for pembrolizumab compared to ipilimumab[78], outcomes with pembrolizumab would be expected to be at least slightly better than ipilimumab, if not substantially so. The following combinations of distributions met both criteria and were therefore included in the sensitivity analyses.
    - Distribution used for RF→LR and RF→DM: Gompertz and Gompertz
    - Distribution used for RF→LR and RF→DM: Gompertz and Log-normal
    - Distribution used for RF→LR and RF→DM: Log-normal and Gompertz
    - Distribution used for RF→LR and RF→DM: Generalized gamma and Gompertz
    - Distribution used for RF→LR and RF→DM: Log-logistic and Gompertz
    - Distribution used for RF→LR and RF→DM: Weibull and Gompertz
    - Distribution used for RF→LR and RF→DM: Log-normal and Log-normal

    - Distribution used for RF→LR and RF→DM: Generalized gamma and Log-normal
    - Distribution used for RF→LR and RF→DM: Exponential and Gompertz
    - Distribution used for RF→LR and RF→DM: Log-logistic and Log-normal
    - Distribution used for RF→LR and RF→DM: Weibull and Log-normal

- Using parametric models with time-varying or time-constant treatment effects for estimating transitions from RF (using the Gompertz and Weibull distributions respectively for RF→LR and RF→DM respectively)

- Varying the exponential rate from LR to DM and death by +/-10 percent

- Varying the exponential rates of OS and PFS failure for advanced melanoma treatments by +/-10 percent

Scenarios for subsequent therapies

- Including the cost of first-line advanced regimens only

- Allowing re-challenge with pembrolizumab following adjuvant therapy in eligible patients (>18 months from commencing adjuvant therapy)

- Allow rechallenge with pembrolizumab or subsequent IO treatment among eligible patients

- Using same mix of advanced treatments in adjuvant pembrolizumab and routine surveillance arm

Utilities

- Health state utilities +/-10%

- All heath-state utilities taken from KEYNOTE-054 (including DM post-progression)

- All health-state utilities taken from Middleton et al. (2017)[64]

- Remove age-adjusted disutilities

- Remove AE disutilities

- AE disutilities +/-10%

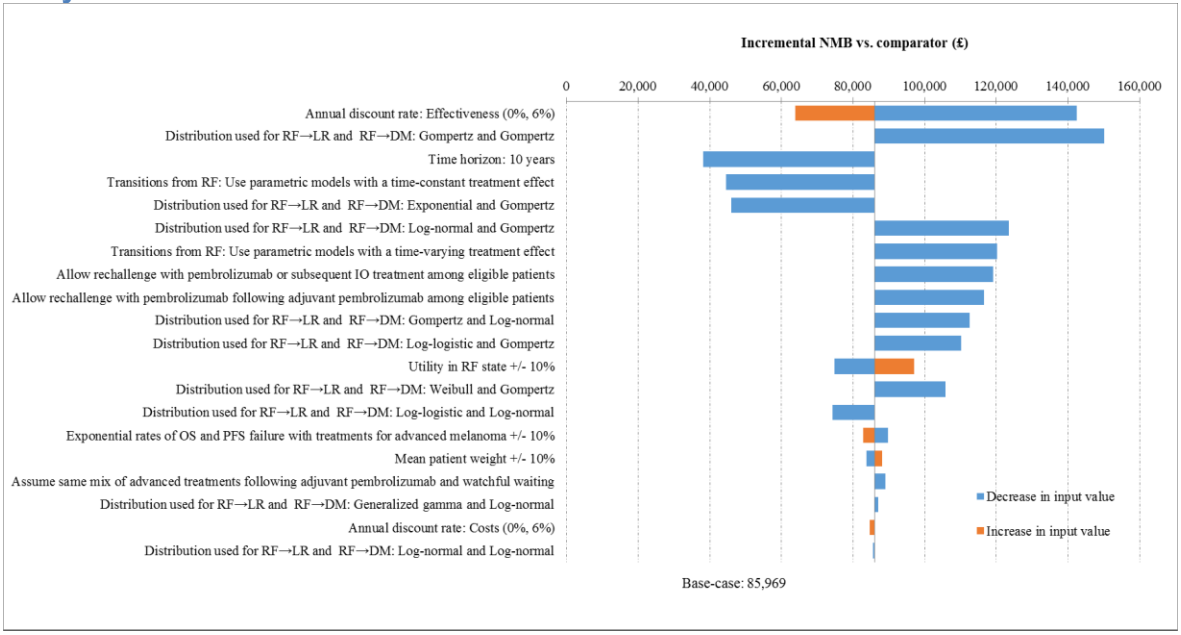
Treatment Costs

- Administration costs and patient weight +/-10%
- No relative dose intensity
- Vial sharing

Adverse event and disease management costs

- AE costs +/-10%
- Medical management costs in RF, LR and DM costs +/-10%
- Salvage surgery costs +/-10%
- Terminal care cost +/-10%
- Alternative terminal care cost source[76]

Figure 22: Tornado diagram presenting the results of the deterministic sensitivity analysis



The results show that pembrolizumab remains a cost-effectiveness treatment option versus routine surveillance in all scenarios. In the cases where it does not dominant routine surveillance, the ICER remains below £10,000, which is well below the cost-effectiveness threshold of £20,000-£30,000.

B 3.8.3 Summary of sensitivity analyses results

We have conducted extensive sensitivity analyses to understand the key determinants of the cost-effectiveness of adjuvant pembrolizumab versus routine surveillance. The results demonstrate that the model is robust to the vast majority of scenarios explored, with pembrolizumab remaining dominant compared to routine surveillance for stage III resected melanoma with high risk of recurrence.

One of the key drivers of cost-effectiveness is the estimation of the efficacy of adjuvant pembrolizumab compared to routine surveillance. The choice of parametric survival distribution for estimating the transition probabilities from the recurrence-free health state to local recurrence, distant metastases and death is one of the main determinants of cost-effectiveness. The choice of the best approach to modelling transition probabilities was explored extensively in section B.3.3, where evidence to support the base case assumptions was provided. Alternative scenarios using a range of different distributions and approaches were also explored, and these showed that pembrolizumab remains cost-effective in the scenarios explored and dominant in the vast majority.

B.3.9 Subgroup analysis

No subgroup analysis has been indication.

B.3.10 Validation

B 3.10.1 Validation of cost-effectiveness analysis

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab as an adjuvant treatment for patients with stage III melanoma. The economic evaluation reflects patients assessed in KEYNOTE-054 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

No study assessing the cost-effectiveness of pembrolizumab for the target population specified above was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Clinical benefit

The validation of the model was assessed by comparing the efficacy outcomes of pembrolizumab observed in the KEYNOTE-054 trial to the outcomes from the cost-effectiveness model. In particular, the RFS curves predicted for the two model arms were plotted alongside the observed Kaplan-Meier curves for RFS to ensure that the curves were well-aligned during the trial period. For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J1.1.

Model predictions were also compared against observed data from an external study. Specifically, data from the placebo arm of the adjuvant ipilimumab trial (5.3 years of median follow up) was used to validate model predictions of RFS, DMFS, and OS for the routine surveillance strategy at 5 years.

Expert validation

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developers to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications. The model was also

independently reviewed by external health economists, who evaluated the model from an overall health economics perspective in addition to checking for implementation errors.

B.3.11 Interpretation and conclusions of economic evidence

B 3.11.1 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the stage III melanoma population eligible for pembrolizumab as per the anticipated licence. As mentioned previously, clinical efficacy estimates from the KEYNOTE-054 trial, which assessed patients in line with the anticipated licenced indication, were used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab in the patient population under consideration.

Generalisability of the analysis to clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-054 is reflective of UK patients with stage III melanoma following complete resection, and the choice of comparator matches the current UK standard of care.
- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions for melanoma, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab.
- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

Strengths and weaknesses of the evaluation

- Use of relevant clinical data versus the current UK standard of care:

The analysis performed makes use of the best available evidence to inform the model. Head-to-head data from the KEYNOTE-054 trial comparing pembrolizumab to routine surveillance, which represents current UK clinical practice, was used in the economic evaluation.

For the extrapolation of the results in the long term, appropriate external sources were used, whenever required, and data from previously NICE appraisals was used for consistency and to reflect UK clinical practice.

- Consistency and stability of cost-effectiveness results to wide-ranging scenario analyses:

The results are stable to a wide variety of exploratory sensitivity and scenario analyses. In the majority of analyses conducted, pembrolizumab continues to dominate routine surveillance, as a more effective and less costly treatment for patients with stage III resected melanoma, with high risk of recurrence.

The main weaknesses associated with this cost-effectiveness analysis are the following:

- Lack of OS data:

At present only recurrence-free survival data is available from the KEYNOTE-054 trial as mature data for distant metastases free survival and overall survival are not available. For this reason, real world data from the FlatIron registry have been used to estimate the transition from local recurrence to distant metastases and data from existing trials in the advanced setting has been used for the transitions from distant metastases to death.

There is strong evidence however that the improvement in RFS seen in KEYNOTE-054 will translate into an overall survival benefit. In a recent meta-analysis of 13 clinical studies (n>5000 patients) involving adjuvant IFN in stage II-III melanoma, RFS was shown to be a valid surrogate endpoint for OS.[25] The paper also validated the model using the data from the EORTC 19071 study of adjuvant ipilimumab – a CTLA-4 inhibitor, for which overall survival data is available.[79] This suggests that the strong correlation between RFS and OS observed in the IFN trials is also correct for ipilimumab. Furthermore, the study predicted that adjuvant studies with an HR ≤0.77 for RFS would demonstrate a treatment benefit on OS. In KEYNOTE-054, the HR for RFS (0.57) is expected to predict an OS benefit.

- Uncertainty regarding the use of pembrolizumab re-challenge

As well as determining whether pembrolizumab has a role as an adjuvant therapy for resected melanoma, the KEYNOTE-054 trial was designed to address the question of whether patients should be re-challenged with pembrolizumab, if they progress following adjuvant therapy. However, this data will not be available for a few years. Clinical experts questioned on the role

of re-challenge have highlighted the current uncertainty as determining their own clinical practice, were adjuvant therapy available in the UK. To address this uncertainty, the base case assumes no re-challenge – based on current clinical practice. A scenario which incorporates re-challenge with pembrolizumab shows pembrolizumab continues to dominate routine surveillance, alleviating some of this uncertainty. It is anticipated that if the KEYNOTE-054 data provides a rationale for re-challenge, this will be adopted into UK practice.

- Use of the exponential modelling approach in the advanced setting

Given the unique shape of the survival curves of immunotherapeutic agents, it is unlikely that the exponential distribution is sufficiently flexible to characterise the plateau which is observed in long term for pembrolizumab in advanced melanoma.[54, 80] It is likely that the approach underestimates the overall survival benefit offered with pembrolizumab and other immunotherapies. Due to the fact this is a Markov model however; other more complicated survival modelling approaches were difficult to implement to estimate transition probabilities from the DM state. As this approach is implemented in both the pembrolizumab and routine surveillance arms however, the incremental effect should not have a significant impact on the overall result and conclusions of this cost-effectiveness analysis.

In summary, the results presented demonstrate the cost-effectiveness of pembrolizumab using the NICE accepted threshold of £20,000-£30,000 and demonstrate a strong rationale for the introduction of pembrolizumab as an adjuvant treatment of resected melanoma with high risk of recurrence.

B.4 References

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B.5 Appendices

Appendix C: Summapry of prouct characteristics (SmPC) and European public assessment report EPAR)

Appendix D: Identification, selection, synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource indentification

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Transition probability estimates

Appendix M: Model inputs and full deterministic sensitivity analysis results

Appendix N: Results for Utility Analysis for KN054

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

Dear Company,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 25 June 2018 from MSD. In general, they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on Thursday 26 July 2018. Your response and any supporting documents should be uploaded to NICE Docs: https://appraisals.nice.org.uk/request/55949.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Joanna Richardson, Technical Adviser (Joanna.Richardson@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Jo Richardson
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

KEYNOTE-054 trial methodology

A1. **Priority question**. Please provide the KEYNOTE-054 trial statistical analysis plan for the interim analysis (date 2nd October 2017), including details of any amendments, where applicable.

A2. **Priority question**. Please confirm whether, for the recurrence free survival (RFS) analyses presented in the company submission (CS) in Table 13 and Table 16, the proportional hazards (PH) assumption was checked. If the PH assumption was checked, please provide any numerical or graphical findings from these checks.

