NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from MSD

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Melanoma Focus
   b. Melanoma UK

4. **Public Health England Study Report**

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRiG)

6. **Evidence Review Group report – factual accuracy check**

7. **Technical engagement response from company**
   a. Response appendix

8. **Technical engagement responses from experts:**
   a. Prof. Paul Lorigan, Professor of Medical Oncology – clinical expert, nominated by Melanoma Focus
   b. Dr Sophia Papa, Consultant Medical Oncologist – clinical expert, nominated by MSD
   c. Ms Diane Cannon, Corporate Partnership Director – patient expert, nominated by Melanoma UK *(see also item 3b)*

9. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group
   a. ERG additional information

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

(CDF Review of TA553) [ID3776]

Company evidence submission for committee

August 2021

File name	Version	Contains confidential information	Date
MSD CDF Review Pembrolizumab (TA553) FINAL_[REDACTED].docx	**1.0**	**No**	**3rd August 2021**

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Tables and figures

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Abbreviations

Abbreviation	Definition
AE	Adverse Event
AJCC	American Joint Committee on Cancer
CDF	Cancer Drugs Fund
CEA	Cost Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CPI	Consumer Price Index
DCA	Data collection agreement
DM	Distant Metastases
DMFS	Distant metastases-free survival
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Groups
HR	Hazard Ratio
HRG	Health Resource Group
IA1/2	Interim Analysis 1/2
ICER	Incremental cost-effectiveness ratio
IO	Immuno-oncology
ITT	Intention to Treat
KOL	Key Opinion Leader
LR	Loco-regional
LYG	Life Years Gained
MSE	Mean Squared Error
NHS	National Health Service
NMA	Network Meta-Analysis
ONS	Office for National Statistics
OS	Overall Survival
PAS	Patient Access Scheme
PD-1	Programmed cell Death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression Free Survival
PRFS2	Progression/Recurrence-Free Survival 2
PS	Performance Status
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
Q3W	Every 3 weeks
Q6W	Every 6 weeks

QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RDI	Relative Dose Intensity
RF	Recurrence Free
RFS	Recurrence-free survival
SACT	Systemic Anti-Cancer Treatment
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of Product Characteristics
TSD	Technical Support Document

Cancer Drugs Fund review submission

A.1 Background

Pembrolizumab is recommended for use within the Cancer Drugs Fund (CDF) as an option for the adjuvant treatment of stage III melanoma with lymph node involvement in adults who have had complete resection. It is recommended only if the conditions in the managed access agreement for pembrolizumab are followed [1].

ICERs within the original submission presented to the committee included a simple patient access scheme discount of [redacted]

The committee did not specify a plausible ICER due to the immaturity of the KEYNOTE-054 data. It did note that pembrolizumab was dominant in the company's base case and the ICERs were within the range usually considered as cost-effective. However, committee were concerned that the ICERs were very uncertain. The ERG did not do any exploratory analyses because the data from KEYNOTE-054 were considered immature.

The committee's key uncertainties were around the long-term benefit of pembrolizumab including recurrence-free survival, distant metastases-free survival, overall survival and the duration of treatment effect with pembrolizumab. It also highlighted that the company's modelling of subsequent treatments was not generalisable to UK clinical practice and this remained uncertain.

The committee recognised that current follow up for KEYNOTE-054 was short (median of 16 months) and that the trial was ongoing and agreed that more data could resolve the key uncertainties.

A.2 Key committee assumptions

Table 1: Key committee assumptions as per the Terms of Engagement

Area	Committee preferred assumptions
Population	The population for the original appraisal were adults with resected melanoma with high risk of recurrence. The key trial supporting the appraisal (KEYNOTE-054) included people with stage IIIA, stage IIIB and stage IIIC melanoma. Pembrolizumab was recommended in people with stage III melanoma with lymph node involvement in adults who have had complete resection. The key trial supporting the appraisal (KEYNOTE-054) included people with stage IIIA, stage IIIB and stage IIIC melanoma. Pembrolizumab was recommended in people with stage III

Area	Committee preferred assumptions
	melanoma with lymph node involvement in adults who have had complete resection. **Adults with completely resected stage III melanoma at high risk of recurrence are the relevant population for the CDF review.**
Comparators	The final scope stated that the relevant comparator is routine surveillance. KEYNOTE-054 was the key phase III randomised controlled trial (RCT) supporting this appraisal and assessed pembrolizumab vs placebo after complete resection of high-risk stage III melanoma. The trial comparator group reflected routine surveillance and the committee concluded that the trial was generalisable to clinical practice in England. **The company should present clinical and cost-effective evidence for pembrolizumab compared to routine surveillance.**
Recurrence-free survival data	An October 2017 KEYNOTE-054 data cut was used in committee decision making. This had a median follow up of 16 months. Pembrolizumab showed a statistically significant improvement in recurrence-free survival, but this result assumed proportional hazards. The ERG were concerned by this and thought it unlikely that the proportional hazards assumption would hold. Committee noted that the trial follow up was short and this made the recurrence-free survival, including the long-term impact, uncertain. Committee concluded that pembrolizumab improves recurrence-free survival compared with placebo but the size of the benefit in the long-term is unclear. **The company should use more mature recurrence-free survival data from KEYNOTE-054. The company should fully explore the most appropriate method to calculate the associated hazard ratio.**
Distant metastases-free survival	To estimate the cost-effectiveness the company used a 4-state transition model. People could move between recurrence-free survival, loco-regional recurrence, distant metastases and death. Data from KEYNOTE-054 informed the model transitions from recurrence-free survival to other states and from loco-regional recurrence to death. However, KEYNOTE-054 did not provide data to inform the transitions between loco-regional recurrence and death, or the transition from distant metastases to death. These came from published literature. Distant metastases-free survival data from KEYNOTE-054 were immature and this led to particular uncertainty in the routine surveillance arm. The committee and ERG considered the modelled estimates of distant metastases-free survival in the routine surveillance arm to be implausible. Committee concluded that more data from KEYNOTE-054 would reduce the uncertainty in the modelling.

Area	Committee preferred assumptions
	The company should use more mature distant metastases-free survival data from KEYNOTE-054 to inform the economic model.
Overall survival	KEYNOTE-054 overall survival data were not available at the time of the October 2017 data cut and the company used external data sources to model overall survival. The key uncertainty was the transition from distant metastases to death because this was not informed by the trial. KEYNOTE-054 informed most other transitions in the model. The company stated that recurrence-free survival is a good surrogate marker for overall survival and used a meta-analysis to justify this assumption. The ERG cautioned against using surrogate endpoints to estimate long-term benefit. The ERG was concerned that the company's model produces clinically implausible overall survival estimates. Committee concluded that the survival benefit cannot be confirmed in the absence of overall survival data from KEYNOTE-054. **The company should use overall survival data from KEYNOTE-054 to inform the economic model.**
Duration of treatment effect	The company assumed a lifetime treatment benefit after stopping pembrolizumab. A clinical expert informed committee that the duration of treatment benefit of adjuvant pembrolizumab treatment is unknown. The ICER was sensitive to changes in the duration of treatment benefit and committee recognised that it was uncertain. It concluded that more mature overall survival data would help reduce this uncertainty. **The company should use more mature data from KEYNOTE-054 to inform assumptions about the duration of treatment effect after stopping treatment.**
Subsequent treatments	The company used market share data to estimate the proportion of people having subsequent treatment for metastatic disease. However this didn't reflect the use of treatments in the NHS. Committee heard that the proportion of people with distant metastases who go on to have subsequent treatments is similar in both arms and therefore should not have a large impact on the ICER. It concluded that even though the model results are not sensitive to this assumption the company's model did not reflect clinical practice. The committee considered that the introduction of PD-1 inhibitors earlier in the treatment pathway may have an impact on the subsequent therapies as it is currently unknown if clinicians will choose to re-treat with a PD-1 inhibitor. The SACT data set will provide data on which subsequent treatments people have in UK clinical practice.

Area	Committee preferred assumptions
	The company should fully explore the most appropriate assumptions about subsequent treatments using data collected through SACT.
Most plausible ICER	Committee considered the ICERs presented by the company which included the commercial arrangement for pembrolizumab. This showed that pembrolizumab was dominant. The ERG also incorporated the commercial arrangements for the subsequent treatments, so the exact ICERs are commercial in confidence and cannot be reported here. In the company base case and the scenario analyses the ICER did not exceed £10,000 per QALY. The ERG did not do any exploratory analyses due to the immaturity of the data from KEYNOTE-054. **Committee felt that it was not possible to specify plausible ICERs due to the immaturity of the data but did agree that the company's ICERs were within the range usually considered cost-effective, and therefore pembrolizumab demonstrated plausible potential to be cost-effective.**
End of life	Pembrolizumab does not meet the end-of-life criteria for this indication.

A.3 Other agreed changes

There have been no further changes to the Terms of Engagement.

A.4 The technology

Table 2: Technology being reviewed

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment [2]
Marketing authorisation/CE mark status	The indication to which this submission relates to is: KEYTRUDA® as monotherapy is indicated for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection

Indications and any restriction(s) as described in the summary of product characteristics	The marketing authorisation for pembrolizumab also covers the following indications:
	• Melanoma
	  ○ KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
	  ○ KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
	• Non-small cell lung carcinoma (NSCLC)
	  ○ KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
	  ○ KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations
	  ○ KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults
	  ○ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma 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.
	• Classical Hodgkin lymphoma (cHL)
	  ○ KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous 3 stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option
	• Urothelial carcinoma
	  ○ 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 and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10
	• Head and neck squamous cell carcinoma (HNSCC)
	  ○ KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1

	○ KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy • Renal cell carcinoma (RCC) ○ KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults • Colorectal cancer (CRC) ○ KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults
Method of administration and dosage	The recommended dose of KEYTRUDA as monotherapy in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes for up to 1 year [3]
Additional tests or investigations	For the indication under consideration, no diagnostic test is required to identify the population for whom pembrolizumab is indicated
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial, the drug cost of a single administration (200mg) being £5,260. The mean number of 200mg administrations within KEYNOTE-054 was [redacted] which leads to an average list price cost for a course of treatment being £[redacted].
Commercial arrangement (if applicable)	A patient access scheme (PAS) has been agreed with NHS England, with a simple discount of [redacted], therefore 200mg administration of pembrolizumab will cost £[redacted]. The average cost of an adjuvant treatment course with PAS is £[redacted].
Date technology was recommended for use in the CDF	19th December 2018.
Data collection end date	3rd April 2020 for KEYNOTE-054 and November 2020 for SACT report

A.5 Clinical effectiveness evidence

Table 3: Primary source of clinical effectiveness evidence

Study title	KEYNOTE-054 Study of pembrolizumab versus placebo after complete resection of high-risk stage III melanoma [4].
Study design	Randomised, placebo-controlled, parallel-group, multi-centre, double-blind
Population	Adults with stage III melanoma having undergone complete surgical resection
Intervention	Intravenous pembrolizumab 200 mg monotherapy every 3 weeks for up to 1 year (or to complete 18 administrations).
Comparator	Placebo
Outcomes collected that address committee's key uncertainties	• **Recurrence-free survival (RFS)** • **Distant metastases-free survival (DMFS)** • Overall survival (OS) • Subsequent treatments used for metastatic disease management after adjuvant pembrolizumab treatment

Reference to section in appendix	A.15.7 to A.15.13

Outcomes in **bold** have been used to inform the updated CEA.

The KEYNOTE-054 trial consisted of two parts (Figure 1). In Part 1, participants received adjuvant pembrolizumab or placebo for up to 18 doses. For Part 2, patients in the placebo arm who had documented recurrence were eligible to crossover to receive pembrolizumab and patients in the pembrolizumab arm who experienced a recurrence after 6 months were eligible to be rechallenged with pembrolizumab [5].

Figure 1: KEYNOTE-054 trial diagram

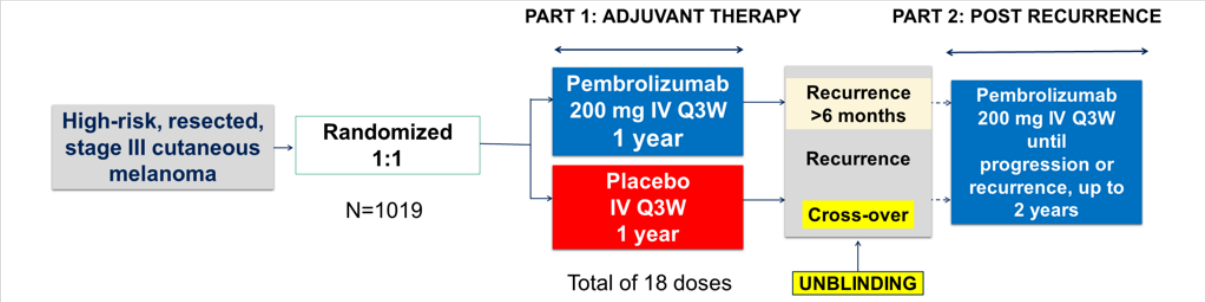


Figure sourced from Eggermont et al, 2021 [5]

Table 4: Secondary source of clinical effectiveness evidence

Study title	**Pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma – SACT data review**
Study design	Cohort study
Population	Patients with stage III melanoma (according to the AJCC 8th edition) that has been completely resected either via sentinel lymph node biopsy or when indicated via completion lymph node dissection.
Intervention	Intravenous pembrolizumab monotherapy 200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year.
Comparator	Not applicable
Outcomes collected that address committee's key uncertainties	• Overall survival (OS) • **Subsequent treatments after adjuvant pembrolizumab treatment**
Reference to section in appendix	A.15.17

Outcomes in **bold** have been used to inform the updated CEA.

A.6 Key results of the data collection

The following primary clinical data for recurrence-free survival (RFS) and distant metastases-free survival (DMFS) are from the prespecified final analysis of the KEYNOTE-054 trial using the latest data cut off from the 3rd April 2020 (interim analysis 2 [IA2]).

All efficacy analyses were conducted using the intention to treat (ITT) population. Additional supplementary information regarding KEYNOTE-054 are provided in the appendix. Secondary data presented are from the Systemic Anti-Cancer Therapy (SACT) cohort study report (dated June 2021). Together, these data provide evidence to address the committee's key uncertainties, as detailed in the Data Collection Agreement (DCA). The sustained RFS benefit observed with the extended follow up is consistent to that presented in the original submission, demonstrating the sustained long-term benefit of pembrolizumab in the adjuvant setting.

A.6.1 *KEYNOTE-054 (ITT population)*

A.6.1.1 *Recurrence-free survival (RFS)*

It was acknowledged by the committee that adjuvant pembrolizumab improves RFS compared with routine surveillance [1]. However, the size of the long-term benefit was noted as unclear.

The descriptive extended RFS analysis at (3rd April 2020 data cut off), showed that pembrolizumab provided a sustained RFS benefit with 45.5 months of median follow-up when compared with placebo (Table 5). The hazard ratio (HR) was 0.59 (95% CI: 0.49, 0.70) in favour of pembrolizumab, with a 41% reduction in the risk of recurrence or death (see Appendix A.15.8).

The median RFS [redacted] in the pembrolizumab arm compared with [redacted] (95% CI: [redacted]) months with placebo. The Kaplan–Meier curves separate from month 3 and this is sustained throughout the follow up period (Figure 2). The RFS results from the later follow up (median follow up 45.5 months) are consistent with the results in the original submission: pembrolizumab demonstrates statistically significant, sustained improvement in RFS over time.

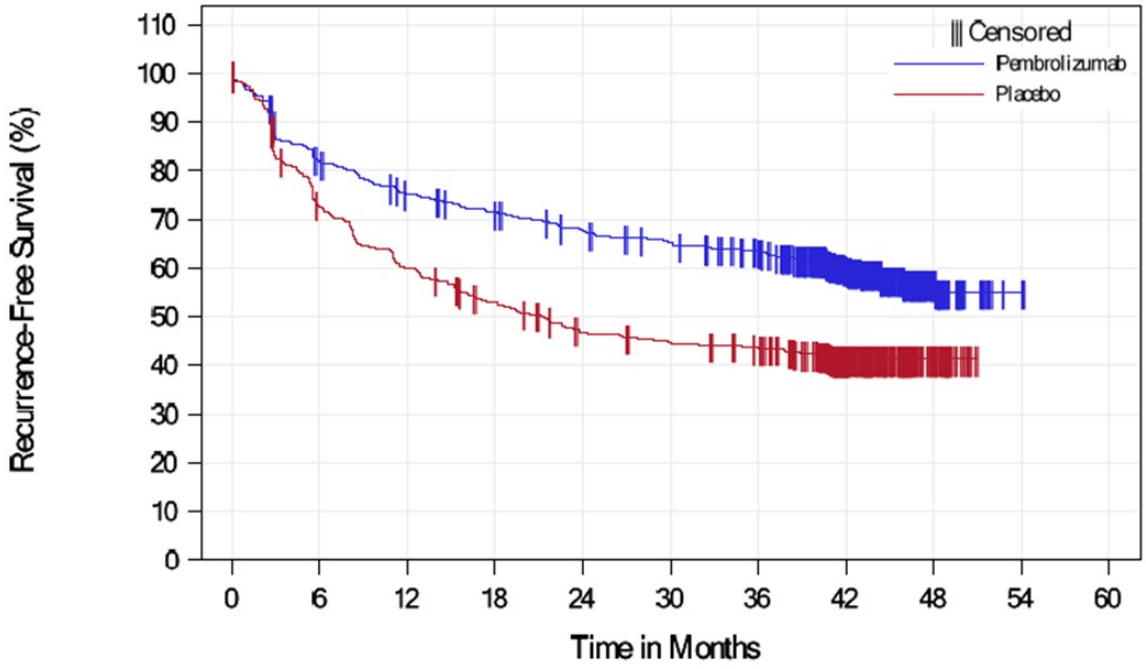
A sustained RFS benefit for pembrolizumab compared with placebo similar to that observed in the ITT population was seen across all subgroups, regardless of cancer stage (AJCC 7th and 8th edition cancer stage classification) and *BRAF*-mutation status amongst others (see Appendix A.15.11).

Table 5: Descriptive extended RFS analysis in the ITT population

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median RFS, months (95% CI)†	RFS rate at month 42, % (95% CI)†	HR (95% CI)‡
Pembrolizumab	514	203 (39.5)	[redacted]	[redacted]	[redacted]	59.8 (55.3, 64.1)	0.59 (0.49, 0.70)
Placebo	505	288 (57.0)	[redacted]	[redacted]	[redacted]	41.4 (37.0, 45.8)	–

RFS 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.
(Database Cutoff Date: 03APR2020).
Updated from original submission: Company submission B.2.6.1 (Table 13, p39)

Figure 2: Kaplan–Meier RFS estimates in the ITT†



n at risk

Pembrolizumab	514	412	375	353	333	316	300	163	30	1	0
Placebo	505	359	297	258	225	213	205	115	26	0	0

Abbreviations: ITT, intention to treat; RFS, recurrence-free survival.
† The last patient was randomised Nov 14, 2016 and data cut-off for IA2 was Apr 3, 2020. Censoring has increased as expected after 40.5 months based on patient time in trial.
Updated from original submission: Company submission B.2.6.1 (Figure 6, p40)

In patients with PD-L1-positive and PD-L1-negative tumours, the HRs were [redacted] and [redacted], respectively (Appendix A.15.7

A.6.1.2 *Distant metastases-free survival*

Within the original submission using interim analysis 1 (IA1) data, DMFS was not analysed due to data immaturity. The analysis conducted at data cut-off 3rd April 2020 (IA2; the first and final analysis for DMFS) showed pembrolizumab provided a statistically significant, and clinically meaningful improvement in DMFS. With 45.5 months of median follow-up when compared with placebo, the HR was 0.60 (95% CI: 0.49, 0.73); p<0.0001) in favour of pembrolizumab, resulting in a 40% reduction in the risk of distant metastases or death. Median DMFS was not yet reached in the pembrolizumab group and was 40.0 months (95% CI: 27.7, -) in the placebo group (Table 6). The DMFS analysis has not been adjusted to account for [redacted] patients in the routine surveillance arm who had a locoregional (LR) recurrence and subsequently crossed over to receive pembrolizumab in part 2 of the trial, until progression or recurrence, up to two years. Therefore, the benefit of pembrolizumab on DMFS compared with placebo could be underestimated. No further DMFS analyses are planned, as the number of events required for analysis has occurred. The Kaplan–Meier curves are presented in Figure 3.

A DMFS benefit of pembrolizumab compared with placebo similar to that of the ITT population was observed across all subgroups, regardless of cancer stage (AJCC 7th and 8th edition cancer stage classification) and *BRAF*-mutation status amongst others (see Appendix A.15.11).

The DMFS benefit alongside the RFS benefit with longer follow-up shows that pembrolizumab provides a sustained benefit and is an efficacious adjuvant treatment for patients with resected, high-risk, stage III melanoma [5].

Table 6: DMFS analysis in the ITT population

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median DMFS, months (95% CI)†	DMFS rate at month 42, % (95% CI)†	HR (95% CI)‡	p-Value§
Pembrolizumab	514	173 (33.7)	16,164	1.1	Not reached (49.6, –)	65.3 (60.9 , 69.5)	0.60 (0.49, 0.73)	<0.0001
Placebo	505	245 (48.5)	13,310	1.8	40.0 (27.7, –)	49.4 (44.8, 53.8)	-	-

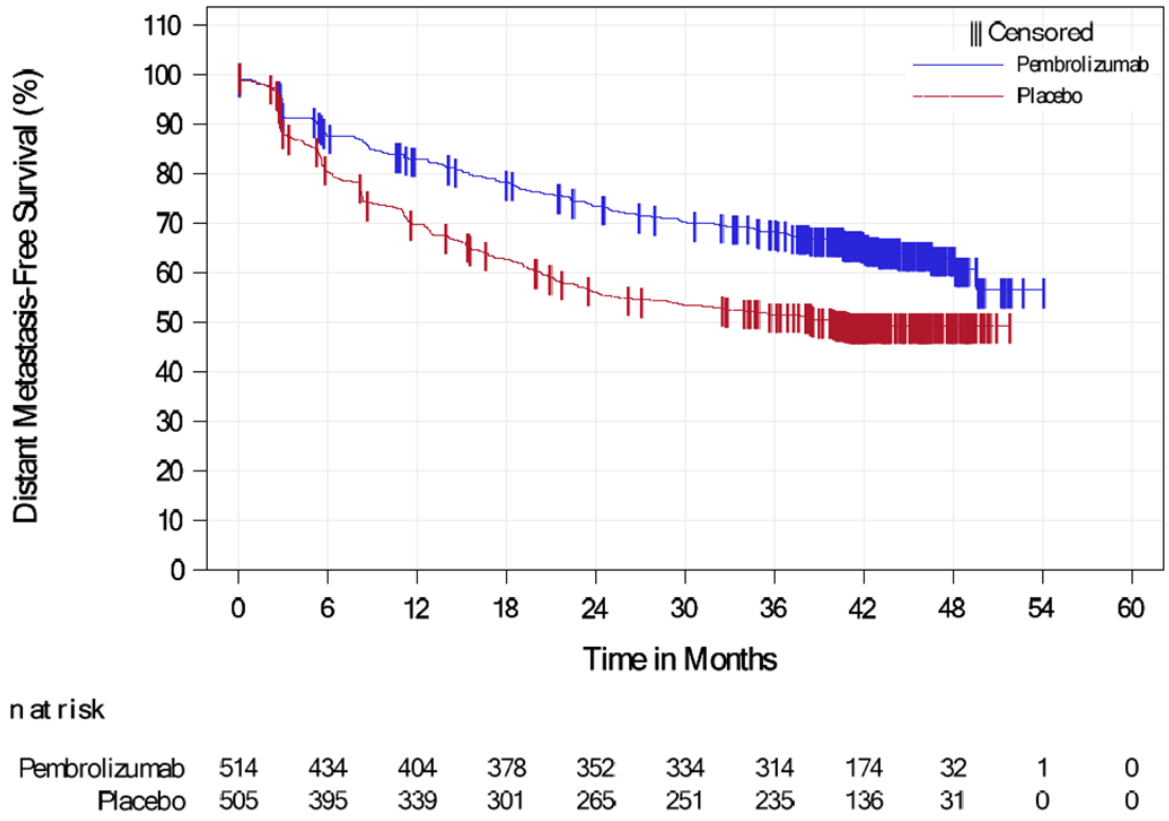
Distant metastasis-free survival is defined as the time between the date of randomization and the date of first distant metastasis or date of death (whatever the cause), whichever occurs first.

† 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: 03APR2020).

Figure 3: Kaplan–Meier DMFS estimates in the ITT population†



Abbreviations: DMFS, distant metastasis-free survival; ITT, intention to treat.

† The last patient was randomised Nov 14, 2016 and data cut-off for IA2 was Apr 3, 2020. Censoring has increased as expected at 40.5 months, based on patient time in trial.

A.6.1.3 *Overall survival*

The trial protocol states that overall survival (OS) analysis will be performed once [redacted] deaths have been reached.