A3. The original protocol for the KEYNOTE-054 trial is provided in Section 16.1.1.1 of the clinical study report (CSR) and the amended protocols are provided in Sections 16.1.1.2 and 16.1.1.3 of the CSR. The amendment finalised on 2 October 2017 relates to the interim analysis of RFS after 330 events. Please clarify the rationale for the other scientific amendments outlined on the title page of Protocol General Amendment No. 2 (CSR, Section 16.1.1.3) which were approved on:

- May 19, 2015
- July 07, 2015
- January 21, 2017
- March 2018, 2017

A4. In the CS (p29), the company highlights that there is a difference between the median follow-up time reported in the KEYNOTE-054 publication (15 months) and that presented in the KEYNOTE-054 CSR (16 months). The approach described for calculating median follow-up in the KEYNOTE-054 publication is clear; however, the description of the company's approach to generate the median follow-up result provided in the CSR is not clear. Please provide details of the approach taken to generate the median follow-up result presented in the CSR and explain how this approach differs from that taken by the authors of the KEYNOTE-054 publication.

A5. In the CS, p29 and Table 10, the company states that 445 patients who were enrolled into the KEYNOTE-054 trial were not randomised, primarily due to meeting the exclusion criteria at randomisation. Please provide a breakdown of which of the seven criteria listed in Section 9.3.2 of the CSR the 445 non-randomised patients met.

A6. In the CS, p27, the company states that in the KEYNOTE-054 trial, cutaneous relapses occurring beyond the periphery of the previous surgical bed (≥2cm) were considered distant metastases. Please explain why the described metastases are considered distant rather than regional metastases as defined in 2(i) on p26 of the CS.

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10 Spring Gardens
London
SW1A 2BU
United Kingdom

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A7. Please provide the numbers and proportions of events, as outlined in Table 15 of the CS (Disease Status; intention to treat [ITT] population), for the following subgroups:
1. Programmed death-ligand 1 (PD-L1) +ve tumours and PD-L1 -ve tumours
2. Stage (IIIA [>1mm metastasis] vs. IIIB vs IIIC 1-3 positive lymph nodes (LN+) vs IIIC ≥4 LN+)
3. Please also provide the RFS rates at 6 months, 12 months and 18 months as outlined in Table 14 of the CS for the Stage subgroups.

A8. The following pre-planned sensitivity analyses are listed in the Protocol General Amendment No. 2 Section 8.2.4.1 (CSR, Section 16.1.1.3) but results from these analyses are not provided within the CS or CSR.

- to ensure true randomisation via minimisation, a re-randomisation test will be performed:
- RFS for ITT population
- RFS for PD-L1 +ve ITT population
- DMFS for ITT population
- DMFS for PD-L1 +ve ITT population
- OS for ITT population
- OS for PD-L1 +ve ITT population
- using the ITT population, but considering the stratification factor (American Joint Committee on Cancer [AJCC] stage) information as indicated on the case report forms, based on pathology report(s) and applying the AJCC staging rules.
- using the per protocol population.

Is it correct to assume that these sensitivity analyses were not performed for the interim analysis but will be performed as part of subsequent analyses?

A9. Please advise when the next results from the KEYNOTE-054 trial are likely to become available. Are the RFS results presented in the CS the final RFS results?

Network meta-analysis (NMA)

A10. In the CS, Table 26, the hazard ratios (HRs) provided for ipilimumab, nivolumab and nivolumab plus ipilimumab are derived from a network meta-analysis (NMA, reference 55 of the CS) in a first-line BRAF wild type population and the HRs provided for vemurafenib, dabrafenib and dabrefenib plus trametinib are derived from an NMA in the first-line BRAF mutation positive population. The ERG notes that the NMA in the first-line BRAF mutation positive population includes all regimens of interest and all HR estimates could have been taken from a single analysis within a consistent population. Please provide the rationale for the use of HRs from the two different sources and two different populations.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

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Section B: Clarification on cost-effectiveness data

B1. **Priority request.** Please provide, the Kaplan-Meier (K-M) analyses listed in a) to e) to the following specifications:

- Data set: KEYNOTE-54 trial, October 2017 data cut (or more recent if available)
- Format: please present outputs from the analyses using the format of the sample table provided at the end of section B (to include censoring times)
- Censoring: for time to each specific event, other competing events should be treated as censoring events. Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off
- Population: ITT
- Stratification: K-M analyses to be stratified by treatment and by melanoma Stage (IIIA, IIIB and IIIC (IIIC in total, and also separated into Stage IIIC [1-3 LN+] and Stage IIIC [>=4LN+])

a) First event (locoregional [LR], distant metastases [DM] or death)

b) First LR event while being recurrence-free

c) First DM event while being recurrence-free

d) Death from all causes while being recurrence-free

e) Time to study treatment discontinuation

B2. **Priority request.** If possible, please provide, the K-M analyses used, in the company model, to represent progression from

- LR to DM
- RF to LR
- RF to DM

Please also provide these data stratified by melanoma stage at time of full resection, i.e., Stage IIIA, IIIB and IIIC (IIIC in total and also separated into Stage IIIC [1-3 LN+] and Stage IIIC [>=4LN+])

B3. Please clarify which data were used to generate the exponential distribution that was used in the company model to represent patient transition from RFS to death (as first event).

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Sample table: Example of output (SAS) required from specified K-M analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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Single technology appraisal

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

Dear Company,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 25 June 2018 from MSD. In general, they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on Thursday 26 July 2018. Your response and any supporting documents should be uploaded to NICE Docs: https://appraisals.nice.org.uk/request/55949.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Joanna Richardson, Technical Adviser (Joanna.Richardson@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Jo Richardson
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

KEYNOTE-054 trial methodology

A1. **Priority question**. Please provide the KEYNOTE-054 trial statistical analysis plan for the interim analysis (date 2nd October 2017), including details of any amendments, where applicable.

The SAP for IA1 can be found in Section 8.3 (interim analyses) of the protocol.

A2. **Priority question**. Please confirm whether, for the recurrence free survival (RFS) analyses presented in the company submission (CS) in Table 13 and Table 16, the proportional hazards (PH) assumption was checked. If the PH assumption was checked, please provide any numerical or graphical findings from these checks.

The proportional hazards assumption was not assessed for RFS analysis. Experience of immunotherapy studies (especially check-point inhibitors) suggests that there is an initial delay in the effect of the intervention, and true proportional hazards are not present. Nevertheless, it is well known that the power to detect differences in time-to-event outcomes using log-rank test or statistical analyses applying the Cox-proportional hazards model is rather insensitive to deviations from proportional hazards.[1]

A3. The original protocol for the KEYNOTE-054 trial is provided in Section 16.1.1.1 of the clinical study report (CSR) and the amended protocols are provided in Sections 16.1.1.2 and 16.1.1.3 of the CSR. The amendment finalised on 2 October 2017 relates to the interim analysis of RFS after 330 events. Please clarify the rationale for the other scientific amendments outlined on the title page of Protocol General Amendment No. 2 (CSR, Section 16.1.1.3) which were approved on:

- May 19, 2015
- July 07, 2015
- January 21, 2017
- March 2018, 2017

The title page of Protocol Amendment N.2 has a table indicating the Final Protocol Versions Approved by the Sponsor (Table 1). The only approved protocol amendment before Protocol Amendment N.2 was the Protocol Amendment N.1 dated July 07, 2015. Sponsor approval was not needed for the following EORTC scientific amendments:

- May 19, 2015 (EORTC version 2.0)
- January 21, 2017 (EORTC version 4.0)

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- March 28, 2017 (EORTC version 5.0)

The rationale has been explained in three NTF documents dated 09-Jul-2015, 14-Feb-2017, 03-Nov-2017, and summarized below.

The amendment published on May 19, 2015 as EORTC version 2.0 was missing some sections that were previously approved by Merck and EORTC. There was a process gap when transferring text from the collaborative space (Engage Zone) into the EORTC publishing system. For this reason, based on their guidelines, EORTC issued administrative version 2.1 to correct the publication, and later on updated further corrections in version 3.0 published on 07-Jul-2015. The EORTC protocol versions 2.0 and 2.1 are non-active due to the publication errors.

The EORTC-1325 protocol version 4.0 (amendment January 21st 2017) required a signature from Merck in order to allow the internal release of the document within the EORTC system and to allow EORTC's editing of a newly corrected version for the upcoming protocol amendment MK-3475-054-02. The signature provided by Merck on EORTC-1325 version 4.0 is not an approval to release the document to Regulatory Agencies, neither Ethical Committees, Investigator sites nor any external party. Therefore, protocol EORTC-1325 version 4.0 is not considered an approved amendment for use in this clinical trial, and will not be filed in Merck's Trial Master File.

The EORTC-1325 protocol version 5.0 required a signature from Merck in order to allow the internal release of the document within the EORTC system and to allow EORTC's editing of a newly corrected version for the final protocol amendment MK-3475-054-02 (EORTC version 6.0). Therefore, the signature provided by Merck on EORTC-1325 version 5.0 was not an approval to release the document to Regulatory Agencies, neither Ethical Committees, Investigator sites nor any external party. The protocol EORTC-1325 version 5.0 is not considered an approved amendment for use in this clinical trial and will not be filed in Merck's Trial Master File.

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Table 1: EORTC protocol version and amendments.

EORTC Protocol versions	Date of EORTC PRC approval/notification	Final Protocol Version Approved by the Sponsor	EORTC Amendment reference	
			N°	Classification
Outline Amended	April 29, 2014 December 12, 2014	n/a	----	----
1.0	December 17, 2014	MK-3475-054-00	----	----
2.0	May 19, 2015	n/a	1	Scientific
2.1	June 12, 2015	n/a	4	Administrative
3.0	July 07, 2015	MK-3475-054-01	5	Scientific
4.0	January 21, 2017	n/a	8	Scientific
5.0	March 28, 2017	n/a	9	Scientific
6.0	October 02, 2017	MK-3475-054-02	12	Scientific

A4. In the CS (p29), the company highlights that there is a difference between the median follow-up time reported in the KEYNOTE-054 publication (15 months) and that presented in the KEYNOTE-054 CSR (16 months). The approach described for calculating median follow-up in the KEYNOTE-054 publication is clear; however, the description of the company's approach to generate the median follow-up result provided in the CSR is not clear. Please provide details of the approach taken to generate the median follow-up result presented in the CSR and explain how this approach differs from that taken by the authors of the KEYNOTE-054 publication.

The CS (page 29) describes the methodology undertaken to calculate median follow-up as presented in the KEYNOTE-054 publication. For the company CSR, the median follow-up was defined as the time from randomisation to the date of death or database cut-off date (2nd October 2017) if the patient was alive. The median follow-up duration was subsequently calculated across both treatment groups for subjects who were randomised. Estimation was undertaken using a Kaplan-Meir approach.

The median duration of follow-up results presented in the CSR differed from those presented in the KEYNOTE-054 publication[2] due to the censoring approach undertaken as described below;

1. KEYNOTE-054 publication[2]; Recurrence-free survival was defined as the time from randomisation until the date of first recurrence (local, regional, or distant metastasis) or death from any cause. For patients without any event, follow-up was censored at the latest disease evaluation performed according to the trial protocol.[2]

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2. CSR: The median follow-up was defined as the time from randomisation to the date of death or database cut-off date (2nd October 2017) if the patient was alive. An event was discontinuation and patients were censored when they had an RFS event.

A5. In the CS, p29 and Table 10, the company states that 445 patients who were enrolled into the KEYNOTE-054 trial were not randomised, primarily due to meeting the exclusion criteria at randomisation. Please provide a breakdown of which of the seven criteria listed in Section 9.3.2 of the CSR the 445 non-randomised patients met.

445 patients were not randomised as outlined below in Table 2.

Table 2: Reasons patients were enrolled but not randomised.

	n (%)
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 tumor 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 human immunodeficiency virus (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)
(Database Cutoff Date: 02OCT2017).	

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A6. In the CS, p27, the company states that in the KEYNOTE-054 trial, cutaneous relapses occurring beyond the periphery of the previous surgical bed (≥2cm) were considered distant metastases. Please explain why the described metastases are considered distant rather than regional metastases as defined in 2(i) on p26 of the CS.

We have used the definition of in-transit metastasis as per protocol definition of distant cutaneous recurrence which logically follows from the definition of in-transit metastasis and does not contradict the definition of distant metastasis. This is also in line with the AJCC criteria. A cutaneous recurrence more than 2cm from the primary lesion but not beyond the regional nodal basin is counted as a regional recurrence. This is described in Section B2.3.2 of the CS under 2i. The note associated with point 3, distant metastasis omits the clarification "not beyond the regional nodal basin".