The cumulative number of deaths in KEYNOTE-054 is accruing more slowly than anticipated. The protocol estimated originally that the [redacted] OS events for final analysis would accrue approximately [redacted] years from the start of trial accrual. With a first patient entry in August 2015, [redacted] events was projected to be reached in August [redacted]. However, the total number of OS events through 3rd April 2020 (IA2 analysis) is [redacted], representing only [redacted]%

of the total [redacted] target events required for analysis of OS. The final OS analysis is event driven and is expected to occur in approximately [redacted] based on current projections.

KEYNOTE-054 OS immaturity may be hindered further by the study design itself (Part 2, which includes a cross-over for routine surveillance patients as well as a pembrolizumab rechallenge component for adjuvant pembrolizumab-treated patients) and the impact of additional effective lines of treatment in the advanced disease setting [5]. Further details are provided in Appendix A.15.14

The immaturity of OS data from KEYNOTE-054 is a good indication that adjuvant treatment with pembrolizumab is associated with positive long-term survival outcomes for patients. During TA684, the appraisal committee understood that due to the adjuvant setting in which the treatment was being used, survival data may take time to be collected [6]. When considering the ongoing clinical benefit of adjuvant melanoma therapy the appraisal committee recommended adjuvant nivolumab for routine commissioning regardless of OS data availability and maturity.

In TA553 there was agreement that the RFS benefit seen with pembrolizumab in KEYNOTE-054 would translate into an improved OS benefit compared with routine surveillance [1]. The latest RFS and DMFS data from KEYNOTE-054 (alongside progression/recurrence-free survival 2 [PRFS2] data in Appendix A.15.14) are consistent with those reported from other adjuvant melanoma trials (including CheckMate238) and suggest that adjuvant pembrolizumab will result in an OS improvement compared with placebo, irrespective of subgroup [7].

A.6.1.4 *Subsequent treatments after adjuvant pembrolizumab*

Data on subsequent treatments after recurrence were collected in KEYNOTE-054. However, these data are still immature and categorisation of treatment regimens (e.g. to ascertain combination therapies) was not performed. Further, Part 2 (cross-over) of KEYNOTE-054 may limit in part the generalisability of these estimates in the UK clinical practice. These data are presented in the Appendix A.15.12 for information purposes.

A.6.1.5 *Summary*

Pembrolizumab provided sustained RFS benefit with 45.5 months of median follow-up when compared with placebo. It also provided a statistically significant improvement in DMFS when compared with placebo. The minimum number of events required to analyse the OS endpoint had not been reached at the 3rd April 2020 data cut-off.

A.6.2 *Systemic Anti-Cancer Therapy (SACT) dataset*

Between 19th November 2018 and 18th November 2020, 1,375 applications were made to the CDF (Blueteq®) for pembrolizumab; of these 1,324 were analysed (9 died before treatment, 30 did not receive treatment, and 12 were not included in the SACT database).

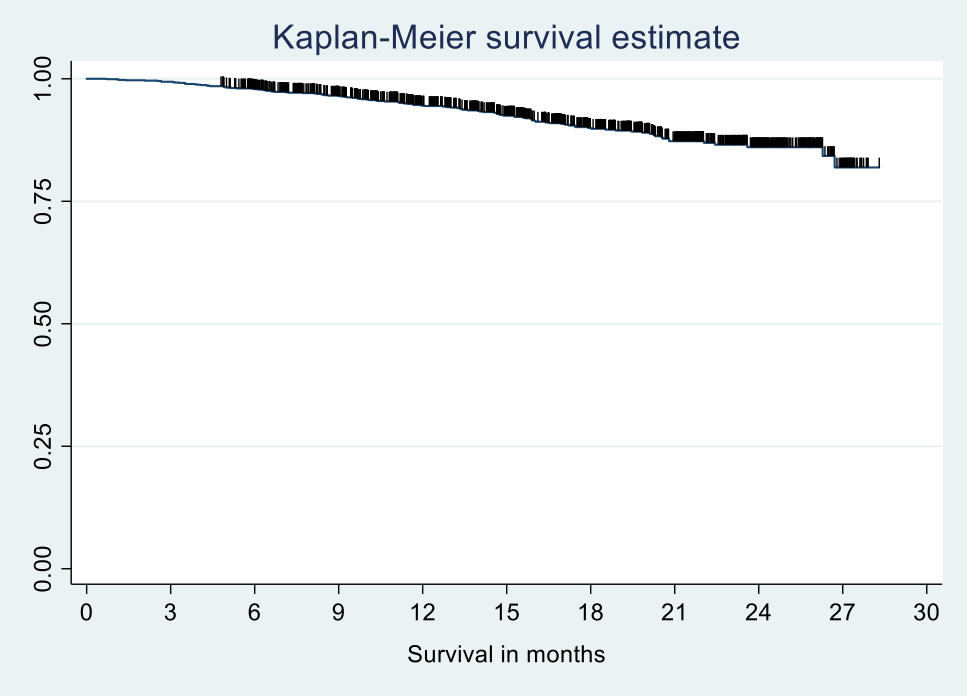
A comparison of the key patient characteristics in the SACT dataset and KEYNOTE-054 pembrolizumab arm is shown in Appendix A.15.13 . The median age of patients in the SACT cohort was higher than those in KEYNOTE-054 (64 years vs. 54 years). A higher number of patients were assessed to have an ECOG performance status (PS) of 0 in KEYNOTE-054 compared with SACT (94.4% vs. 69%). The proportion of patients with a *BRAF* V600 positive mutation was lower in the SACT dataset (19%) versus KEYNOTE-054 (47.5%). . This is reflective of the standard of care at the time of data collection for each study and may also be attributed to the positive TA544 recommendation for adjuvant *BRAF* combination therapies in routine commissioning.

A.6.2.1 *Overall survival*

Of the 1,324 patients with a treatment record in the SACT dataset, the median follow-up time was 15.7 months (minimum 5.3 months to a maximum of 29 months). Median follow up was defined as the observed time from the start of treatment to death or censored date (28th April 2021).

The Kaplan–Meier curve for OS is shown in Figure 4. As of the 28th April 2021, 8.8% (n=117) of the cohort who received pembrolizumab had died, therefore median OS was not reached. The OS at 6 months was 98% [95% CI: 97%, 99%], 12 months OS was 95% [95% CI: 93%, 96%] and OS at 18 months was 90% [95% CI: 88%, 92%].

Figure 4: Kaplan-Meier Survival estimate



A.6.2.2 *Subsequent treatments after pembrolizumab*

In total, 153 patients had a subsequent treatment recorded in the SACT dataset, accounting for 12% of the cohort. The median time from last pembrolizumab cycle to the subsequent treatment was 49 days. Table 7 describes the distribution of first treatments prescribed after a patient's last pembrolizumab cycle. The majority of patients received ipilimumab + nivolumab (54.2%) followed by ipilimumab (19.0%) and is reflective of the systemic anticancer therapies recommended by NICE for stage IV melanoma [8].

Table 7: Distribution of first treatments prescribed after a patient's last pembrolizumab cycle (SACT dataset)

Regimen	Patients with subsequent treatments (n=153)	%
Ipilimumab + nivolumab	83	54.2%
Ipilimumab	29	19.0%
Dabrafenib + trametinib	21	13.7%
Binimetinib + encorafenib	13	8.5%
Nivolumab	4	2.6%
Carboplatin + paclitaxel	1	0.7%
Talimogene laherparepvec	1	0.7%
Trial	1	0.7%

Abbreviations: SACT, Systemic Anti-Cancer Therapy.

Table 8 details the distribution of further lines of therapy received by patients, which are interpreted to represent second line therapies in the metastatic setting. Of the 46 patients who were recorded as having further lines of therapy after the last pembrolizumab cycle, 60.9% received nivolumab followed by 15.2% for Binimetinib + encorafenib. It was noted in the SACT report that subsequent therapies could be related to a second primary tumour and had not been confirmed with NHS hospital trusts or validated with UK clinicians.

Table 8: Distribution of further lines of therapy following a patients last pembrolizumab cycle (SACT dataset; interpreted as 2L metastatic)

Regimen	Patients with subsequent treatments (n=46)	%
Nivolumab	28	60.9%
Binimetinib + encorafenib	7	15.2%
Ipilimumab + nivolumab	3	6.5%
Carboplatin + paclitaxel	1	2.2%
Cisplatin + dacarbazine	1	2.2%
Cisplatin + dacarbazine + vinblastine	1	2.2%
Dabrafenib + trametinib	1	2.2%
Dacarbazine	1	2.2%
Ipilimumab	1	2.2%
Rituximab	1	2.2%
Trial	1	2.2%

Abbreviations: 2L, second line; SACT, Systemic Anti-Cancer Therapy.

A.6.2.3 *Summary of SACT dataset*

The SACT dataset report has provided information on subsequent treatments following adjuvant pembrolizumab treatment and OS projections to address the appraisal committee's uncertainty regarding assumptions in the TA553 submission. The median OS was not reached for patients within the cohort as only 8.8% of patients had died (n=117) by the time of the latest follow update, 28th April 2021. The analysis showed OS at 18 months was 90%. Subsequent treatments for patients who had received pembrolizumab are in line with NICE recommendations for stage IV melanoma, including a mix of targeted therapies and immunotherapy agents [8].

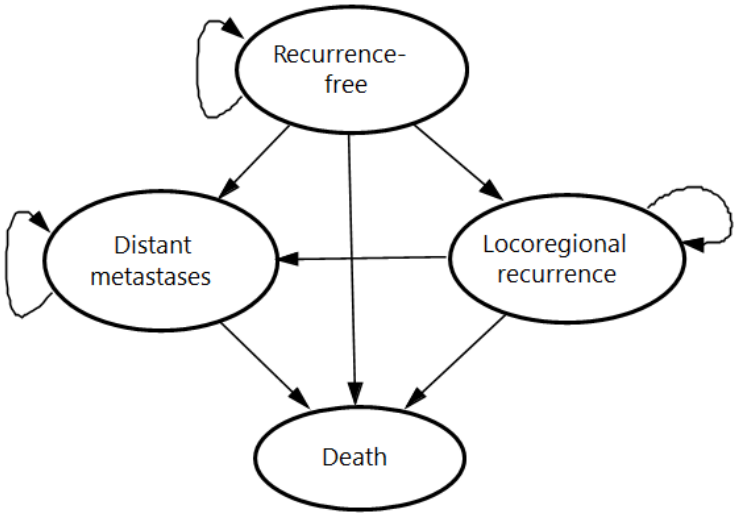
A.7 Evidence synthesis

KEYNOTE-054 is the only trial reporting outcomes for adjuvant pembrolizumab and direct evidence comparing pembrolizumab versus routine surveillance is available, therefore meta-analysis and indirect treatment comparison was not required.

A.8 Incorporating collected data into the model

A cost-effectiveness analysis (CEA) was conducted comparing adjuvant pembrolizumab versus routine surveillance from the perspective of the NHS in England. A four-state Markov cohort model with a lifetime horizon was used to capture the differential prognosis by type of recurrence observed in the adjuvant setting (Figure 5) [9, 10]. Survival was driven based on RFS and DMFS estimates from the KEYNOTE-054 clinical trial and corresponding survival estimates for patients who transition to the locoregional (LR) recurrence and distant metastatic (DM) health states compared with patients remaining in the recurrence-free (RF) health state.

Figure 5: Model structure



The collected data are incorporated into the CEA model as described in this section. Additional details regarding methods for updating the model to address the committee's uncertainties are provided in the Appendix.

A.8.1 *Transition probabilities*

Transitions from recurrence-free state

Clinical data for RFS and DMFS collected from KEYNOTE-054 at IA2 (3rd April 2020 data cut) were used to update the model transition probabilities from the RF health state, using the parametric multistate modelling approach described by Williams et al. (2017a & 2017b) [11, 12]. Cause-specific hazards for 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 (therefore the model does not rely on proportional hazards), modified to account for competing risks [11-13]. Six different parametric models were considered: exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions [13]. The descriptive extended RFS analysis from KEYNOTE-054 IA2 (3rd April 2020 data cut) demonstrates that the RFS treatment benefit of pembrolizumab is sustained after completion of 1 year of adjuvant therapy, supporting the assumption from the original submission, and expert clinical opinion [14], that the treatment effect of adjuvant pembrolizumab on RFS is maintained as long as patients remain in the RF health state. This assumption is further supported by the DMFS analysis at IA2.

At the latest data cut of KEYNOTE-054 (IA2, 3rd April 2020), insufficient death events had occurred to enable analysis of OS (see A.6.1.3). In the CEA, transitions from RF to death were modelled conservatively using a constant exponential rate in each arm, and OS was modelled as a function of all transition probabilities in the model (using the same methodology as in the original submission [company submission B.3.3.1, p56], owing to the limited number of events observed). Note that, conservatively, the model does not apply any additional OS benefit for patients who were treated with adjuvant pembrolizumab after DM recurrence (i.e. survival after DM recurrence is dependent only upon therapies received in the metastatic setting, rather than the adjuvant treatment arm).