A7. Please provide the numbers and proportions of events, as outlined in Table 15 of the CS (Disease Status; intention to treat [ITT] population), for the following subgroups:
1. Programmed death-ligand 1 (PD-L1) +ve tumours and PD-L1 -ve tumours
2. Stage (IIIA [>1mm metastasis] vs. IIIB vs IIIC 1-3 positive lymph nodes (LN+) vs IIIC ≥4 LN+)
3. Please also provide the RFS rates at 6 months, 12 months and 18 months as outlined in Table 14 of the CS for the Stage subgroups.

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1. PD-L1 status

a. Table 3: Disease status; ITT population (PD-L1 positive)

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	428	425
Type of First Event in RFS Analysis		
No event	326 (76.2)	249 (58.6)
Event	102 (23.8)	176 (41.4)
Locoregional recurrence	39 (9.1)	61 (14.4)
Distant metastasis	55 (12.9)	93 (21.9)
Both diagnosed within 30 days from each other	6 (1.4)	21 (4.9)
Death	2 (0.5)	1 (0.2)
DMFS Status		
No event	353 (82.5)	294 (69.2)
Event	75 (17.5)	131 (30.8)
Survival Status		
Alive	409 (95.6)	399 (93.9)
Dead	19 (4.4)	26 (6.1)
Database Cutoff Date: 02OCT2017		

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b. Table 4: Disease status; ITT population (PD-L1 negative)

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	59	57
Type of First Event in RFS Analysis		
No event	39 (66.1)	30 (52.6)
Event	20 (33.9)	27 (47.4)
Locoregional recurrence	11 (18.6)	10 (17.5)
Distant metastasis	8 (13.6)	15 (26.3)
Both diagnosed within 30 days from each other	1 (1.7)	2 (3.5)
Death	0 (0.0)	0 (0.0)
DMFS Status		
No event	46 (78.0)	33 (57.9)
Event	13 (22.0)	24 (42.1)
Survival Status		
Alive	55 (93.2)	50 (87.7)
Dead	4 (6.8)	7 (12.3)
Database Cutoff Date: 02OCT2017		

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2. AJCC staging classification

a. Table 5: Disease status; ITT population; Cancer stage IIIA (>1mm LN metastasis)

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	80	80
Type of First Event in RFS Analysis		
No event	74 (92.5)	62 (77.5)
Event	6 (7.5)	18 (22.5)
Locoregional recurrence	4 (5.0)	10 (12.5)
Distant metastasis	1 (1.3)	7 (8.8)
Both diagnosed within 30 days from each other	0 (0.0)	0 (0.0)
Death	1 (1.3)	1 (1.3)
DMFS Status		
No event	77 (96.3)	67 (83.8)
Event	3 (3.8)	13 (16.3)
Survival Status		
Alive	78 (97.5)	78 (97.5)
Dead	2 (2.5)	2 (2.5)
Database Cutoff Date: 02OCT2017		

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b. Table 6: Disease status; ITT population; Cancer Stage IIIB

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	237	230
Type of First Event in RFS Analysis		
No event	177 (74.7)	134 (58.3)
Event	60 (25.3)	96 (41.7)
Locoregional recurrence	23 (9.7)	34 (14.8)
Distant metastasis	35 (14.8)	52 (22.6)
Both diagnosed within 30 days from each other	2 (0.8)	10 (4.3)
Death	0 (0.0)	0 (0.0)
DMFS Status		
No event	194 (81.9)	159 (69.1)
Event	43 (18.1)	71 (30.9)
Survival Status		
Alive	230 (97.0)	217 (94.3)
Dead	7 (3.0)	13 (5.7)
Database Cutoff Date: 02OCT2017		

c. Table 7: Disease status; ITT population; Cancer stage IIIC (1-3 LN+)

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	95	93
Type of First Event in RFS Analysis		
No event	70 (73.7)	50 (53.8)
Event	25 (26.3)	43 (46.2)
Locoregional recurrence	10 (10.5)	14 (15.1)
Distant metastasis	12 (12.6)	25 (26.9)
Both diagnosed within 30 days from each other	2 (2.1)	4 (4.3)
Death	1 (1.1)	0 (0.0)
DMFS Status		
No event	74 (77.9)	60 (64.5)
Event	21 (22.1)	33 (35.5)
Survival Status		
Alive	89 (93.7)	84 (90.3)
Dead	6 (6.3)	9 (9.7)
Database Cutoff Date: 02OCT2017		

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d. Table 8: Disease status; ITT population; Cancer Stage IIIC (≥4 LN +)

	Pembrolizumab n (%)	Placebo n (%)
Subjects in population	102	102
Type of First Event in RFS Analysis		
No event	58 (56.9)	43 (42.2)
Event	44 (43.1)	59 (57.8)
Locoregional recurrence	18 (17.6)	19 (18.6)
Distant metastasis	21 (20.6)	30 (29.4)
Both diagnosed within 30 days from each other	5 (4.9)	10 (9.8)
Death	0 (0.0)	0 (0.0)
DMFS Status		
No event	71 (69.6)	54 (52.9)
Event	31 (30.4)	48 (47.1)
Survival Status		
Alive	92 (90.2)	91 (89.2)
Dead	10 (9.8)	11 (10.8)
Database Cutoff Date: 02OCT2017		

3. RFS rates at 6, 12 and 18 months for the Cancer stage subgroups.

a. Table 9: Recurrence free survival rate over time; ITT population; Stage IIIA (>1mm LN metastasis)

	Pembrolizumab (N=80)	Placebo (N=80)
RFS rate at 6 Months in % (95% CI)†	95.0 (87.1, 98.1)	91.2 (82.5, 95.7)
RFS rate at 12 Months in % (95% CI)†	93.7 (85.5, 97.3)	79.2 (68.3, 86.8)
RFS rate at 18 Months in % (95% CI)†	90.2 (77.5, 95.9)	72.2 (57.3, 82.6)
Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. † From the product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 02OCT2017).		

b. Table 10: Recurrence free survival rate over time; ITT population; Stage IIIB

	Pembrolizumab (N=237)	Placebo (N=230)
RFS rate at 6 Months in % (95% CI)†	83.6 (78.2, 87.8)	74.8 (68.6, 80.0)
RFS rate at 12 Months in % (95% CI)†	76.2 (70.0, 81.2)	62.6 (55.9, 68.6)
RFS rate at 18 Months in % (95% CI)†	72.7 (66.1, 78.3)	55.9 (48.6, 62.5)
Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. † From the product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 02OCT2017).		

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c. Table 11: Recurrence free survival rate over time; ITT population; Stage IIIC (1-3 LN+)

	Pembrolizumab (N=95)	Placebo (N=93)
RFS rate at 6 Months in % (95% CI)†	81.8 (72.4, 88.3)	71.4 (61.0, 79.6)
RFS rate at 12 Months in % (95% CI)†	75.2 (65.0, 82.8)	57.0 (46.1, 66.4)
RFS rate at 18 Months in % (95% CI)†	70.7 (58.8, 79.7)	46.4 (31.5, 60.0)
Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. † From the product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 02OCT2017).		

Table 12: Recurrence free survival rate over time; ITT population; Stage IIIC (≥4 LN+)

	Pembrolizumab (N=102)	Placebo (N=102)
RFS rate at 6 Months in % (95% CI)†	69.3 (59.3, 77.3)	57.8 (47.7, 66.7)
RFS rate at 12 Months in % (95% CI)†	59.3 (49.1, 68.2)	46.7 (36.8, 56.1)
RFS rate at 18 Months in % (95% CI)†	54.1 (43.1, 63.9)	39.4 (29.3, 49.4)
Recurrence-free survival is defined as time from randomization to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. † From the product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 02OCT2017).		

A8. The following pre-planned sensitivity analyses are listed in the Protocol General Amendment No. 2 Section 8.2.4.1 (CSR, Section 16.1.1.3) but results from these analyses are not provided within the CS or CSR.

- to ensure true randomisation via minimisation, a re-randomisation test will be performed:
  - RFS for ITT population
  - RFS for PD-L1 +ve ITT population
  - DMFS for ITT population
  - DMFS for PD-L1 +ve ITT population
  - OS for ITT population
  - OS for PD-L1 +ve ITT population
  - using the ITT population, but considering the stratification factor (American Joint Committee on Cancer [AJCC] stage) information as indicated on the case report forms, based on pathology report(s) and applying the AJCC staging rules.
  - using the per protocol population.

Is it correct to assume that these sensitivity analyses were not performed for the interim analysis but will be performed as part of subsequent analyses?

Sensitivity analyses for the two primary analyses (RFS for the ITT population and RFS for the PD-L1 positive ITT population) were performed using a re-randomisation test. The distribution of the p-value under the null hypothesis was generated as follows;

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1. Patients were randomly reassigned to the treatment groups using the randomisation algorithm applied in this study. All units randomised in the original randomisation procedure (including second randomisation for two patients randomised twice) were re-randomised.

2. The re-randomised dataset was analysed in the same way as the true dataset (i.e. excluding two second randomisations of the same patient using the log-rank test stratified by stage).

3. The p-value of the re-randomisation test was calculated as the proportion of the p-values from the re-randomised samples that were lower than the p-value in the original sample. 2000 replications were used.

The results of the re-randomisation tests were consistent with the main analysis ($p<0.001$) both for the test in the overall study population and among PD-L1 positive patients.

Re-randomisation tests were not performed for the DMFS and OS endpoints since the required number of events for these endpoints has not been reached and will be performed as part of subsequent analyses. Timelines are reported below (Question 9).

A9. Please advise when the next results from the KEYNOTE-054 trial are likely to become available. Are the RFS results presented in the CS the final RFS results?

[redacted]

Network meta-analysis (NMA)

A10. In the CS, Table 26, the hazard ratios (HRs) provided for ipilimumab, nivolumab and nivolumab plus ipilimumab are derived from a network meta-analysis (NMA, reference 55 of the CS) in a first-line BRAF wild type population and the HRs provided for vemurafenib, dabrafenib and dabrefenib plus trametinib are derived from an NMA in the first-line BRAF mutation positive population. The ERG notes that the NMA in the first-line BRAF mutation positive population includes all regimens of interest and all HR estimates could have been taken from a single analysis within a consistent population.

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Please provide the rationale for the use of HRs from the two different sources and two different populations.

Results from the BRAF-wild type NMA were used for non-BRAF inhibitors (that is, pembrolizumab, nivolumab, ipilimumab and nivolumab+ipilimumab), based on the assumption that most patients receiving these treatments as first-line treatment in the advanced melanoma setting would be BRAF-wild type. This assumption is supported by the composition of the trial populations in KEYNOTE 006[7], CHECKMATE 067[8] and 069[3], in which 30%-40% of patients were BRAF-positive at baseline.

The BRAF-wild type NMA focused on trials that reported results for either a mixed population (e.g., KEYNOTE 006, CHECKMATE 067 and 069) or a BRAF-wild type population (e.g., CHECKMATE 066[5]), and was therefore believed to be more representative of real-world patients who would receive non-BRAF inhibitors as first-line treatment for advanced melanoma.

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Section B: Clarification on cost-effectiveness data

B1. **Priority request.** Please provide, the Kaplan-Meier (K-M) analyses listed in a) to e) to the following specifications:

- Data set: KEYNOTE-54 trial, October 2017 data cut (or more recent if available)
- Format: please present outputs from the analyses using the format of the sample table provided at the end of section B (to include censoring times)
- Censoring: for time to each specific event, other competing events should be treated as censoring events. Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off
- Population: ITT
- Stratification: K-M analyses to be stratified by treatment and by melanoma Stage (IIIA, IIIB and IIIC (IIIC in total, and also separated into Stage IIIC [1-3 LN+] and Stage IIIC [>=4LN+])

a) First event (locoregional [LR], distant metastases [DM] or death)

b) First LR event while being recurrence-free

c) First DM event while being recurrence-free

d) Death from all causes while being recurrence-free

e) Time to study treatment discontinuation

The analyses are provided in the accompanying Excel files from the October 2017 data cut. Please note that interpretation of subgroups analyses as presented, is associated with limited statistical power in detecting an effect.[6]

Furthermore, there are also a number of limitations associated with this analysis request which have been highlighted below.

Presenting results for cause-specific hazards using standard survival analysis will be misleading. First of all, it is not possible to interpret this information as an event-specific risk when some other risks are operating, which may be actually related, and are unaccounted for.

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In the presence of competing risks, the cumulative incidence derived from Kaplan-Meier estimator is always larger than that obtained by accounting for competing risks.

- In Kaplan-Meier estimation, an individual is removed from the risk set when the individual experiences a competing event. Within competing risk framework, the individual is an event in the calculation of overall survival probability. Therefore, the overall survival of any event is lower when competing risks are considered.
- When event 2 is considered as non-informative censoring in Kaplan-Meier estimator, the overall survival will be larger.
- In competing risk analysis, individuals experiencing the competing risk event have zero probability of experiencing the event of interest.
- In contrast, the naïve Kaplan-Meier approach assumes that these individuals would experience the same probability of the event of interest, resulting in an overestimation of the cumulative incidence of the event of interest.[9]

B2. **Priority request.** If possible, please provide, the K-M analyses used, in the company model, to represent progression from

- LR to DM
- RF to LR
- RF to DM

Please also provide these data stratified by melanoma stage at time of full resection, i.e., Stage IIIA, IIIB and IIIC (IIIC in total and also separated into Stage IIIC [1-3 LN+] and Stage IIIC [>=4LN+])

Please be aware that the request for the breakdown of LR→DM by melanoma stage at diagnosis has not been provided. The data from the overall population has been provided, however, the requested subgroups were too small to provide any meaningful analysis. All other requested analyses are provided in the accompanying Excel files. Please note that interpretation of subgroups analyses as presented, is associated with limited statistical power in detecting an effect.[6]

B3. Please clarify which data were used to generate the exponential distribution that was used in the company model to represent patient transition from RFS to death (as first event).

Further to the explanation provided on page 56 and 76 of Document B, manufacturer's submission:

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Exponential models were fitted to the transition from recurrence-free to death in each treatment arm due to the small number of direct transitions from recurrence-free to death observed in the KEYNOTE-054 trial (i.e., two in the pembrolizumab arm, one in the placebo arm). Within each cycle, the transition probability from recurrence-free to death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in the UK were from the Office for National Statistics (ONS).[4]

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr [redacted] and Dr [redacted], on behalf of the Therapy & Guidelines sub-committee**
2. Name of organisation	**British Association of Dermatologists (BAD)**

3. Job title or position	**Consultant Dermatologists**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD's charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To stop progression in this context i.e. as an adjuvant treatment

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Progression free survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes as there is no adjuvant therapy available for earlier stage of Melanoma
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Surgery Interferon has been used but is not currently generally used due to side effects and lack of effectiveness (Of note there are other adjuvant studies in melanoma that have also been published recently looking at Nivolumab, Ipilumumab and Dabrafenib combined with Trametinib as adjuvant treatments but these are not currently available outside trials)
• Are any clinical guidelines used in the	NICE melanoma guidelines

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is generally well defined
• What impact would the technology have on the current pathway of care?	From the results of the recently published trial: Eggermont et al N Engl J Med 2018; 378:1789-1801 there was a significant increased progression free survival in these patients on pembrolizumab compared to placebo
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be a new addition to treatment of Stage III melanoma as it is adjuvant therapy but it is currently used for Stage IV metastatic melanoma. It will only be given for 12 months and will still be given every 3 weeks as per the metastatic regime
• How does healthcare resource use differ between the technology and current care?	Not currently available as adjuvant therapy

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist clonics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As it is currently used already for metastatic melanoma the facilities, equipment and training are in place however it will now include Stage III patients so more resources will be required however as it leads to increased progression free survival less resources will be required for more advanced melanoma if patients are not progressing also the number of surgical interventions should decrease
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As it is already being used for metastatic the answer is basically no The adjuvant study showed no differences in terms of toxicity and patients will generally be fitter with earlier stage melanoma

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – toxicity and likely be given only for 12 months as per trial
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is likely to if patients don't progress Patients with metastatic melanoma will need further treatments including targeted treatments and immunotherapy, and may also require in patient treatment and palliative care It would be difficult to calculate for these benefits at this stage
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes there has been no effective adjuvant treatment available for Stage III melanoma
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There have been reported significant side effects with this medication that can in some instances have long term consequences such as endocrine and neurological side effects In this study adverse events of grades 3 to 5 that were related to the trial regimen were reported in 14.7% however a significant number of these are likely to be reversible on stopping the medication
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	For adjuvant studies progression free survival and ultimately overall survival need to be measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Some adverse events are seen after discontinuation of immunotherapies but these are often similar to those seen in the trials however as it effects the immune system it is possible that adverse events may occur subsequently that wont be reported specifically in trials but this is likely to be rare
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	There are other comparators including Nivolumab, Ipilumumab, Dbarafenib and trametinib but I think NICE are aware of these comparators as a lot are also going through NICE appraisals
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Step change in treatment of Stage III melanoma
- Significantly improved progression free survival
- Generally well tolerated
- Defined period of treatment i.e. 12 months
- Potentially will decrease need for surgery that will have long term consequences for e.g. lympoedema secondary to lymph node dissections

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**British Association of Skin Cancer Specialist Nurses**
3. Job title or position	**Specialist Skin Cancer Nurse**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BASCSN is a member organisation for specialist skin cancer nurses. It is funded through its annual conference and occasional grants from pharmaceutical companies to support educational activities.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Increased patient numbers in oncology clinics.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities already in place.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Will mean increased workload for staff in oncology outpatients, chemotherapy units, A&E and acute settings

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment generally well tolerated. Favourable risk-benefit.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- This is a new approach to treatment
- The treatment is generally well tolerated
- There would be an additional burden of work for departments managing skin cancer
- The treatment has the potential to provide significant benefits for patients
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

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2. Name of organisation	Melanoma UK
3. Job title or position	Freelance Project Manager, Melanoma UK Digital Patient Registry Passionate aunty – my personal link to melanoma follows the death of my niece in [redacted]. [redacted] died at the young age of [redacted] leaving behind a young family and a trail of devastation.
4a. Brief description of the organisation (including who funds it). How many members does it have?	Melanoma UK is a patient support and advocacy group, set up in 2007. The group was set up in memory of Jon Herron, a young man from Larne in Northern Ireland who sadly passed away in May 2008. Initially the aim was to fund raise and raise awareness of melanoma. The group started off as Factor 50 and became Melanoma UK in 2013. Our aim at Melanoma UK is to give patients and their families much needed support during the very difficult times faced upon diagnosis. We aim to get them access to the best care available and support them throughout the journey. Patients, families, carers and clinicians are at the heart of our work. We are passionate about our work and will work tirelessly to get results.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Melanoma UK not only provide face-to-face opportunities to meet and discuss how patients and carers deal with their condition, we now have a lot of our interaction taking place online, through blogs, internet forums and websites. Through the launch of the Melanoma UK Patient Registry we are also able to capture real time information on patient experience dealing with melanoma. These various platforms provide patients and carers a safe space to post their hopes for the short, medium and long-term future. They can share their fears with other patients. Melanoma UK try to help people to understand their condition. We are a hands-on patient support group.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I am not a patient but as a carer, I felt overwhelmed, helpless and uncertain every minute of the day. Knowing that my niece faced physical and emotional challenges bought on a wide range of feelings including, fear, shock, desperation and isolation because I was uncertain of her future and couldn't talk to the rest of the family as I knew the news would rip their heart out. I was also unsure of what support was available for me as her carer and didn't like to ask because this was her journey not mine.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	It can be confusing with some patients (and carers) and depends where they are in their diagnosis. A lot of patients are not fully aware of what treatments are available on the NHS and rely heavily on having a good specialist/oncologist and/or clinical nurse specialist to explain options.
8. Is there an unmet need for patients with this condition?	Patients need HOPE and understand what their quality of life will look like. There is no real support following diagnosis when dealing with anxiety, depression, social isolation, etc. NHS resources are already stretched, and a patient needs to know that someone can help them 24/7 if needed. They have unanswered questions linked to not just themselves but also the impact this disease will have on the family, finances, work life balance – they need emotional support. The main unmet needs we hear from patients include uncertainty about their future, lack of information about risk of recurrence, outcomes if melanoma were to spread, fears of cancer returning, what next? The cancer care pathway can also be very confusing with patients. When a patient is given NED status they experience a rush of relief, but, then quickly realise that although they can wear the imaginary badge of 'survivor', they still need reassurance that they are not going to be forgotten.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	This could improve a patient's overall condition and extend their life Ease of use HOPE

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Severity of side effects Difficulty in use (injection rather than tablet) Downtime as the technology has to be used at hospital rather than home
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	NO Melanoma is a disease that affects young, old, black, white……melanoma does not discriminate so neither should the treatment available.

Other issues	
13. Are there any other issues that you would like the committee to consider?	As a business woman I appreciate this has to be a commercial decision based on all the facts shown today. As a devastated aunty and an ambassador of Melanoma UK, I just want you all to take a moment and 'try' to step in to a patient's shoes. Most patients do not know the significance of QALY, they are fighting for their life. Not everything can be put into a box and I know there is a need to evaluate and assess the value for money, but, please remember a patient would give anything to have another year to spend time with their family. Melanoma UK are so grateful to NICE for the approval of all the treatments that have come along since the days when we had nothing. The patient community recall the days when there was nothing in melanoma apart from dacarbazine and radiotherapy. Many patients who are now in the melanoma arena are able to benefit from the therapies that previous patients had only heard about as treatments that might be around in the future. We hope that this treatment is going to be another success story, not only for the patients and the clinicians, but for NICE as well.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission:	

- This technology is vital for our patients – it gives them hope and help them live longer.
- The success of this treatment could potentially improve a patient's life
- Don't let it all be about the numbers - most patients do not know the significance of QALY, they are too busy fighting for their life.
- There is more need for transformational drugs/treatments for melanoma sufferers

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission in September 2018 for the 1st meeting on the NICE appraisal of adjuvant pembrolizumab in stage III malignant melanoma

1. The likely marketing authorisation for adjuvant pembrolizumab in melanoma will be in stage III disease. The more advanced categories within stage III disease (eg stage IIIB, IIIC) carry much worse prognoses than stage IIIA disease. The adjuvant pembrolizumab trial was done in patients with stage III disease of which 84% of patients had stage IIIB and IIIC disease (AJCC 7th edition). This case mix is likely to be similar to that in clinical practice in England should adjuvant PD-L1- directed therapy be approved by NICE. NHS England thus considers that stage III disease is a marker of sufficiently high risk for identification of patients in practice for consideration of adjuvant treatment.
2. NHS England does not consider that the new AJCC staging system (8th edition) in melanoma should make any difference to the consideration of options in stage III patients which include that of adjuvant PD-L1-directed therapy (if this active treatment option is recommended by the Appraisal Committee).
3. The benefit of adjuvant pembrolizumab on recurrence rates when compared with routine surveillance looks very clinically significant as the rates of 12 month recurrence free survival (RFS) are 75% in the adjuvant pembrolizumab arm and 61% in the placebo (routine surveillance)arm. It is unusual for adjuvant therapies to show this degree of difference so early in follow-up.
4. NHS England notes that the median duration of follow-up in the adjuvant pembrolizumab study is very short at 16 months and that there are very few patients at risk of recurrence after 16 months. The dataset is thus very immature in terms of observing what the long term difference might be for recurrence-free survival, let alone for overall survival. NHS England notes that a more mature analysis of overall survival in the adjuvant pembrolizumab trial is planned and has been set out in the company's submission (it is event-driven and likely to occur in [redacted]).
5. NHS England observes that on the basis of the early data cut described in this appraisal, there was no statistically significant difference in RFS between PD-L1 positive and negative subgroups. There were however relatively few events in these analyses and this question of differential benefit according to PD-L1 status will thus only be properly answered with further follow-up. The same applies to the outcomes according to the various substages of stage III disease.
6. NHS England notes the ERG observation that the assumption of proportional hazards may not hold for the long term modelling of RFS with pembrolizumab. This issue will only be answered with further follow up.
7. Although pembrolizumab given for advanced disease does probably cure a significant proportion of patients (probably about 20-25%), the majority of patients relapse and die of their metastatic melanoma. There are precedents from other malignancies in which even non-curative systemic therapy in the advanced disease setting nevertheless increases the cure rate as adjuvant treatment in early disease post-surgery eg breast cancer, colorectal cancer, non small cell lung cancer. NHS England would therefore consider it likely for adjuvant pembrolizumab to have a long term survival benefit in melanoma (as adjuvant ipilumumab has already shown).