As discussed in section A.6.1.3 and in the recent appraisal for TA684 [6], the immaturity of OS data is a positive indication that adjuvant treatment with pembrolizumab is associated with positive long-term survival outcomes for patients. The risk of melanoma recurrence is highest in the first 3 years post-surgical resection [15], and there is also strong published evidence that an improvement in RFS, such as that seen in KEYNOTE-054, will translate into an OS benefit [7, 16, 17]. The EORTC-18071 trial has demonstrated that the RFS and OS benefit of adjuvant treatment with an immune checkpoint inhibitor (ipilimumab) is sustained over the long-term (median follow up 7 years) [18], and in a recent meta-analysis

of 13 clinical studies (n>5,000 patients) involving adjuvant interferon in stage II-III melanoma, RFS was shown to be a good predictor for OS [17]. The findings of this study have since been supplemented by inclusion of data from EORTC-18071 which demonstrated that the association between RFS and OS is maintained when data specific to checkpoint inhibitors (in this case ipilimumab) in the resected stage III population are considered [7].

Transitions from locoregional recurrence state

Patient-level data on DMFS from KEYNOTE-054 were used to inform transitions from the LR state to DM (LR → DM) and death (LR → death) and replaced the data from the Flatiron real-world database used in the original submission. Exponential models were fitted to the patient-level data for each treatment arm. The exponential distribution is commonly assumed when estimating transition probabilities starting from intermediate health states in a Markov model, as the hazard rate does not depend on time since entry into the health state [19]. The analytical sample was restricted to patients who experienced LR recurrence as their first RFS failure event. Patients were followed from the time of LR until the transition of interest, or until censoring at the end of follow-up or the occurrence of the competing transition. The DMFS analysis from IA2 demonstrates that adjuvant pembrolizumab also provides a sustained DMFS benefit over time. However, no adjustments were performed to account for rechallenge or crossover regimens within the LR state in KEYNOTE-054 ([redacted] and [redacted] of patients with LR recurrence had rechallenge or crossover to pembrolizumab in the pembrolizumab and routine surveillance arms, respectively); thus, the resulting transition probabilities incorporate any effect of crossover/rechallenge in KEYNOTE-054 on risk of distant metastases or death and the long-term DMFS benefit of adjuvant pembrolizumab therefore may be underestimated (Appendix A.15.9).

Transitions from distant metastasis state

Transitions from the DM state to death were modelled, as per the original submission, based on the distribution of first-line subsequent therapies in the advanced melanoma setting in each adjuvant treatment arm (see section A.8.2). The efficacy of pembrolizumab was sourced from patient-level data in the KEYNOTE-006 trial and modelled using exponential models of OS and progression-free survival (PFS) (Appendix A.15.3).

Hazard ratios (HRs) for other subsequent treatments (with the exception of encorafenib + binimetinib) vs pembrolizumab were obtained from a network meta-analysis (NMA) of therapies for advanced melanoma [20]. For encorafenib + binimetinib, HRs for OS and PFS

vs vemurafenib were obtained from published results of the COLUMBUS trial [21], and HRs for encorafenib + binimetinib vs pembrolizumab were then calculated using HRs for OS and PFS for vemurafenib vs pembrolizumab from the NMA described above [20]. These estimates were not part of the original NMA and therefore the HRs are not adjusted to account for heterogeneity between COLOMBUS and the other trials in the network; however, we have taken this pragmatic approach to permit inclusion of this treatment regimen in the model based on advice from clinical experts regarding UK clinical practice [14] (see section A.8.2).

Selection of base-case parametric functions

The selection of the most suitable combination of parametric models for the RF → LR and RF → DM transitions was performed considering all 36 possible combinations based on mean squared error (MSE), visual assessment of fit, and plausibility of long-term extrapolations of RFS, DMFS and OS (Appendix A.15.3). External validation of RFS, DMFS and OS estimates was performed by comparison to data from CheckMate238 [22] and EORTC-18071 [18, 23], and the plausibility of potentially suitable curves was validated by clinical experts [14].

Additional validation of OS projections was conducted using data from the COMBI-AD trial [24], the SACT dataset [25], the AJCC staging manual [26], the Surveillance, Epidemiology, and End Results (SEER) database [27], and alternative data from SEER previously explored by the Evidence Review Group (ERG) in TA553 [1] (a detailed description of the external validation is provided in Appendix A.15.2).

In line with the guidance provided in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 [13], the models were selected such that the same combination of parametric models could be used in the pembrolizumab and routine surveillance arms. In effect, this is also a conservative approach potentially biasing against pembrolizumab due to the potential for immune memory due to the unique mode of action of immuno-oncology (IO) agents. The visual fit of the predicted cumulative incidence of transitions from RF → LR and RF → DM for the 36 combinations against the observed KEYNOTE-054 data is presented in Figure 6 and Figure 7, respectively; additional goodness of fit data are presented in Appendix A.15.3 .

Figure 6: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence (A) Pembrolizumab; (B) Routine surveillance

Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence free.
Different shades within a colour set represent the 6 parametric functions explored for the RF→DM transition.
Updated from original submission: Company submission B.3.3.1 (p62-63)

Figure 7: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases (A) Pembrolizumab; (B) Routine surveillance

[redacted]

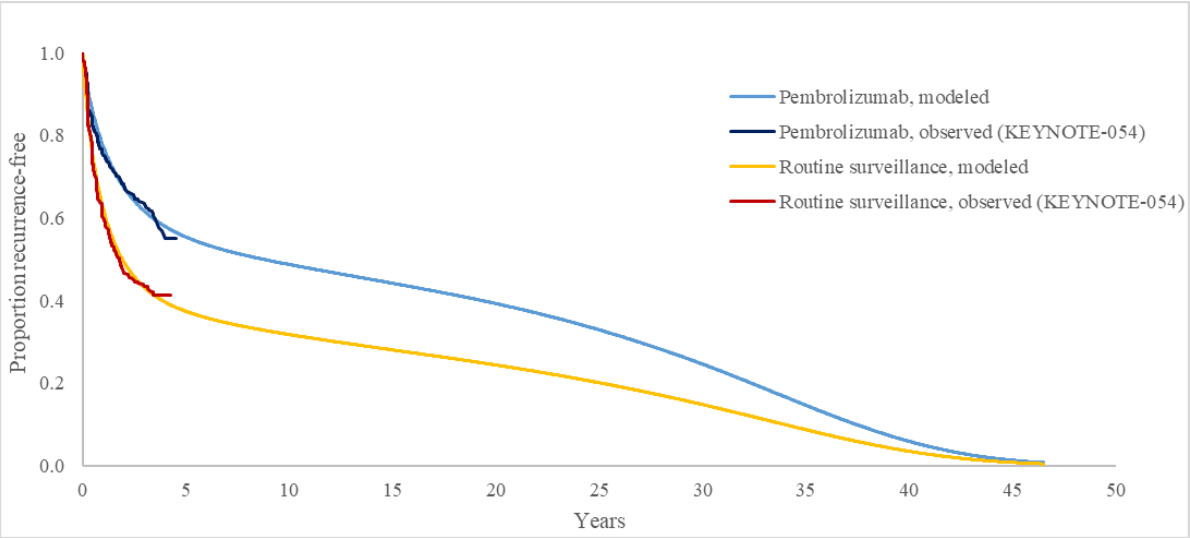
Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence free.
Different shades within a colour set represent the 6 parametric functions explored for the RF→LR transition.
Updated from original submission: Company submission B.3.3.1 (p64-65)

Based on these assessments, the combination of Generalised gamma and Gompertz functions for the RF → LR and RF → DM transitions, respectively, was considered to provide the best balance of goodness of fit and long-term plausibility and therefore was selected for the base case analysis (Appendix A.15.2). This was the second-best fitting combination in the routine surveillance arm by MSE for both RFS and DMFS, and clinical experts advised that the long-term projections were reasonable (Appendix A.15.2).

The best-fitting parametric function for the observational arm based on MSE, Gompertz – Gompertz, was also considered plausible, however long-term projections (at 30–40 years) may be higher than would be expected, therefore it was not deemed appropriate for use in the base case model. Gompertz – Gompertz and Lognormal – Gompertz were tested in scenario analyses to explore more optimistic and pessimistic projections, respectively.

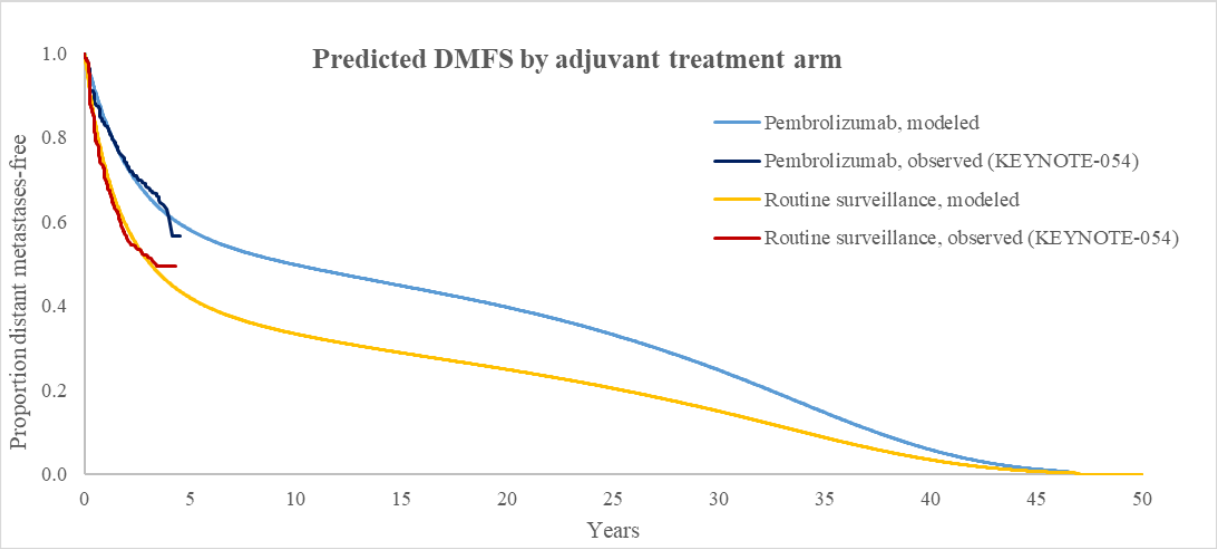
The resulting predictions of RFS and DMFS used in the base case analysis (Generalised gamma – Gompertz) are presented in Figure 8 and Figure 9, respectively. A summary of the approaches used to estimate transitions between all health states is provided in Table 9.

Figure 8: Predicted RFS over the modelled time horizon under the base-case parametric distributions



Abbreviations: RFS, recurrence-free survival.
Updated from original submission: Company submission B.3.3.1 (Figure 14, p67)

Figure 9: Predicted DMFS over the modelled time horizon under the base-case parametric distributions



Abbreviations: DMFS, distant metastasis-free survival.

Table 9: 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†	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: *RF → LR: Generalised gamma* *RF → DM: Gompertz* *RF → Death: Exponential* Separate parametric models were fitted for each treatment arm of KEYNOTE-054	Treatment-specific patient-level data from KEYNOTE-054 Life tables for England & Wales (2017-2019) – *to supplement transitions to death*	Alternative combinations of parametric distributions fitted to RF→ LR and RF→ DM transitions (Gompertz – Gompertz and Lognormal – Gompertz)
LR → DM LR → Death†	Exponential models of LR → DM, and LR → Death were separately fitted to each treatment arm of KEYNOTE-054.	Treatment-specific patient-level data from KEYNOTE-054 Life tables for England & Wales (2017-2019) – *to supplement transitions to death*	Differentiate exponential rates in each arm based on timing of LR recurrence.
DM → Death†	In each adjuvant treatment arm, the transition probability from DM to death was assumed to depend on the expected mix of subsequent treatments for advanced melanoma, and the efficacy of these subsequent treatments in terms of mean OS	Patient-level data from KEYNOTE-006 NMA comparing treatments for advanced melanoma. HR for encorafenib + binimetinib vs vemurafenib from COLUMBUS Life tables for England & Wales (2017-2019) – *to supplement NMA*	Alternative assumptions about subsequent treatments in each model arm

Abbreviations: DM, distant metastases; LR, locoregional recurrence; NMA, network meta-analysis; RF, recurrence-free.

† 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.

Updated from original submission: Company submission B.3.3.2 (Table 28, p79)

A.8.2 *Subsequent treatments*

All patients progressing to the DM state are eligible for systemic treatment with one of the immuno-oncology (IO) therapies or targeted agents approved by NICE and outlined in the

NICE pathway for advanced melanoma [8]. In the initial review, the committee concluded there was uncertainty regarding the use of each subsequent treatment in the metastatic setting and around the role of rechallenge with pembrolizumab after adjuvant therapy.

Current approved first-line treatment options for advanced melanoma include nivolumab + ipilimumab, nivolumab monotherapy, pembrolizumab monotherapy and ipilimumab monotherapy. Treatment options available for *BRAF* V600 mutation positive patients include dabrafenib + trametinib, dabrafenib monotherapy, or encorafenib + binimetinib [8]. Vemurafenib monotherapy, a *BRAF*-targeted agent, was included as a subsequent treatment option in the original submission but has been omitted in this update as it is no longer used in routine practice due to toxicity concerns [14]. Encorafenib + binimetinib was recommended by NICE in 2019 (TA562) for patients with unresectable or metastatic *BRAF* mutation-positive melanoma [28]. Clinical experts indicated that during the COVID-19 pandemic this combination has been widely used in practice for *BRAF* V600 mutation positive patients instead of dabrafenib + trametinib as dabrafenib + trametinib is commonly associated with fever-type adverse events which are difficult to distinguish from symptoms of COVID-19. Treatment with encorafenib + binimetinib has therefore been included in the model as a subsequent therapy option for first-line advanced melanoma, using HR data from the COLOMBUS trial [21] applied to the vemurafenib vs pembrolizumab estimates in the advanced melanoma NMA [20] (see section A.8.1).

Data from part 2 of KEYNOTE-054 showed that 203 patients randomised to pembrolizumab had a recurrence (either LR or DM); of these, 20/203 (9.9%) opted to receive rechallenge with pembrolizumab [5]. The efficacy data are still immature and based on a very small number of patients, and it remains unclear whether rechallenge with pembrolizumab would be observed in real world practice. The SACT dataset reports 153 patients who received subsequent anti-cancer therapies after adjuvant pembrolizumab. In the first line setting, most patients received ipilimumab + nivolumab (54.2%) or ipilimumab monotherapy (19.0%). A small proportion of patients received nivolumab monotherapy, while no patients received rechallenge with pembrolizumab. The treatment regimens observed in SACT are reflective of the NICE guidance for systemic anticancer therapies in stage IV melanoma [8], with the exception that IO monotherapies (pembrolizumab or nivolumab) are expected to be a common choice in the advanced setting when adjuvant pembrolizumab has not been given.

UK clinical experts also advised that patients who had a distant recurrence while, or within 6 months of, receiving adjuvant treatment with pembrolizumab, would be unlikely to receive pembrolizumab again in the advanced setting [14]. However, rechallenge with an IO

monotherapy may be an option for some patients who recurred >6 months after adjuvant treatment (in TA684, a 2-year threshold for rechallenge with IOs was used [6]). Clinicians indicated that IO combination therapy with nivolumab + ipilimumab would often be the preferred choice after adjuvant pembrolizumab for patients deemed to be fit enough [14].

Consequently, as in the original submission and observed in the SACT cohort, in the base case it was conservatively assumed that patients who received adjuvant pembrolizumab were unable to receive further treatment with pembrolizumab; this assumption was explored in scenario analyses (section A.12 and Appendix A.15.1). However, treatment with other IOs (nivolumab monotherapy and nivolumab + ipilimumab) was permitted, to reflect the usage observed in the SACT cohort and clinical expert opinion. In the SACT dataset, the median time from a patient's last pembrolizumab cycle to their next treatment was 49 days [25], therefore it was assumed that there was no delay to a patient receiving another IO after adjuvant pembrolizumab in the first line advanced setting. Note that permitting rechallenge with pembrolizumab is likely to shift some patients away from expensive first line combination therapy with nivolumab + ipilimumab, thus increasing the cost-effectiveness of adjuvant pembrolizumab (Appendix A.15.1).

Data from KEYNOTE-054 on the use of subsequent treatments for patients who develop distant metastases were incomplete with respect to the use of combination regimens (Appendix A.15.12) and were therefore deemed to not be reflective of UK clinical practice based on UK clinical expert opinion [14]. Instead, the distribution of therapies administered in the advanced setting for patients in the adjuvant pembrolizumab arm was taken from the SACT data report, as these are the best available real-world data to reflect the clinical practice observed while adjuvant pembrolizumab has been in the CDF [25].

Based on clinical expert opinion, market research data on current UK treatment patterns from Ipsos Oncology Monitor [29] were not considered to be fully reflective of UK practice as the use of nivolumab + ipilimumab was considered to be low, and the use of *BRAF*-targeted agents was considered to be high [14]. However, clinical experts agreed that the market share of pembrolizumab seen in the Ipsos research ([redacted]%) was reasonable [29]. Therefore, in the base case analysis, the SACT data were also used for the routine surveillance arm [25], with the exception that the market share of pembrolizumab was sourced from the Ipsos research [29] and market shares of non-targeted agents (nivolumab, ipilimumab, and nivolumab + ipilimumab) from SACT were proportionally adjusted (i.e. lowered) to account for pembrolizumab usage. The resulting first-line advanced melanoma market share distributions used in the model are presented in Table 10.

Clinical input confirmed that these base case market shares (based on real-world research) were appropriate to reflect clinical practice in the NHS [14]. A scenario using the unadjusted Ipsos market research for the routine surveillance arm was explored [29]. Since the Ipsos data were not considered fully reflective of UK practice by UK clinicians, several alternative scenarios exploring adjustments to the SACT and Ipsos data (based on clinical expert opinion) were also explored (section A.12 , Appendix A.15.1 and Appendix A.15.4).

Table 10: Market share assumptions for advanced melanoma therapies (base case and scenario)

Treatment regimen	Base case		Scenario analysis‡
	Pembrolizumab	Routine surveillance	Routine surveillance
Source	SACT 1L [25]	SACT 1L [25], adjusted by Ipsos Oncology Monitor [29]†	Ipsos Oncology Monitor data, unadjusted [29]
Pembrolizumab	0.00%	[redacted]	[redacted]
Ipilimumab	19.33%	[redacted]	[redacted]
Nivolumab	2.67%	[redacted]	[redacted]
Nivolumab + ipilimumab	55.33%	[redacted]	[redacted]
Vemurafenib	0.00%	[redacted]	[redacted]
Dabrafenib	0.00%	[redacted]	[redacted]
Dabrafenib + trametinib	14.00%	[redacted]	[redacted]
Encorafenib + Binimetinib	8.67%	[redacted]	[redacted]
Total	**100%**	**100%**	**100%**

Abbreviations: 1L, first line; Systemic Anti-Cancer Therapy.
† Pembrolizumab market share sourced from Ipsos Oncology Monitor [29] as pembrolizumab rechallenge was not observed in the SACT dataset but would be expected in practice for patients on routine surveillance in the adjuvant setting. Market shares of other non-targeted therapies (ipilimumab, nivolumab, and nivolumab + ipilimumab [obtained from SACT]) were proportionally adjusted to account for pembrolizumab usage.
‡ Unadjusted Ipsos data were not considered reflective of UK clinical practice. Please refer to Appendix A.15.4 for all alternative subsequent treatment data sources, calculations and alternative scenarios considered.
Updated from original submission: Company submission B.3.5.2 (Table 40, p92).

A proportion of patients are assumed to go on to receive second-line treatment in the advanced setting (Table 11). The proportion of patients assumed to receive no active treatment at second-line (due to death, deterioration of performance status or patient/clinician choice) was estimated from the latest Ipsos market research to be [redacted]% [29]. Clinical experts advised that this was reasonable for the adjuvant pembrolizumab arm,

however more patients in the routine surveillance arm would be expected to have second line treatment before moving to supportive care [14], therefore this is a conservative assumption that is explored in scenario analyses (Table 15 section A.12 and Appendix A.15.4).

As in the first-line advanced setting, the distribution of second-line therapies for the pembrolizumab arm was sourced from SACT [25] as the best available real-world data, and these market shares were proportionally adjusted to allow pembrolizumab use in the routine surveillance arm based on Ipsos market research [29]. All other assumptions relating to second-line treatment remain unchanged.

Table 11: Market share assumptions for advanced melanoma therapies – second line metastatic

Treatment regimen	Pembrolizumab	Routine surveillance
Source	SACT 2L [25]	SACT 2L [25], adjusted by Ipsos Oncology Monitor [29]†
Pembrolizumab	0%	[redacted]
Ipilimumab	0.95%	[redacted]
Nivolumab	26.54%	[redacted]
Nivolumab + ipilimumab	2.84%	[redacted]
Vemurafenib	0.00%	[redacted]
Dabrafenib	0.00%	[redacted]
Dabrafenib + trametinib	0.95%	[redacted]
Encorafenib + Binimetinib	6.64%	[redacted]
No active treatment	62.08%	[redacted]
Total	**100.00%**	**100.00%**

Abbreviations: 2L, second line; Systemic Anti-Cancer Therapy.
† Pembrolizumab market share sourced from Ipsos Oncology Monitor [29] as pembrolizumab rechallenge was not observed in the SACT dataset but would be expected in real world practice for patients who on routine surveillance in the adjuvant setting. Market shares of other non-targeted therapies (ipilimumab, nivolumab, and nivolumab + ipilimumab) were proportionally adjusted to account for pembrolizumab usage.
Updated from original submission: Company submission B.3.5.3 (Table 46, p96-97).

A.8.3 *Other model inputs*

The following model inputs were updated to reflect the latest data available from KEYNOTE-054 at the IA2 data-cut off (3rd April 2020): Risks and mean durations of drug-related adverse events (AEs); mean relative dose intensity (RDI) of pembrolizumab; the proportion of patients who underwent salvage surgery in the LR recurrence state; and the health state

utility values (and AE-related disutility) from an updated regression analysis of EQ-5D data (Appendix A.15.5).

In addition, all cost inputs were updated to reflect the latest available costing data (Appendix A.15.5). A patient access scheme (PAS) for pembrolizumab is in place for patients with melanoma which gives a discount of [redacted], equating to a drug cost per 100mg vial of [redacted].

A.8.4 *Pembrolizumab dosing schedule*

The SmPC for pembrolizumab was amended in March 2019 following European Medicines Agency (EMA) approval to allow treatment to be administered at a dose of 200 mg every 3 weeks (Q3W) or at a dose of 400 mg every 6 weeks (Q6W), across all monotherapy indications [3]. To align with the original submission and the KEYNOTE-054 data, the base case retains Q3W dosing and a Q6W scenario is explored by adjusting the frequency and dose of IV administration (Appendix A.15.1). The dosing schedule for pembrolizumab in the advanced melanoma setting was amended from weight-based dosing to 200 mg Q3W, to reflect the updated SmPC [3].

Clinical experts explained that the Q6W dosing schedule for pembrolizumab is highly beneficial to patients and the NHS as it reduces the number of clinic visits and increases treatment capacity, whilst maintaining the results observed with Q3W dosing in the KEYNOTE-054 trial with no increase in toxicity [3, 14]. They also described the reduced burden on NHS resources regarding frequency of blood tests, consultations, and pharmacy dispensing, and consequently Q6W dosing has been particularly crucial in assisting with capacity and social distancing measures during the COVID-19 pandemic. They inferred it will remain part of practice after the pandemic. Ipsos market research (April 2021) found that [redacted]% of adjuvant pembrolizumab schedules are administered Q6W [29], although clinical experts have suggested to MSD that this proportion may be even higher in routine practice [14].

A.9 Key model assumptions and inputs

Table 12: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Clinical data from KEYNOTE-054			
RFS data [Company submission B.3.3.1]	RFS analysis from KEYNOTE-054, IA1 data cut-off October 2017	Descriptive extended RFS analysis from KEYNOTE-054, IA2 data cut-off April 2020	As part of the DCA, further data on RFS were collected in KEYNOTE-054 and used to conduct a descriptive extended analysis at IA2 following the April 2020 data cut-off. These data are used to inform transitions from the RF health state.
DMFS data [Company submission B.3.3.1]	Number of DM events observed in KEYNOTE-054, IA1 data cut-off October 2017 (DMFS analysis not available at October 2017 data cut-off)	Final DMFS analysis from KEYNOTE-054, IA2 data cut-off April 2020	As part of the DCA, DMFS data continued to be collected in KEYNOTE-054 and were used to conduct the DMFS analysis at IA2 following the April 2020 data cut-off. These data are used to inform transitions from the RF and LR health states.
Model transition probabilities			
RF → LR and RF → DM transitions [Company submission B.3.3.1]	<u>RF→LR transitions:</u> Gompertz model fitted to IA1 treatment-specific RFS data from KEYNOTE-054 <u>RF→DM transitions:</u> Generalized gamma model fitted to treatment-specific DM events from KEYNOTE-054 Both models modified to account for competing risks. The committee did not state a preferred curve combination due to clinical uncertainty	<u>RF→LR transitions:</u> Generalised gamma model fitted to IA2 treatment-specific RFS data from KEYNOTE-054 <u>RF→DM transitions:</u> Gompertz model fitted to IA2 treatment-specific DMFS data from KEYNOTE-054 Both models modified to account for competing risks.	Statistical fit (based on MSE), visual inspection, assessment of the plausibility of long term RFS, DMFS and OS extrapolations and clinical expert opinion suggests that this combination of models provides the best balance of fit to the observed KEYNOTE-054 data and long-term plausibility. This combination of parametric functions was validated using published external data sources [18, 22, 23, 30, 31]. In line with guidance in NICE DSU TSD 14 [13], the same combination of parametric functions was used in both treatment arms.