8. The company's model produces optimistic differences in rates of RFS at 5 years between pembrolizumab and placebo (approximately 60% vs 35%, respectively) and at 10 years (approximately 42% vs 18%, respectively). The main reason for considering these differences to be optimistic and in particular for the figures for routine surveillance to be pessimistic is because immunotherapy for those patients relapsing after routine surveillance with metastatic melanoma produces a significant proportion of patients who appear to remain progression-free: in a recent publication, the 3 year progression-free rate with nivolumab monotherapy was 32% (and thus the probable cure rate is 20-25%) and that of the combination of nivolumab plus ipilimumab was 39% (and thus the probable cure rate is about 30%). This long term treatment effect needs to be added on to the proportion of patients who never relapse after complete resection of stage III disease.
9. The subsequent treatments used at relapse in the economic model are important to consider. MSD has used a survey to describe what is used currently for the treatment of advanced melanoma. The survey states that about 15% of patients are currently treated with vemurafenib monotherapy: such treatment is rarely used as almost all the patients with BRAF positive disease are treated with the superior combination of dabrafenib plus trametinib. The survey used by MSD also states that 6% of patients receive ipilimumab monotherapy: such treatment is rarely used as ipilimumab when used is in combination with nivolumab. NHS England therefore doubts some of the subsequent treatments modelled by the company.
10. On the basis of current knowledge (ie without mature follow-up of the adjuvant pembrolizumab and nivolumab monotherapy trials), later relapses on adjuvant pembrolizumab (eg beyond 1 year after completing treatment) will be managed similarly to those relapsing on routine surveillance ie with dabrafenib and trametinib if BRAF positive and with consideration of nivolumab monotherapy/pembrolizumab monotherapy/nivolumab plus ipilimumab combination therapy. However, there will be some differences in management in those that relapse early (eg <6 months after completing adjuvant pembrolizumab) with less initial nivolumab monotherapy/pembrolizumab monotherapy and greater consideration of ipilimumab monotherapy as well as nivolumab and ipilimumab combination therapy in some cases. Patients who relapse during adjuvant pembrolizumab will not receive subsequent pembrolizumab/nivolumab monotherapy. Mature follow up will give some guide to the profiles of subsequent treatments for those patients treated with adjuvant pembrolizumab as well as pointers to their efficacies in patients treated with adjuvant pembrolizumab.
11. NHS England observes that no administration costs for adjuvant therapies appear to have been included in the economic model. This is incorrect. The NHS England chemotherapy delivery tariff in 2017/18 for pembrolizumab is coded as SB13Z and should be £299 per cycle (ie every 3 weeks). If these costs have been omitted, then the cost of administering pembrolizumab for a full 1 year of treatment would be about £5K.
12. NHS England notes that the trial only recruited patients of ECOG performance status (PS) 0 or 1. That the population was a very fit one is clear in that 94% of patients were of PS 0. Adjuvant therapies carry potentially significant and enduring toxicities which make the justification for continuing therapy more difficult when the long term benefits of adjuvant pembrolizumab are as yet unclear. The fittest patients tolerate treatment best and as adjuvant therapy, toxicities of grade 2 are still very important when the long term benefit is

unknown. NHS England notes that 15% of patients treated with pembrolizumab had a grade 3-5 adverse event, 34% had immune-related adverse events (mainly grade 1 and 2) and 14% had an adverse event which led to treatment discontinuation. Immunotherapies such as pembrolizumab can induce uncommon but potentially severe and distressing side-effects (eg pneumonitis, colitis). Given the uncertainty as to the degree of benefit and the significant toxicity of pembrolizumab, NHS England would therefore wish for adjuvant pembrolizumab be used in patients who are of good performance status (ie ECOG PS 0 or 1).

13. NHS England regards adjuvant pembrolizumab as offering promising but uncertain benefits at the expense of significant toxicity. It therefore regards adjuvant pembrolizumab as being a good candidate for the CDF on the basis of its clinical uncertainty. Time in the CDF would allow mature data to better model the longer term projections of RFS, distant metastasis-free survival and overall survival. The validity of the assumption of Cox proportional hazards holding for the at least the duration of follow-up would be able to be tested. A more accurate answer will also be obtained as to the question of how long the duration of treatment benefit can be assumed to last. More mature follow up would also address whether the routine surveillance arm has been modelled pessimistically. Finally, more mature follow up would help address the uncertainty as to the treatment benefit of further immunotherapy after previous adjuvant pembrolizumab.
14. NHS England notes that this appraisal offers the unusual contrast between a company model which concludes that adjuvant pembrolizumab is cost saving and the ERG's position which is to not offer any ICERs (other than a very wide range) given the uncertainty of the inputs into the cost effective modelling. Should the committee recommend adjuvant pembrolizumab to the CDF without its usual conclusions as to a plausible range of ICERs following a variety of scenario analyses, NHS England nevertheless considers that a satisfactory financial arrangement between MSD and NHS England is possible for inclusion of adjuvant pembrolizumab for melanoma in the CDF.

Prof [redacted]

[redacted]

September 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	
2. Name of organisation	**King's College London and Guy's and St Thomas' NHS Foundation Trust**

3. Job title or position	**Senior Lecturer and Honorary Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent recurrence and cure a population of patients who would otherwise develop incurable advanced disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Absence of recurrent disease
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The NICE guidance for management of malignant melanoma (2015)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Adjuvant treatment of melanoma in the NHS is uniform at the moment as there is currently no licensed available therapy Management of the disease in the advanced setting is largely uniform, there are some academic questions about sequencing of therapy that remain to be answered.
• What impact would the technology have on the current pathway of care?	We would use anti-PD1 directed therapy in high risk resected patients. A significant proportion of whom would then not develop advanced disease requiring multiple lines of systemic therapy. The use of anti-PD1 systemic therapy on relapse for patients exposed to anti-PD1 therapy in the adjuvant setting remains an area of uncertainty that will benefit from further clinical data as it emerges.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used at an earlier time point in the disease.

• How does healthcare resource use differ between the technology and current care?	The technology will be delivered every 3 weeks for 12-months in the adjuvant setting. In advanced disease it is delivered until progressive disease, unacceptable toxicity or 2-years of treatment. It is also notable that different anti-PD1 monoclonal antibodies are also used in the advanced setting alone or in combination with other immunotherapy agents (anti-CTLA4). In the sub set of patients who would receive this technology and then not develop progressive disease (be cured) there need for further costly systemic therapy will be removed.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Stage III and stage IV resected malignant melanoma. There is some uncertainty over the need to treat IIIa melanoma with metastatic deposits of less than 1mm in the sentinel lymph node, but this requires further clinical data to confirm or refute.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Centres will need to give attention to capacity in clinics and cancer day units. Anti-PD1 therapy is associated with a risk of auto-inflammatory side effects that may require medical intervention to manage. The risk is low at 14.7% grade ¾ toxicity in the Keynote 054 study (of which a proportion experience thyroid toxicity alone)

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Current guidelines on the management of anti-PD1 therapy adverse events (SmPC, ESMO guidelines) will be applied to guide the need to stop in the event of toxicity. This is standard practice in the advanced setting.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes in that it has the potential to bring forward benefit with anticipated significant improvement in overall survival for the high risk resected melanoma population.
• Does the use of the technology address any particular unmet need of the patient population?	Risk reduction for high risk resected melanoma
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicity rates are low with anti-PD1 therapy. Patients will be monitored according to established practice for the use of anti-PD1 therapy in the advanced setting and toxicities managed in accordance with ESMO guidelines.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK	Yes

clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Relapse free survival at one year. Overall survival for Keynote 054 is expected after more time has passed. We have evidence that ipilimumab at 10mg/kg improves OS versus placebo in this population. We also have evidence that Nivolumab (an alternative anti-PD1 monoclonal antibody with very similar efficacy to pembrolizumab in the advanced setting) improves RFS at one year compared to ipilimumab. The incremental improvement in RFS for the anti-PD1 monoclonal antibodies combined with the reduced toxicity rates makes their use in this setting indicated.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	We do not have real world adjuvant data yet. We have our own real world advanced audit data which compares favourably with published data in the advanced setting.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Does treatment with	It permanently cures disease in my opinion. We know that ipilimumab significantly improves OS for this

pembrolizumab mainly postpone disease recurrence or permanently cure the disease?	population. We know anti-PD1 drugs are superior to ipilimumab in the advanced (for RFS and survival) and adjuvant setting (for RFS to date). Bringing forward this chance of long term cure is therefore highly justified.
25. Would you expect the benefit of pembrolizumab given as adjuvant treatment to continue after treatment discontinuation? If so, for how long?	Yes, indefinitely. The nature of the immune system is its ability to remember and reject through immunological memory. To the best of our ability we believe that patients are obtaining permanent cure from immune therapy
26. What conclusions can be drawn or what is the relationship between recurrence free survival and overall survival?	RFS predicts reliably for OS in this setting
27. The American Joint Committee on Cancer (AJCC) 8th edition has redefined stage III groupings and included an	The IIID patients in AJCC 8 would previously have been staged as IIIB or IIIC depending on the absence or presence of nodal metastases under the AJCC 7th staging used in Keynote 054. As such this population were included in Keynote 054 and should be considered eligible for the resultant licensed therapy

additional stage IIID subgroup. Does this affect the generalisability of KEYNOTE-054 to clinical practice in England in the future?	
28. In clinical practice, what treatment options are available for people who develop metastatic disease after pembrolizumab? Are there treatments that are used more commonly than others?	Immune therapy with anti-PD1+ Anti-CTLA4, single agent anti-PD1, single agent anti-CTLA4 and combination targeted therapy in patients with BRAF mutations.
29. In clinical practice, would people who receive pembrolizumab as adjuvant therapy be treated with a PD-1/PD-L1 inhibitor in the advanced setting?	This is still the subject of clinical study. In my opinion in the event of relapse post anti-PD1 therapy in the adjuvant setting further immunotherapy with combination therapy or anti-PD1 therapy would remain appropriate.

30. In clinical practice, would there be wastage of pembrolizumab (e.g. if there is discontinuation)?	It is a flat dose so no.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Pembrolizumab improves survival for stage III melanoma
- Long term cure is likely for some treated patients
- RFS is an appropriate surrogate for OS at this stage in this population
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Assocaition of Skin Cancer Specialist Nurses**

3. Job title or position	**Clinical Nurse Specialist – Skin Cancers**
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	X☐ yes

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STA REPORT ID1266

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

[ID 1266]

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

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

Produced by: Liverpool Reviews and Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Tosin Lambe, Research Associate (Health Economics), LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Eleanor Kotas, Research Associate (Information Specialist), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool

Ernie Marshall, Consultant in Medical Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust

Correspondence to: Janette Greenhalgh, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 23rd August 2018

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Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: Within the last 3 years**,** Neil Steven has provided consultancy to Amgen, Merck Serono and Incyte. His fees are to be directed to the Fighting Skin Cancer Charity at University Hospital Birmingham. Dr Steven has also received fees for speaking from Bristol Myers Squibb and Amgen.

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervision of the collation of the final report
James Mahon	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the adverse event data
Eleanor Kotas	Cross checking of the submission search strategies
Joanne McEntee	Critical appraisal of the company submission
Ernie Marshall	Clinical advice and critical appraisal of the clinical sections of the company submission

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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).

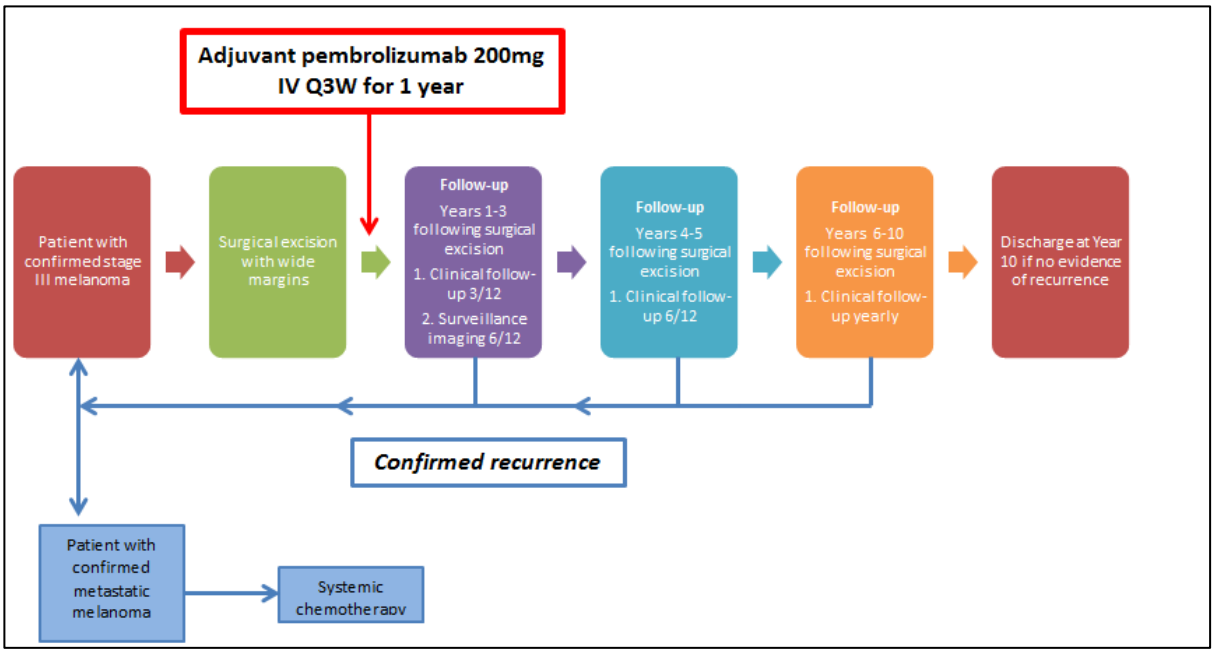

Figure 1 Current clinical pathway of care showing the context of the proposed use of the technology

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.

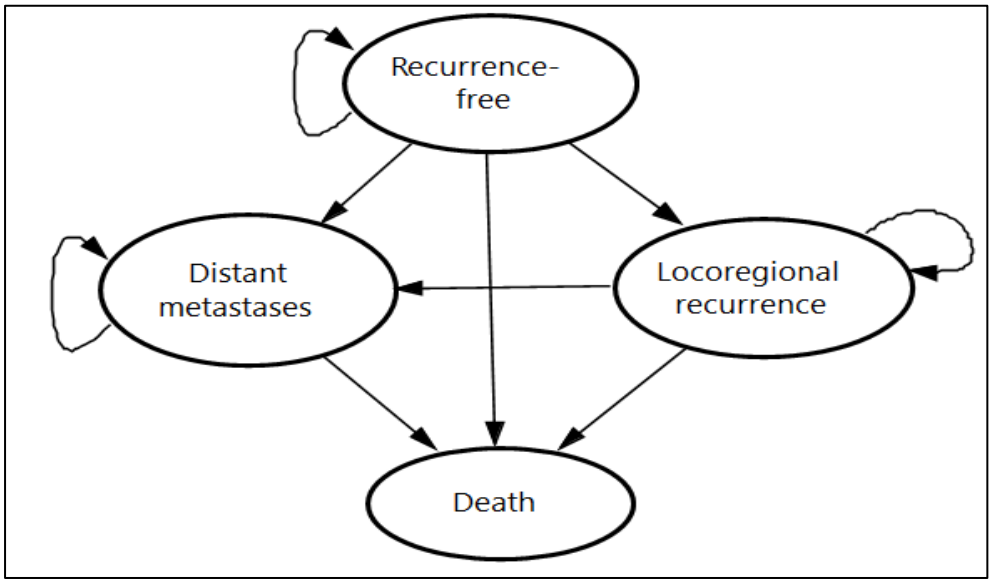

Figure 2 Health state structure of the company model

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.

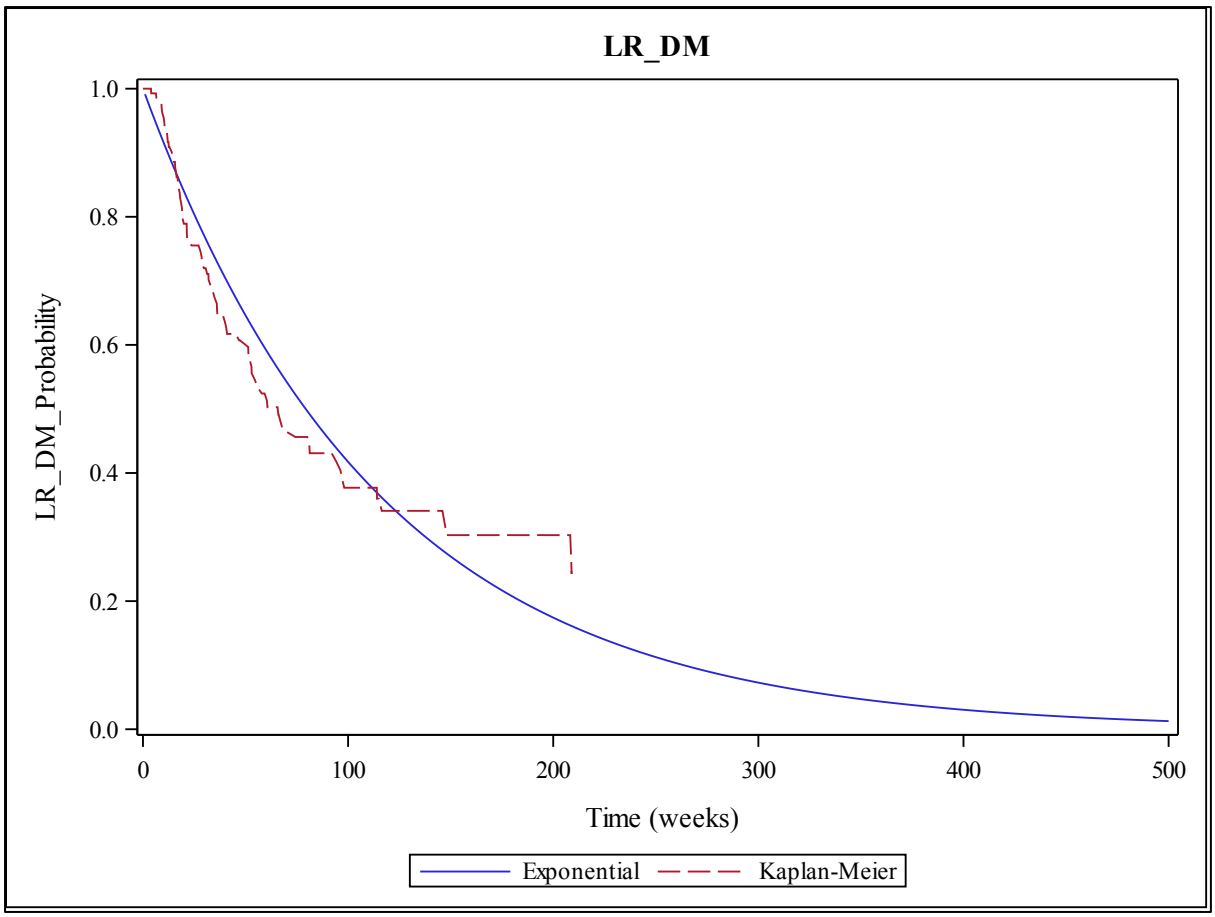

Figure 3 Exponential model fitted to the observed LR-to-DM data from the Flatiron database

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).

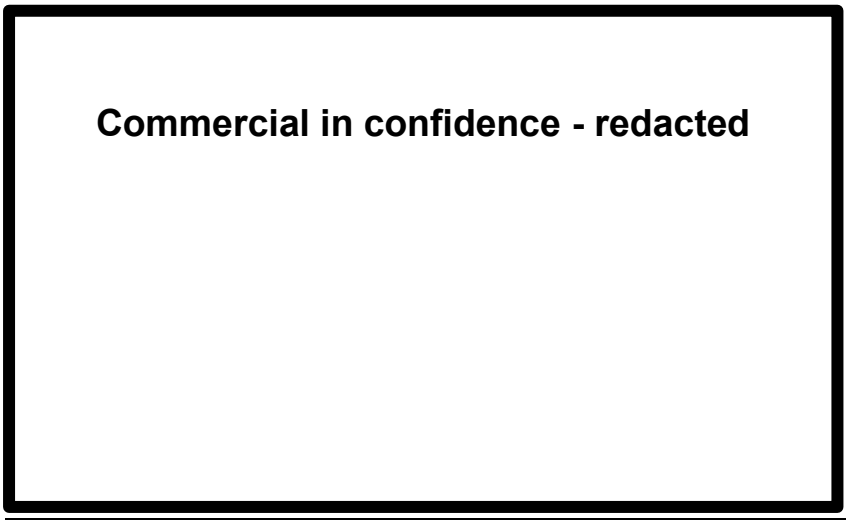

Figure 4 Observed Kaplan-Meier curve for time to treatment discontinuation in the pembrolizumab arm of the KEYNOTE-054 trial

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.

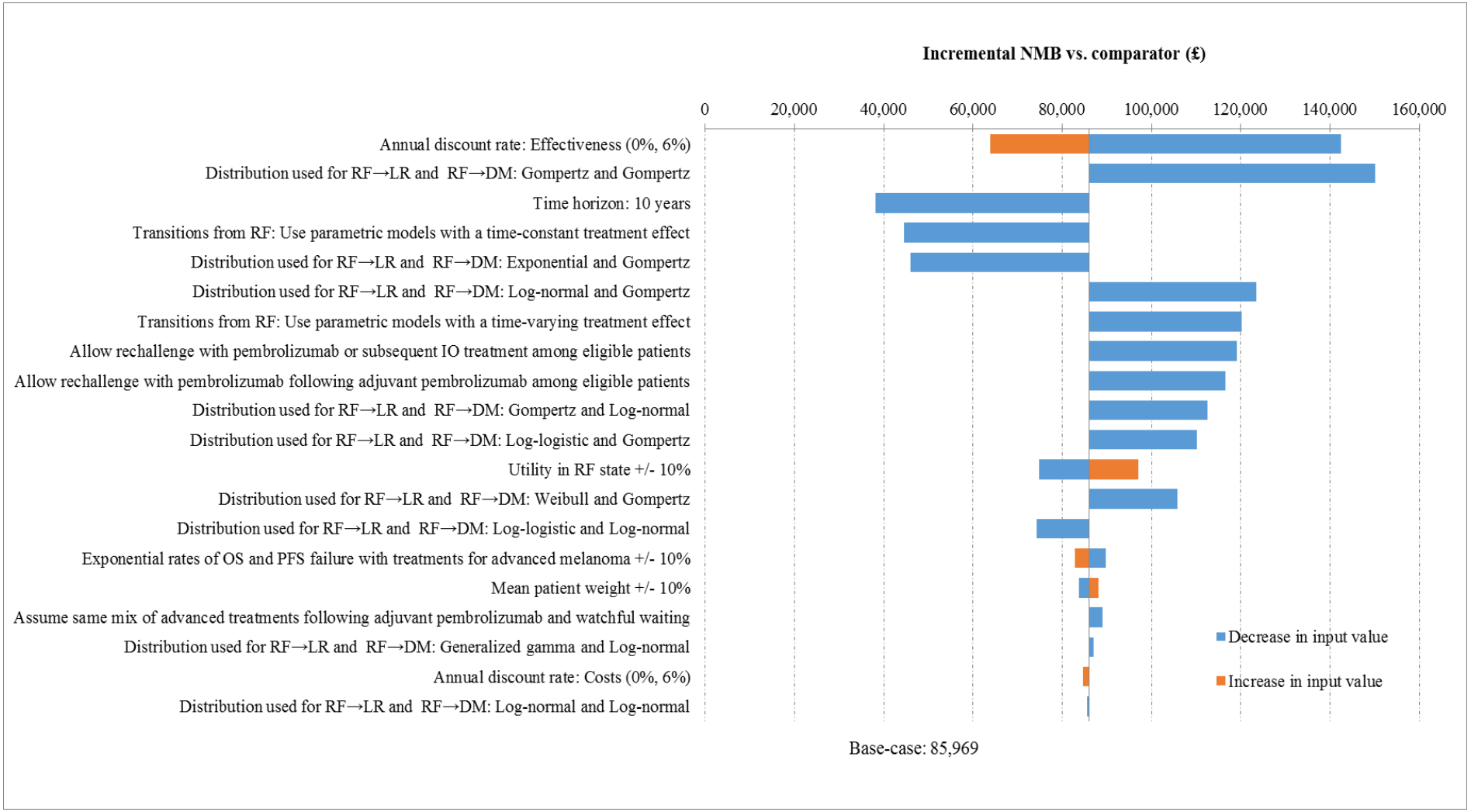

Figure 5 Tornado diagram shown one-way sensitivity analysis results for treatment with pembrolizumab versus routine surveillance DM=distant metastases; ICER=incremental cost-effectiveness ratio; IO=immune-oncology; LR=locoregional; OS=overall survival; PFS=progression-free survival; RF=recurrence-free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