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
RF → Death transition [Company submission B.3.3.1]	Exponential model fitted to treatment-specific death events observed in KEYNOTE-054 Life tables for England & Wales (2014-2016) used to ensure mortality ≥ general population mortality	Exponential model fitted to treatment-specific death events observed in KEYNOTE-054 Life tables for England & Wales (2017-2019) used to ensure mortality ≥ general population mortality.	At the latest data cut of KEYNOTE-054 (April 2020), the minimum number of events required to enable appropriate analysis of OS had not been reached, therefore exponential models were used as a conservative approach to modelling survival. The immaturity of OS data is a positive indication that adjuvant treatment with pembrolizumab is associated with positive survival outcomes for patients. Note that the model does not apply any additional OS benefit after DM recurrence for patients who were treated with adjuvant pembrolizumab.
LR → DM transition [Company submission B.3.3.1]	Exponential model fitted to real-world patient-level data from the Flatiron database. Transition probabilities assumed to be equal between pembrolizumab and routine surveillance arms	Exponential models fitted to treatment-specific patient-level data of LR → DM, from DMFS analysis in KEYNOTE-054	At the IA2 April 2020 data cut-off, sufficient LR recurrence and DM events had occurred to facilitate estimates of transitions from LR → DM for each arm of the KEYNOTE-054 trial. However, the DMFS analysis did not adjust for patients in the routine surveillance arm who were crossed over to receive pembrolizumab, therefore the DMFS benefit of adjuvant pembrolizumab may be underestimated.
LR → Death transition [Company submission B.3.3.1]	Approximated based on exponential model for RF→ Death in pembrolizumab arm Life tables for England & Wales (2014-2016) used to ensure mortality ≥ general population mortality.	Exponential model fitted to treatment-specific patient-level data from DMFS analysis in KEYNOTE-054 Life tables for England & Wales (2017-2019) used to ensure mortality ≥ general population mortality.	At the IA2 April 2020 data cut-off, sufficient LR recurrence and death events had occurred to facilitate estimates of transitions from LR → death for each arm of the KEYNOTE-054 trial.

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
DM → Death transition [Company submission B.3.3.1]	Transition probabilities depend on the distributions of first-line treatments received for advanced melanoma in each adjuvant treatment arm. Exponential models fitted to patient-level OS data for all patients in the pembrolizumab arm of KEYNOTE-006 (trial in 1L advanced melanoma); HRs for alternative subsequent treatments sourced from NMA of advanced melanoma treatments. Life tables for England & Wales (2014-2016) used to ensure mortality ≥ general population mortality.	Transition probabilities depend on the distributions of first-line treatments received for advanced melanoma in each adjuvant treatment arm. Exponential models fitted to patient-level OS data for all patients in the pembrolizumab arm of KEYNOTE-006 (trial in 1L advanced melanoma); HRs for alternative subsequent treatments sourced from NMA of advanced melanoma treatments. Life tables for England & Wales (2017-2019) used to ensure mortality ≥ general population mortality.	No change in modelling approach. Distribution of first-line treatments has been updated, and encorafenib + binimetinib has been added as a treatment option – see below.

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Other parameters			
Subsequent therapies [Company submission B.3.5.2]	Ipsos market research 2018	Pembrolizumab arm: SACT report June 2021 Routine surveillance arm: SACT report June 2021, adjusted to permit pembrolizumab use based on Ipsos Oncology Monitor, April 2021 Encorafenib + binimetinib added as subsequent therapy option to reflect NICE TA562	SACT data represent real-world practice observed for patients who received adjuvant pembrolizumab through the CDF. Rechallenge with pembrolizumab for patients in the adjuvant pembrolizumab arm is assumed to not be appropriate, however clinical experts stated that it may be done in practice and therefore this is a conservative assumption. In the routine surveillance arm, pembrolizumab would be a commonly used regimen in the advanced setting, therefore the market share for pembrolizumab was sourced from Ipsos market research and the SACT market shares were used for other regimens after proportionally adjusting non-*BRAF* targeted agents to account for pembrolizumab use. Data sources used in the model have been validated by UK clinical experts. Data on subsequent treatment use in KEYNOTE-054 are incomplete with respect to the use of combination regimens and were therefore deemed to not be reflective of UK clinical practice.
Health state costs [Company submission B.3.5.2]	Cost inputs based on 2017 reference year	Costs updated to latest available sources (2019-2020 reference year)	Costs updated to reflect the current NHS-PSS perspective.
Pembrolizumab dosing schedule [Company submission B.3.5.1]	Adjuvant setting: 200 mg Q3W Advanced setting: Weight-based dosing at 2 mg/kg Q3W	Adjuvant and advanced settings: 200 mg Q3W Scenario with 400 mg Q6W in the adjuvant setting explored.	Changing clinical practice and updated SmPC to permit Q6W administration of pembrolizumab in all monotherapy indications. Weight-based dosing of pembrolizumab no longer included in SmPC.

Abbreviations: 1L, first line; CDF, Cancer Drugs Fund; DCA, data collection agreement; DM, distant metastatic; DMFS, distant metastasis-free survival; DSU, decision support unit; HR, hazard ratio; IA, interim analysis; LR, locoregional recurrence; MSE, mean squared error; NHS PSS, National Health Service and Personal Social Services; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; Q3W, every 3 weeks; Q6W, every 6 weeks; RF, recurrence free; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy; SmPC, summary of product characteristics; TSD, technical support document.

A.10 Cost-effectiveness results (deterministic)

Table 13: Cost-effectiveness results (deterministic) with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	6.61	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Cost-effectiveness analysis 2: As above incorporating updated clinical evidence (RFS; DMFS from KEYNOTE-054 IA2) †							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	7.73	[redacted]	[redacted]	[redacted]	[redacted]	2,743
Cost-effectiveness analysis 3: New company base-case (RFS; DMFS; new survival extrapolations; subsequent treatments; cost inputs)‡							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	9.02	[redacted]	[redacted]	[redacted]	[redacted]	9,357

Abbreviations: CDF, Cancer Drugs Fund; DMFS, distant metastasis-free survival; ICER, incremental cost-effectiveness ratio; LYG, life years gained; RFS, recurrence free survival; PAS, patient access scheme; QALYs, quality-adjusted life years.

† The impact of changes to the efficacy data and base case assumptions versus the original submission were explored using the version of the model developed for the current submission and then reverting inputs/settings to match those used in the original submission. Although care was taken to replicate the settings as far as possible, due to the nature of some of the model edits that were required to update the efficacy data and base case assumptions, there may be some minor discrepancies.

‡ Iterative scenarios showing the impact of additional changes to the inputs and assumptions for the new base case analysis are presented in Appendix A.15.16 .

Updated from original submission: Company submission B.3.7.1 (Table 53, p106).

A.11 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the CEA, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 iterations. The results are presented in Table 14 and Figure 10. The distributions around the means used to draw random estimates for each parameter are detailed in Appendix M of the original company submission. The cost-effectiveness acceptability curve (CEAC) for the updated analysis is provided in Appendix A.15.1 .

The PSA showed an 84.2% probability that pembrolizumab is cost-effective or dominant versus routine surveillance at a £30,000/QALY willingness to pay (WTP) threshold. The results of the PSA support the base case findings, providing confidence that adjuvant treatment with pembrolizumab is a highly cost-effective treatment strategy and demonstrating that the model is robust to parameter variability.

Table 14: Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	9.03	[redacted]	[redacted]	[redacted]	[redacted]	10,378

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Updated from original submission: Company submission B.3.8.1 (page 107)

Figure 10: Scatterplot of probabilistic results

Abbreviations: QALY, quality adjusted life year; WTP, willingness to pay.
Updated from original submission: Company submission B.3.8.1 (page 108)

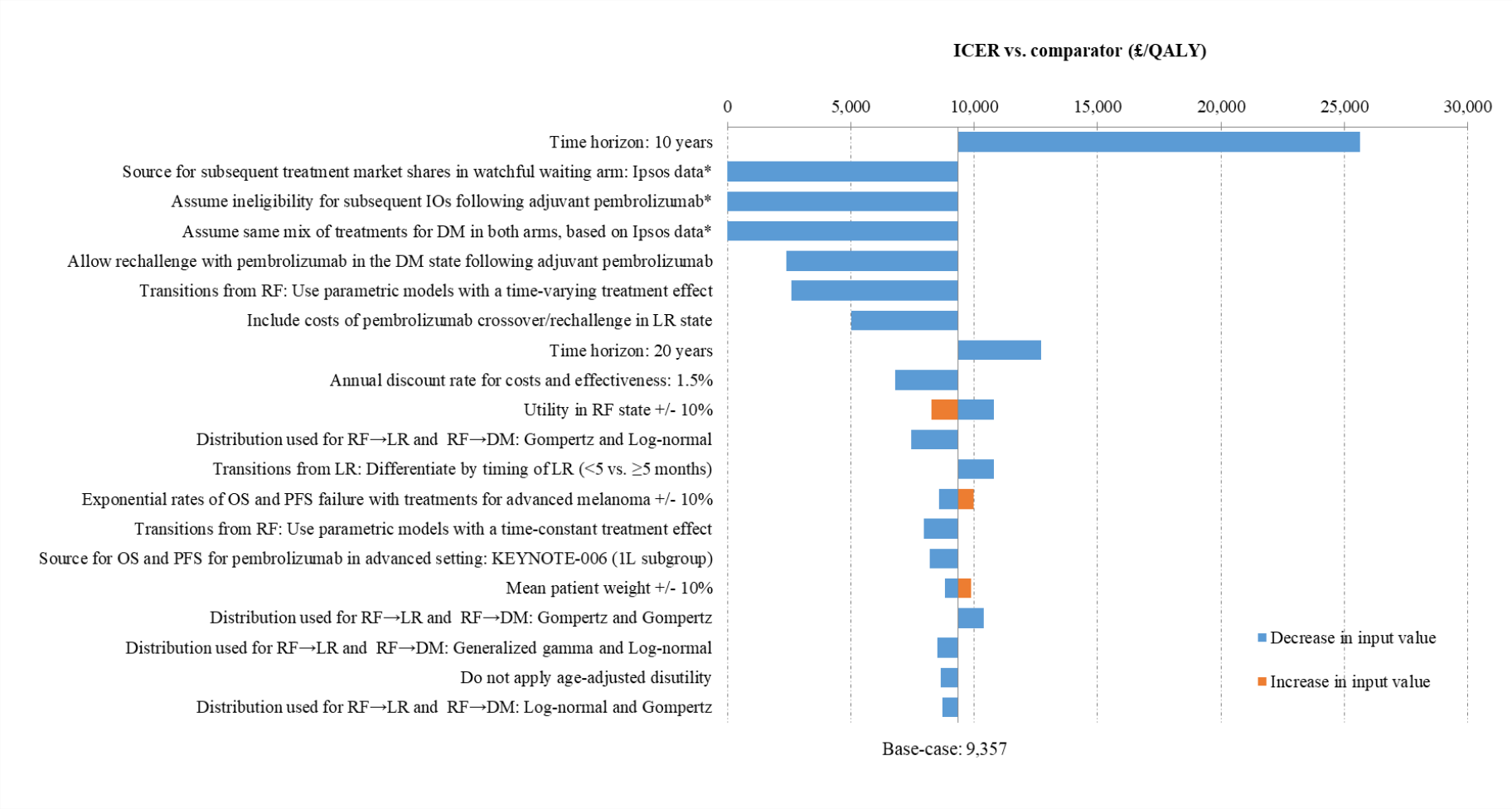
A.12 Key sensitivity and scenario analyses

Sensitivity and scenario analyses were performed to explore the impact of key parameters on the ICER. The outcome of these analyses demonstrated that the model results are robust to alternative parameter assumptions and provide reassurance that the ICER is expected to remain below the WTP threshold across a wide range of scenarios.

The tornado diagram in Figure 11 shows the impact of parameter variation on the ICER for adjuvant pembrolizumab versus routine surveillance, as assessed in a one-way sensitivity analysis. The model was most sensitive to the use of a 10-year time horizon, however this is not considered to be relevant to this indication where a lifetime horizon is the most appropriate to capture the effect of pembrolizumab on survival. Alternative assumptions relating to the market shares of subsequent therapies were also key model drivers that resulted in lower ICERs for pembrolizumab.

Key scenarios are summarised in Table 15, and additional exploratory scenarios are presented in Appendix A.15.1 . Alternative plausible parametric function combinations had a small impact on the ICER, while the use of alternative sources of market share data for subsequent treatments resulted in lower ICERs, indicating that the base case market share assumptions are highly conservative.

Figure 11: Tornado diagram



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

*Indicates sensitivity analyses in which pembrolizumab is dominant over the comparator (less costly and QALY accruing). Note that the tornado now shows ICER rather than NMB, as base case ICER is now positive (rather than dominant as in original submission).

Updated from original submission: Company submission B.3.8.2 (page 112).

Table 15: Key scenario analyses

#	Scenario and cross reference	Scenario detail	Brief rationale	ICER (£/QALY)
Base case				**9,357**
1	Alternative best-fitting curves	RF→LR Gompertz; RF→DM Gompertz	Alternative combination of curves for RF→LR and RF→DM transitions, based on goodness of fit and plausibility of long-term projections in both arms. Best-fitting combination in the routine surveillance arm and provides the most optimistic survival estimates in both arms.	10,404
		RF→LR Lognormal; RF→DM Gompertz	Alternative combination of curves for RF→LR and RF→DM transitions, based on goodness of fit and plausibility of long-term projections in both arms. Third best-fitting combination in the routine surveillance arm and provides slightly more conservative survival estimates in both arms.	8,718
2	Alternative market shares for treatments of advanced melanoma, Ipsos (unadjusted)	1L and 2L market shares for Routine Surveillance arm only from Ipsos, April 2021 (see Appendix A.15.4)	Alternative market shares available to represent UK clinical practice.	Dominant
3	Alternative market shares for treatments of advanced melanoma, KOL scenario 1	1L and 2L market shares for both adjuvant treatment arms based on KOL input (see Table 30 & Table 31, Appendix A.15.4)	Clinical experts suggested adjustments to the available market share data for 1L and 2L to further reflect UK clinical practice.	4,891
4	Alternative best-fitting curves AND Alternative market shares for treatments of advanced melanoma (Scenario 1 + 2)	RF→LR Gompertz; RF→DM Gompertz; 1L and 2L line market shares from Ipsos, April 2021	Combined effect of alternative plausible curves and available market shares.	537
		RF→LR Lognormal; RF→DM Gompertz; 1L and 2L line market shares from Ipsos, April 2021		Dominant
5	Baseline age from SACT cohort	Baseline age 64.0 years	To reflect the older age of patients in the SACT cohort used to inform subsequent treatment market shares. Age affects the ICER as it impacts mortality.	12,293

Abbreviations: 1L, first line; 2L, second line; DM, distant metastatic; ICER, incremental cost-effectiveness ratio; KOL, key opinion leader; LR, locoregional recurrence; QALY, quality-adjusted life year; OS, overall survival; RF, recurrence-free; SACT, Systemic Anti-Cancer Therapy.

A.13 Key issues and conclusions based on the data collected during the CDF review period

The data presented to address the issues identified for the CDF review period are summarised in Table 16.

Table 16: Summary of data collected during CDF period addressing key issues

Committee assumption	Data collected	Conclusion
The company should use more mature RFS data from KEYNOTE-054. The company should fully explore the most appropriate method to calculate the associated hazard ratio	A descriptive extended analysis of RFS was conducted with 45.5 months median follow up. This has been included in the economic model.	The HR was 0.59 (95% CI: 0.49, 0.70) in favour of pembrolizumab, with a 41% reduction in the risk of recurrence or death and is consistent with the findings in the original submission. Additional context on methodology methods of calculating associated HRs is provided in Appendix A.15.15 .
The company should use more mature DMFS data from KEYNOTE-054 to inform the economic model	Final DMFS analysis was conducted with 45.5 months median follow up. This has been included in the economic model.	The HR was 0.60 (95% CI: 0.49, 0.73); p<0.0001) in favour of pembrolizumab. Median DMFS was not reached in the pembrolizumab arm. No adjustment for cross over or rechallenge has been performed therefore the benefit for adjuvant pembrolizumab may be underestimated.
The company should use OS data from KEYNOTE-054 to inform the economic model.	At the latest data cut off (3rd April 2020) insufficient OS events had occurred to enable OS analysis (see Appendix A.15.14).	As of 3rd April 2020, [redacted] OS events out of the [redacted] required had occurred. The final OS analysis is event driven and is expected to occur in [redacted] based on current projections.
The company should use more mature data from KEYNOTE-054 to inform assumptions about the duration of treatment effect after stopping treatment.	A descriptive extended analysis of RFS, and the final DMFS analysis, was conducted with 45.5 months median follow up	The extended follow up data for pembrolizumab demonstrated a statistically significant, sustained improvement in RFS and DMFS over time (Appendix A.15.8).
The company should fully explore the most appropriate assumptions about subsequent treatments using data collected through SACT	During the data collection period the SACT report provided information on subsequent treatments received by patients after adjuvant pembrolizumab.	A total of 153 patients in the SACT cohort had a subsequent treatment recorded, with ipilimumab + nivolumab being the most common (52.3%). Clinical expert opinion noted that the SACT data are consistent with subsequent therapy

Committee assumption	Data collected	Conclusion
		usage post-adjuvant IO treatment. Alternative sources of data for the routine surveillance arm were explored in scenarios. Additional scenarios based on KOL feedback were also explored.

Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; DMFS, distant-metastasis-free survival; HR, hazard ratio; IO, immuno-oncology; OS, overall survival; RFS, recurrence-free survival; SACT, Systemic Anti-Cancer Therapy.

The additional evidence collected in KEYNOTE-054 for RFS and DMFS demonstrated a significant and sustained RFS and DMFS treatment benefit for adjuvant pembrolizumab versus routine surveillance. The effect of patient crossover from routine surveillance to adjuvant pembrolizumab after LR recurrence has not been adjusted for in the DMFS analysis, therefore it is likely that the treatment effect of adjuvant pembrolizumab on DMFS has been underestimated.

The minimum number of events required to enable appropriate analysis of OS had not been achieved at the latest KEYNOTE-054 data cut-off and the final OS analysis is estimated to be available in [redacted] (based on current projections). As such, an OS analysis from KEYNOTE-054 could not be presented for this submission. However, the lack of mature OS data in the adjuvant setting is a good indication that adjuvant treatment is associated with positive long-term survival outcomes for patients. During TA684 the Appraisal Committee understood the challenges and time required to collect OS data in the adjuvant setting. In line with the current clinical literature (including recent trials of adjuvant therapies), clinical experts have noted that clinically meaningful differences in RFS and DMFS would be anticipated to translate into an OS benefit.

The latest RFS and DMFS data from KEYNOTE-054 (April 2020) contribute further evidence that the sustained benefit of adjuvant treatment with pembrolizumab is maintained over a longer follow up period (45.5 months). The result of incorporating these data into the model was more accurate and optimistic projections of long-term RFS, DMFS and OS for the routine surveillance arm as well as for adjuvant pembrolizumab. The OS projections aligned well with published OS estimates from recent trials of adjuvant therapies and were also supported by clinical expert opinion. Whilst the lack of mature OS data from KEYNOTE-054 (which is to be expected in the adjuvant setting, as the committee understood in TA684) may appear to be a limitation of the analysis, extensive validation of long term projections

provides confidence that the model results in robust long term predictions to inform decision making.

Incorporating the latest KEYNOTE-054 clinical data into the economic model validated the findings of the original submission, demonstrating the clinical effectiveness and cost-effectiveness of adjuvant pembrolizumab (base case: £9,357/QALY versus “Dominant” in the original submission). The ICER remained highly cost-effective, ranging from £8,718/QALY to £10,404/QALY across a variety of sensitivity and scenario analyses exploring alternative plausible survival projections, aimed at exploring the long term RFS, DMFS, and OS projections.

The latest SACT data on the use of subsequent therapies in advanced melanoma after adjuvant pembrolizumab provide a realistic assessment of the survival and costs associated with patients in real-world UK clinical practice who have a DM recurrence and therefore address any uncertainty associated with this element of the original NICE submission. Alternative scenario analyses exploring several different distributions of subsequent therapies at first and second line in the metastatic setting were explored for the adjuvant pembrolizumab and routine surveillance arms; adjuvant pembrolizumab remained highly cost-effective across all distributions of subsequent therapies. An additional scenario reflecting the patient characteristics of the SACT cohort also supports the base case cost-effectiveness findings. All scenarios resulted in adjuvant pembrolizumab being highly cost-effective compared with routine surveillance, with ICERs below £20,000 per QALY.

KEYNOTE-054 has demonstrated that 1 year of treatment with adjuvant pembrolizumab is highly efficacious and significantly reduces the risk of locoregional and distant metastatic recurrence compared with routine surveillance, thus reducing the need for costly ongoing care associated with complex advanced/metastatic disease. This benefit is shown to be maintained after completion of adjuvant therapy. The significant, sustained treatment benefit observed in the trial results in adjuvant pembrolizumab being a highly cost-effective intervention.

In summary, the updated clinical data validate the conclusions of the original submission, reducing clinical uncertainty and demonstrating that adjuvant treatment with pembrolizumab provides a highly cost-effective treatment approach versus routine surveillance for patients with resected melanoma at high risk of recurrence.

A.14 References

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A.15 Appendices

A.15.1 *Supplementary results*

Additional scenario analyses

Additional scenarios were performed to explore the impact of further assumptions and data sources on the ICER.

Table 17: Additional scenarios

#	Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case				**£9,357**
6	Q6W dosing frequency for pembrolizumab	Pembrolizumab 400 mg administered Q6W at adjuvant therapy	The SmPC for pembrolizumab permits Q6W dosing. Clinical experts explained that this schedule is highly beneficial to patients, clinicians and the NHS as it reduces the number of clinic visits required and increases treatment capacity. This has been particularly relevant throughout the COVID-19 pandemic. MSD expects this to remain standard practice after the pandemic	£8,756
7	Subsequent treatment market shares, KOL scenario 2 (2L only)	Market shares based on KOL input (see Table 30 and Table 31, Appendix A.15.4)	Clinical experts suggested adjustments to the available market share data for 1L and 2L to further reflect UK clinical practice	£3,942
8	Subsequent treatment market shares, KOL scenario 3 (1L only)			£10,406
9	Subsequent treatment market shares, Pembrolizumab rechallenge permitted	SACT 1L market shares for pembrolizumab arm adjusted to permit rechallenge (see Table 28 and Table 31, Appendix A.15.4)	KOLs advised that some patients may be rechallenged with pembrolizumab in practice. Permitting rechallenge with pembrolizumab is likely to shift some patients away from expensive first line combination therapy with nivolumab + ipilimumab, thus increasing the cost-effectiveness of adjuvant pembrolizumab.	£8,215

#	Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
10	Include costs of crossover/rechallenge with adjuvant pembrolizumab for patients who have LR recurrence as observed in KEYNOTE-054	Cost of adjuvant pembrolizumab applied for patients with LR recurrence who crossed over or were rechallenged with pembrolizumab in KEYNOTE-054: Pembrolizumab: [redacted] Routine surveillance: [redacted] Median [redacted] days duration (see Appendix A.15.6)	DMFS data from KEYNOTE-054 were not adjusted to account for patients who had a LR recurrence and were crossed over or rechallenged with pembrolizumab. Therefore, including the costs of crossover/rechallenge more accurately reflects the efficacy captured in the model.	£5,028
11	Only first-line subsequent treatment in DM state	Costs of second-line treatments for advanced melanoma excluded	The cost of second-line treatments for advanced melanoma is a key driver of the ICER, however there is uncertainty regarding how many patients would receive second-line therapy and which therapies they would receive. This should be considered a conservative scenario, as second-line treatments would be relevant costs to the NHS in practice.	£9,460
12	Advanced melanoma efficacy from KEYNOTE-006 first line subgroup	Efficacy of pembrolizumab in the advanced melanoma setting (OS and PFS) based on patient-level data from the first line subgroup from KEYNOTE-006	The all-comer (ITT) population, which included some patients who had received previous treatment in the advanced setting, is used in the base case. However, the subgroup of patients who were treatment-naïve in the advanced setting better reflects the cohort considered in this model.	£8,190
13	Differentiate transitions from LR recurrent state by timing of LR recurrence	Transition probabilities differentiated between patients who had a LR recurrence before vs after 5 months from treatment initiation	Patients who have LR recurrence sooner after treatment initiation may have a higher risk of DM. In addition, statistical fit of the parametric functions to DMFS was improved by making this assumption.	£10,787

Probabilistic sensitivity analysis

The PSA showed an 84.2% probability that pembrolizumab is cost-effective versus routine surveillance at a £30,000/QALY willingness to pay (WTP) threshold (Figure 12).