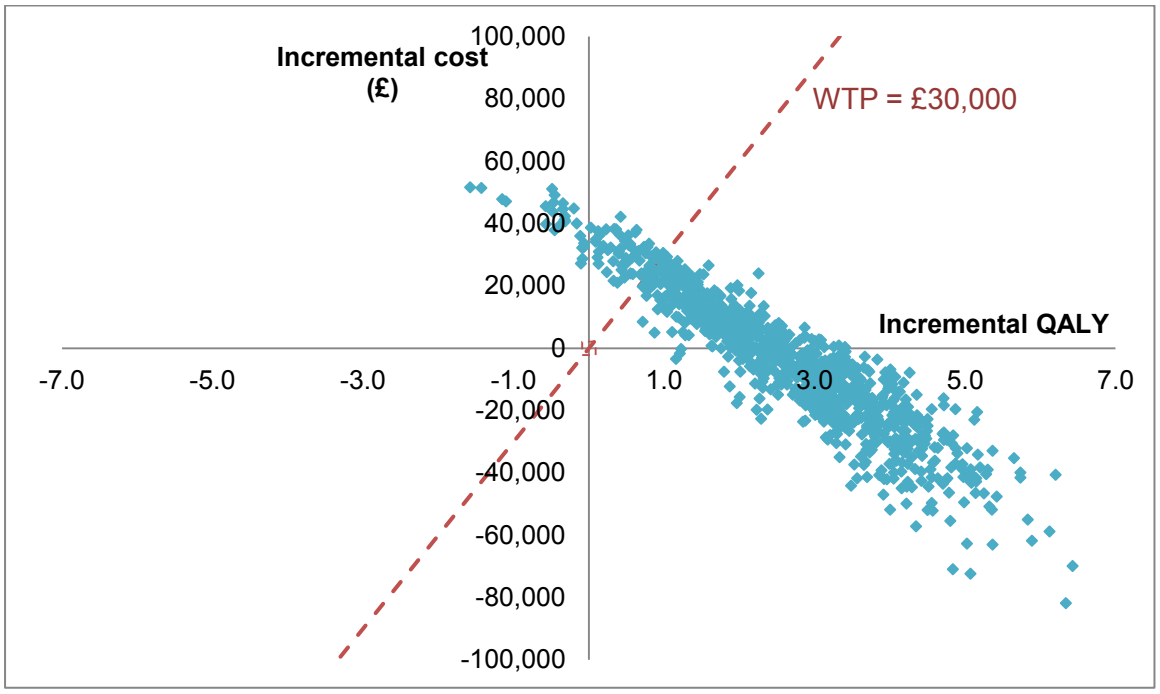

Figure 6 Scatter plot of incremental cost and incremental QALY for pembrolizumab versus routine surveillance (1000 iterations) ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; WTP=willingness-to-pay
Source: Company model, probabilistic sensitivity analysis worksheet

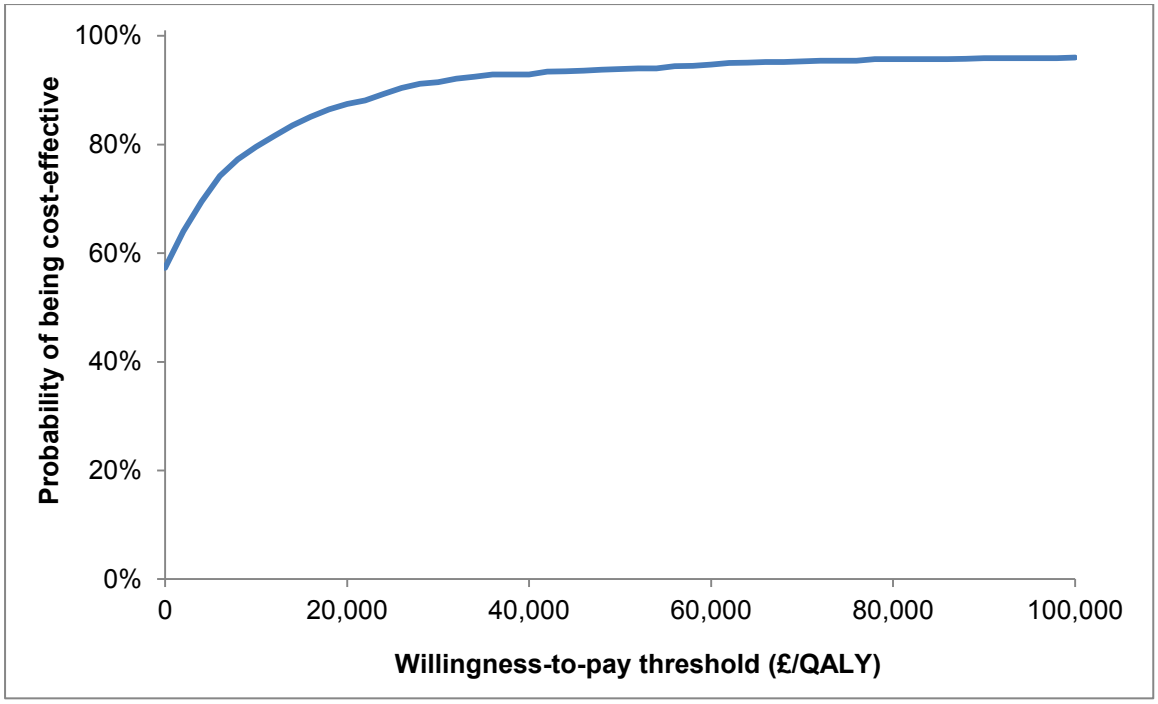

Figure 7 Cost effectiveness acceptability curve of treatment with pembrolizumab vs routine surveillance QALY=quality adjusted life year
Source: Company model, probabilistic sensitivity analysis worksheet

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.

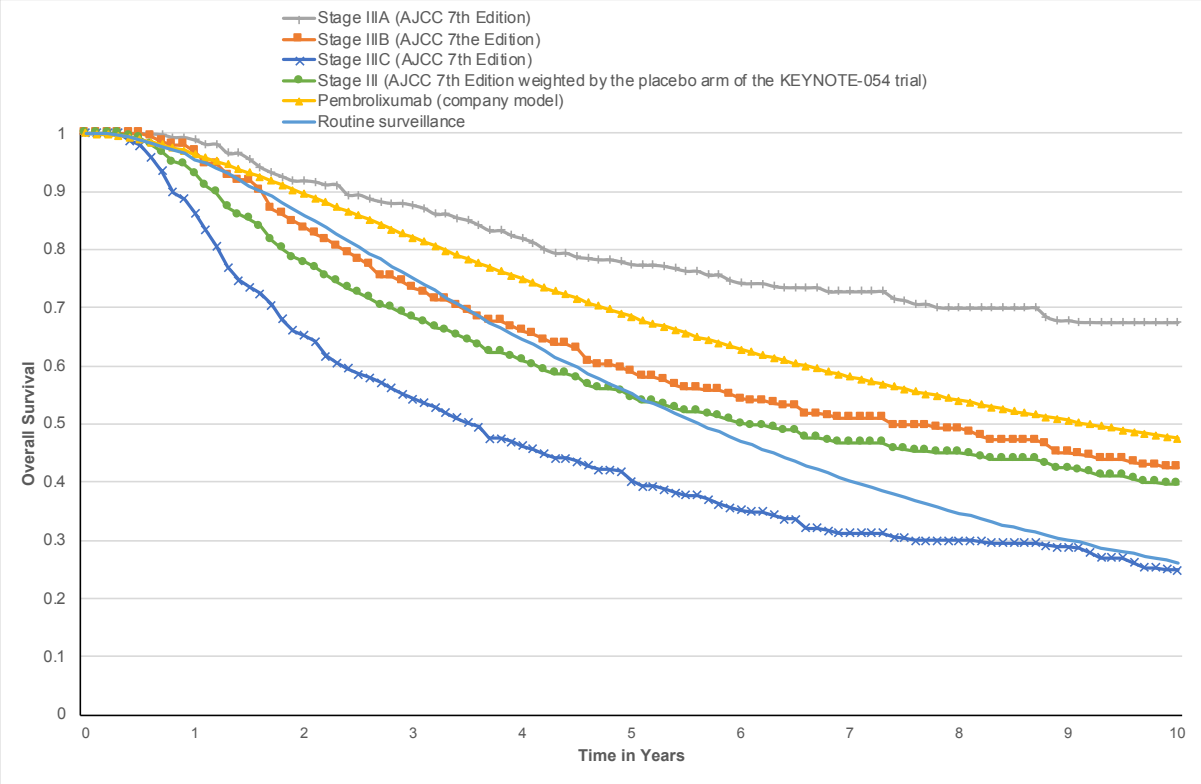

Figure 8 10-year OS for patients with Stage III melanoma: SEER data from 2010 based upon AJCC 7th Edition staging classifications and data from the pembrolizumab and routine surveillance arms of the company model

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).

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence [ID1266]

You are asked to check the ERG report from Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 5 September 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8 Paragraph 4, line 2	"..expects an opinion to be published **********." Amend to; "..expects an opinion to be published **********	This has been updated since the submission. CHMP opinion is currently expected to be granted in **********.	For completeness, the ERG report will be updated accordingly

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 Paragraph 4, line	"Transitions from the LR health state to the DM or death health states were estimated using patient-level data from the Flatiron database." Amend to; "Transitions from the LR health state to the DM health state were estimated using patient-level data from the Flatiron database."	No transitions were observed from LR to death in the Flatiron database. Therefore, this data was not used to estimate transitions from LR to death in the economic model.	This is an error. The ERG report will be updated to read: 'Transitions from the LR health state to the DM health state were estimated using patient-level data from the Flatiron database'

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 Bullet 7	"…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" This statement is factually inaccurate and should be removed.	The EQ-5D compliance data are provided in the Appendix on page 96. A signpost to this data is provided on page 83 of Document B as per "Full results and information on compliance of EQ-5D are provided in Appendix N."	This is an error on our part. The bullet point will be removed

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15	"In the patient population under consideration, the definition of	MSD disagree with the ERG's implication that the definition of patients eligible for treatment with pembrolizumab is unclear. The patient population under consideration is well defined in the KEYNOTE-054 trial and will be reflected in the expected marketing authorisation wording, as follows: [redacted]	The ERG agrees with the company that the patient population in the KEYNOTE-054 trial is well-defined in terms of disease stage and classification and other baseline characteristics. The ERG also agrees with the company that the patient population of the KEYNOTE-054 trial is reflected in

	high risk is unclear and it is uncertain whether, in the NHS, the whole of the KEYNOTE-054 trial population would be considered as high risk of death or disease recurrence." Suggest to remove		the expected marketing authorisation, i.e. [redacted]. However, the ERG notes that the term 'high risk' is not used in the description of the patient population of the KEYNOTE-054 trial, nor is the term 'high risk' used in the text of the expected marketing authorisation. As stated on page 24 of the ERG report: The ERG has been unable to unable to identify a definitive definition of high risk of either disease recurrence or death 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. No amendment required.

	this statement		

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 Paragraph 2	"re-challenge with pembrolizumab following progression at Stage III" Amend to "re-challenge with pembrolizumab following recurrence at Stage III"	This would more accurately reflect the terminology used in KEYNOTE-054.	The ERG report will be updated to read: 're-challenge with pembrolizumab following recurrence at Stage III'

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23-24	"Clinical advice to the ERG is that there is	Although we appreciate the interlink between disease recurrence and subsequent mortality, the NICE defined scope relates to high risk of recurrence. Furthermore, the patient population under consideration is well defined in the KEYNOTE-054 trial and will be reflected in the expected marketing authorisation wording, as follows:	This is clinical opinion not a factual

	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 at high risk of death." Suggest removing this statement.	[redacted]	error. No amendment required.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24	"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	The patient population under consideration is well defined in the KEYNOTE-054 trial and will be reflected in the expected marketing authorisation wording, as follows: [redacted]	Please see ERG response to Issue 4 and Issue 6. No amendment required.

	considered to be at high risk of death or disease recurrence." Suggest removing this statement.		

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 Table 3, row 6	"Jun 2017" Amend to "July 2018"	TA531 was updated following the CDF review, which was published in July 2018.	This is an error on our part. The date will be changed in the ERG report to July 2018

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25	"Clinical advice to the ERG is that the Q3W protocol used to deliver pembrolizumab places a high burden on NHS nursing and pharmacy staff." Suggest removing this statement as the delivery of pembrolizumab in this	Delivery of pembrolizumab Q3W is approved by NICE and in use in clinical practice for the following indications; 1. *KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.*	The ERG is aware that pembrolizumab is recommended by NICE for use in several disease areas. Nonetheless, clinical advice to the ERG is that the Q3W use of pembrolizumab

	indication is in line with previous licenses.	2. *KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.* 3. *KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.* 4. *KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.* 5. *KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.* 6. *KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.*	places a high burden on NHS nursing and pharmacy staff. No amendment required

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35, 39	Page 35; "However it should be noted that that a HR estimated from a Cox PH model has no meaningful interpretation when the PH assumption is violated" Page 39; "The ERG notes that the HR result must be interpreted with caution due to the likely violation of the PH assumption in this analysis." This statement is factually incorrect.	This is on the basis of the paper by Alexander et al (NEJM, 2018) suggesting evidence of the PH assumption being relaxed when modelling for delayed treatment effects (Sit T et al, Stat Med, 2016). This method would be appropriate given the hypothesis that immunotherapies demonstrate a delayed treatment response particularly in patients with progressive disease	This is not a factual error. The ERG does not consider that the paper by Alexander supports the relaxation of the PH assumption in trials where the treatment effects are delayed. No amendment required.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46 Paragraph 5, line 4	"The ERG notes that more patients in the placebo arm than in the pembrolizumab arm developed cellulitis (0.6% versus 1.4%)" Amend to "The ERG notes that more patients in the placebo arm than in the pembrolizumab arm developed cellulitis (1.4% versus 0.6%)"	These numbers are the wrong way around.	This is a factual error. The ERG report will be updated

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48	"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." This statement is factually inaccurate and should be removed.	The EQ-5D compliance data are provided in the Appendix on page 96. A signpost to this data is provided on page 83 of Document B as per "Full results and information on compliance of EQ-5D are provided in Appendix N."	This is an error on our part. The statement will be removed. The following text will be added to the report: The ERG notes that the patient response rates to the EQ-5D questionnaire were high across the time points reported (Weeks 12 to 48). Response rates ranged between 88.4% and 94.1%. In addition, the text on page 54, final bullet point has been amended to read: The CS does, however, include a discussion of the EQ-5D-3L data which were also collected during the KEYNOTE-054 trial.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53 to 54	"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 support the company's claim." Suggest to remove this statement as the first sentence does not support the conclusion of the second sentence.	Pembrolizumab is a checkpoint inhibitor. Therefore the conclusions of authors would support the company's claim, rather than question it.	This is an error on our part. The text is amended to read: 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.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60	"The company states that the expected completion data that will allow for the OS analysis is in 2021." Amend to "The company states that the	This information should be marked as commercial in confidence.	This is an error on our part and the ERG report will be updated accordingly

	expected completion data that will allow for the OS analysis is in ****."		

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60 Paragraph 2	"which the company interprets to mean no systemic chemotherapy until LR or DM." Amend to "which the company interprets to mean no systemic chemotherapy until DM."	This is a more accurate reflection of the economic model.	This is not a factual error. For clarity, the ERG will be amended as requested

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60 Paragraph 4	"…drug acquisition costs, drug administration costs…" Amend to "… adjuvant therapy drug acquisition costs, adjuvant therapy drug administration costs…"	This is a more accurate reflection of the economic model.	For clarity, the ERG report will be amended as suggested

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 Paragraph 1	"…partitioned survival model, which is the modelling approach often used in economic evaluations of treatments for cancer…" Amend to "…partitioned survival model, which is the modelling approach often used in economic evaluations of treatments for advanced or metastatic cancer…"	This is a more accurate reflection of the use of partitioned survival models versus Markov models, given the use of Markov models in other NICE appraisals of adjuvant and neoadjuvant therapies (i.e. TA424 and ID1192.	For clarity, the ERG report will be amended as suggested

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 Table 16	"The company assumed that mortality hazard for LR and DM health states are the same." Amend to "The company assumed that mortality hazard for LR and RF health states are the same."	This sentence is factually inaccurate. Morality hazard for LR is assumed to be the same as the mortality hazard from RF in KEYNOTE-054.	This is a factual error. The ERG report will be amended accordingly

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64	"The company reported that the median OS was 66 weeks" Amend to "The company reported that the median survival (where survival means reaching the distant metastases state) was 66 weeks"	Figure 3 presents Kaplan-Meier data for transition from LR-to-DM not overall survival data.	For clarity, the ERG report will be amended accordingly

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65 Paragraph 2	"…that people with advanced melanoma receive before the occurrence of DM." Amend to "…that people with advanced melanoma receive after the occurrence of DM."	This sentence is factually inaccurate.	This is a factual error. The ERG report will be updated accordingly

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 Table 22, row 5	"KEYNOTE-054 trial and Beusterien [59]" Amend to "Beusterien [59]"	The base case health state utility values for distant metastases (post-progression) are taken only from the Beusterien paper.	This is a factual error. The ERG report will be updated accordingly

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83 Paragraph 2, line 1	"The company does not use the mature RFS data" Amend to "The company does not use the RFS data"	Whilst not a factual inaccuracy, the use of the phase 'the mature RFS data' indicates that there is more mature data which the company have chosen not to use. We believe this is potentially misleading as we have used the most mature, available data to populate the cost-effectiveness model.	For clarity, the ERG report will be updated accordingly

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 Table 26	Please add academic in confidence marking to the rates of salvage surgery in rows 4-6. Amend to [redacted]	This data will be published and should remain academic in confidence until that point.	Confidential marking added by NICE.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 Table 27	Please add academic in confidence marking to the rates of salvage surgery in rows 4-6. Amend to [redacted]	This data will be published and should remain academic in confidence until that point.	Confidential marking added by NICE.

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]

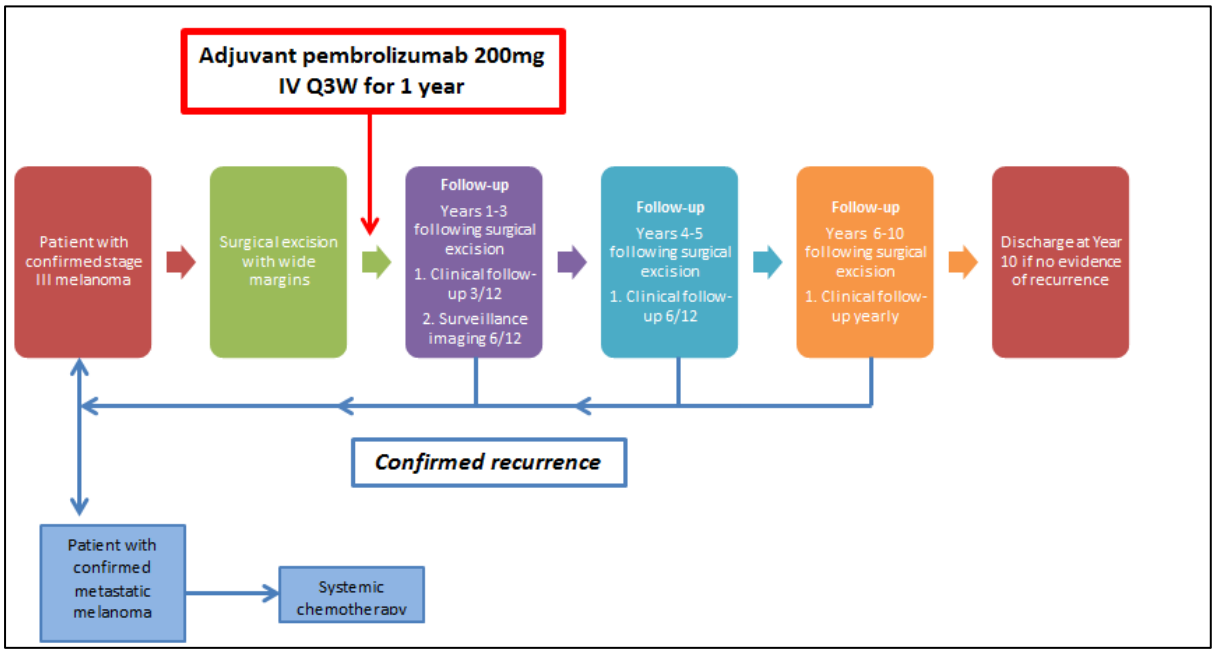

Figure 1 Current clinical pathway of care showing the context of the proposed use of the technology

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 • 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 the mortality hazard for LR and RF health states 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

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.

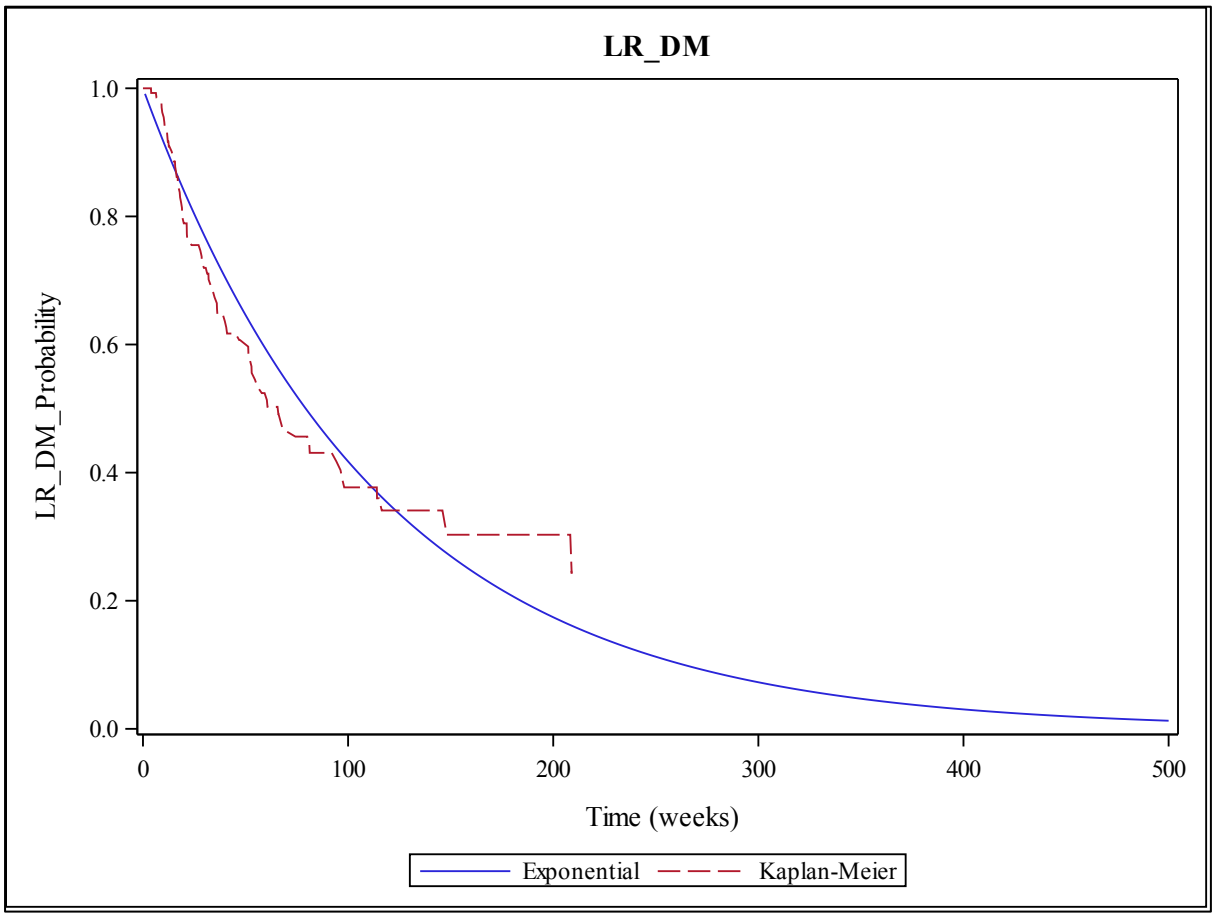

Figure 3 Exponential model fitted to the observed LR-to-DM data from the Flatiron database

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