Figure 12: Cost-effectiveness acceptability curve

Abbreviations: QALY, quality-adjusted life year.

A.15.2 *Approach to parametric curve fitting and validation of survival estimates*

The selection of the most suitable combination of parametric models for the RF → LR and RF → DM transitions was performed considering all 36 possible combinations based on internal validity (mean squared error [MSE] and visual assessment of fit), and external validity (plausibility of long-term extrapolations of RFS, DMFS and OS). Extra effort was taken to validate model projections for both treatment arms using internal and external data where possible.

In line with the guidance provided in NICE DSU TSD 14 [13], the parametric functions were selected such that the same combination of parametric models could be used in the pembrolizumab and routine surveillance arms. The selection of the most suitable combination of parametric functions is anchored from the best fitting and most externally plausible parametric distributions in the routine surveillance arm for RFS, DMFS, and OS. This is because there was more variability in statistical fit across the routine surveillance arm, while most combinations in the pembrolizumab arm yielded good statistical fit. The curves selected based on fit for routine surveillance were then checked for clinical plausibility in both treatment arms by comparison with external data sources and verified by UK clinical experts (external validity checks).

As OS data were not available from KEYNOTE-054, particular attention was paid to the OS projections for both the intervention and routine surveillance. In the routine surveillance arm, short-term OS projections for the key parametric functions aligned well with placebo data from the COMBI-AD trial. Longer-term extrapolations for the Generalised gamma – Gompertz, Gompertz – Gompertz, and Lognormal – Gompertz combinations were aligned with the composite curve previously provided by the ERG and with 7 year data from EORTC-18071. Projected OS for the pembrolizumab arm across all parametric functions was aligned with the observed OS for nivolumab reported in the CheckMate238 trial over a follow up of approximately 5 years.

Based on these assessments, the combination of Generalised gamma and Gompertz functions for the RF → LR and RF → DM transitions, respectively, was considered to provide the best balance of goodness of fit and long-term plausibility and therefore was selected for the base case analysis. The impact of alternative plausible parametric functions (Gompertz – Gompertz, and Lognormal – Gompertz) was explored in scenario analyses.

Details of the approach for selection of parametric function are provided below.

Internal validity

Internal validity of survival estimates was assessed for statistical fit to the observed Kaplan-Meier data from KEYNOTE-054 for both RFS and DMFS, based on MSE. In addition, visual inspection of the best fitting curve combinations by MSE and the RFS and DMFS model predictions versus the RFS and DMFS KEYNOTE-054 estimates was performed. Of note, predicted RFS in the model depends only upon the transition probabilities starting from the RF state, while predicted DMFS also depends upon the transition probabilities starting from the LR recurrence state. 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 Williams et al. (2017) [11]. Specifically, predicted versus observed cumulative incidence curves were plotted for both RF → LR recurrence and RF → DM (see section A.8.1).

In the routine surveillance arm, combinations of parametric functions that used Gompertz for RF → DM resulted in a close visual fit with the observed data. Certain combinations of parametric functions that used either Gompertz or generalized gamma for RF → LR yielded a close visual fit with the observed cumulative incidence of RF → LR. In the pembrolizumab arm, combinations of parametric functions that used generalized gamma or Gompertz for RF → LR appeared to achieve the best fit with the observed cumulative incidence of RF → LR, although close fits were also achieved with other combinations of functions that used log-normal, log-logistic, or Weibull. For RF → DM, several different combinations of parametric functions produced a close fit with the observed cumulative incidence of RF → DM in the pembrolizumab arm, including combinations that used generalized gamma and Gompertz.

In the pembrolizumab arm, most combinations of parametric functions yielded comparably low MSEs relative to observed RFS and DMFS and compared to MSEs obtained for combinations in the routine surveillance arm and were therefore considered to provide reasonable statistical fit. The choice of base-case parametric distributions therefore prioritised fit within the routine surveillance arm (where the statistical fit was more variable and thus some combinations clearly more appropriate) and clinical plausibility in both arms.

Consequently, the four best fitting parametric functions for the routine surveillance arm were explored further for clinical plausibility (Gompertz – Gompertz, Generalised gamma – Gompertz [updated base-case], Lognormal – Gompertz, Gompertz – Lognormal). The best fitting function combination for the pembrolizumab arm was also explored for comparative purposes (Generalised gamma – Lognormal).

External validity

External validity, including the plausibility of long- and short-term extrapolations, for the top five curve combinations (including the updated base-case) that had acceptable internal validity based on statistical and visual fit, was assessed by comparing the projections of RFS, DMFS and OS with data from several published sources (Table 18). Both recent clinical trial data and alternative long-term datasets were considered since each dataset has its own potential limitations (discussed below).

Table 18: Sources used to validate modelled survival projections

Source	Description	Used to validate endpoints:
CheckMate238 nivolumab arm data [22]	Phase III trial comparing adjuvant nivolumab vs adjuvant ipilimumab in patients with resected stage III melanoma. Data available up to 4 years.	RFS, DMFS and OS projections for **Pembrolizumab**
SACT data report for pembrolizumab [25]	Real world data collected for patients who received pembrolizumab in the CDF. Data available up to 1.5 years	OS projections for **Pembrolizumab** collected from SACT
EORTC-18071 Placebo arm [18, 23]	Phase III comparing adjuvant ipilimumab vs. placebo in patients with resected stage III melanoma. Data available up to 7 years.	RFS, DMFS and OS projections for ***Routine Surveillance***
COMBI-AD placebo arm data [30, 31]	Phase III trial comparing adjuvant dabrafenib + trametinib vs vemurafenib in patients with *BRAF* V600 mutation positive stage III melanoma. Data available up to 3 years.	RFS, DMFS and OS projections for ***Routine Surveillance***
TA553 original ERG report [1]	Composite curve of 10-year OS for patients with stage III melanoma, produced by ERG in review of original company submission. Based on data from 2010 SEER database by disease stage, weighted by the percentage of patients for each disease stage in KEYNOTE-054. MSD have been unable to replicate the original source data, but a digitised version of the curve from the ERG's TA553 report has been used.	OS projections for ***Routine Surveillance***
SEER 2000-2017 [27]	Real world data reported by NCI SEER Program. Survival rates by time since diagnosis (2000-2017), weighted by proportion of males and females in KEYNOTE-054. Data available up to 10 years.	OS projections for ***Routine Surveillance***
AJCC v8 (Gershenwald et al, 2017) [26]	Real world data on melanoma-specific survival by stage III subgroups (based on AJCC 8th edition cancer staging), weighted by staging distribution in KEYNOTE-054. Data available up to 10 years.	OS projections for ***Routine Surveillance***

Abbreviations: AJCC, American Joint Committee on Cancer; CDF, Cancer Drugs Fund; DMFS, distant metastasis free survival; ERG, Evidence Review Group; NCI, National Cancer Institute; OS, overall survival;

RFS, recurrence free survival; SACT, Systemic Anti-Cancer Therapy; SEER, Surveillance, Epidemiology, and End Results.

RFS, DMFS and OS estimates from these external sources are compared with projections for the five curves of interest in Table 19, Table 20 and Table 21, respectively. Figure 13 depicts the predicted OS for key parametric functions over a lifetime horizon.

In the routine surveillance arm, short-term observed RFS and DMFS at years 1–3 were slightly higher than the placebo arm in the EORTC-18071 trial which may be attributed to changes in the treatment pathway since EORTC was conducted, and were similar to the results seen in the placebo arm of the COMBI-AD trial. The RFS and DMFS values estimated by the explored parametric functions were consistent with this trend.

In the pembrolizumab arm, observed RFS and DMFS in KEYNOTE-054 in years 1–3 were higher than the corresponding results reported for the ipilimumab arm in EORTC-18071, as would be expected, and were similar, if slightly higher, compared to the nivolumab arm of CheckMate238, most likely due to the lack of stage IV resected patients in KEYNOTE-054.

Table 19: Validation of base case modelled projections vs. published data, for RFS

Source	RFS by year from baseline					
	1	2	3	4	5	7
Routine surveillance arm - RFS						
KEYNOTE-054 observed [32, 33]	60%	47%	44%	41%	-	-
COMBI-AD placebo [30, 31, 34]	56%	44%	39%	38%	36%	-
EORTC-18071 placebo [18, 36]	56%	44%	35%	35%	30%	31%
TA533 projections [1]	62%	45%	37%	31%	27%	22%
Gompertz- Gompertz	*61%*	*48%*	*43%*	*41%*	*39%*	*38%*
Generalised gamma - Gompertz	***62%***	***49%***	***43%***	***40%***	***37%***	***35%***
Lognormal – Gompertz	*63%*	*49%*	*43%*	*39%*	*37%*	*33%*
Gompertz – Lognormal	*63%*	*50%*	*43%*	*39%*	*36%*	*31%*
Generalised gamma - Lognormal	*64%*	*51%*	*44%*	*38%*	*34%*	*28%*
Pembrolizumab arm - RFS						
KEYNOTE-054 observed [32, 33]	75%	68%	64%	57%	55%†	-
CheckMate238 nivolumab [22, 35]	70%	62%	58%	52%	-	-
TA533 projections [1]	76%	67%	61%	57%	54%	48%
EORTC-18071 ipilimumab [18, 36]	64%	52%	47%	46%	41%	39%
Gompertz- Gompertz	*77%*	*67%*	*61%*	*58%*	*56%*	*54%*
Generalised gamma - Gompertz	***77%***	***67%***	***62%***	***58%***	***55%***	***52%***
Lognormal – Gompertz	*78%*	*68%*	*62%*	*58%*	*55%*	*51%*
Gompertz – Lognormal	*77%*	*67%*	*62%*	*58%*	*56%*	*51%*
Generalised gamma - Lognormal	*77%*	*68%*	*62%*	*58%*	*55%*	*49%*

Abbreviations: RFS, recurrence-free survival.
Bold font indicates curve used for base case analysis; Underlined font indicates value was digitised from published figure.
† At 54 months follow-up.

Table 20: Validation of base case modelled projections vs. published data, for DMFS

Source	DMFS by year from baseline					
	1	2	3	4	5	7
Routine surveillance arm - DMFS						
KEYNOTE-054 observed [32, 33]	70%	56%	52%	49%†	-	-
COMBI-AD placebo [30, 31, 34]	70%	60%	57%	56%	54%	
TA553 projections [1]	72%	55%	44%	36%	30%	23%
EORTC-18071 placebo [18, 36]	66%	53%	45%	42%	39%	37%
Gompertz- Gompertz	*72%*	*58%*	*50%*	*45%*	*42%*	*39%*
Generalised gamma - Gompertz	***72%***	***59%***	***51%***	***45%***	***42%***	***37%***
Lognormal – Gompertz	*73%*	*59%*	*51%*	*45%*	*42%*	*36%*
Gompertz – Lognormal	*74%*	*60%*	*51%*	*44%*	*39%*	*32%*
Generalised gamma - Lognormal	*74%*	*61%*	*51%*	*44%*	*39%*	*31%*
Pembrolizumab arm - DMFS						
KEYNOTE-054 observed [32, 33]	83%	74%	68%	65%†	-	-
CheckMate238 nivolumab [22, 35]	80%	70%	66%	59%	-	-
TA553 projections [1]	84%	73%	66%	60%	56%	49%
EORTC-18071 ipilimumab [18, 36]	75%	62%	55%	51%	48%	45%
Gompertz- Gompertz	*84%*	*73%*	*66%*	*61%*	*58%*	*55%*
Generalised gamma - Gompertz	***84%***	***73%***	***66%***	***61%***	***58%***	***54%***
Lognormal – Gompertz	*84%*	*73%*	*66%*	*61%*	*58%*	*53%*
Gompertz – Lognormal	*83%*	*73%*	*66%*	*61%*	*57%*	*52%*
Generalised gamma - Lognormal	*83%*	*74%*	*67%*	*61%*	*57%*	*51%*

Abbreviations: DMFS, distant metastasis-free survival
Bold font indicates curve used for base case analysis; Underlined font indicates value was digitised from published figure.
† At 42 months follow-up.

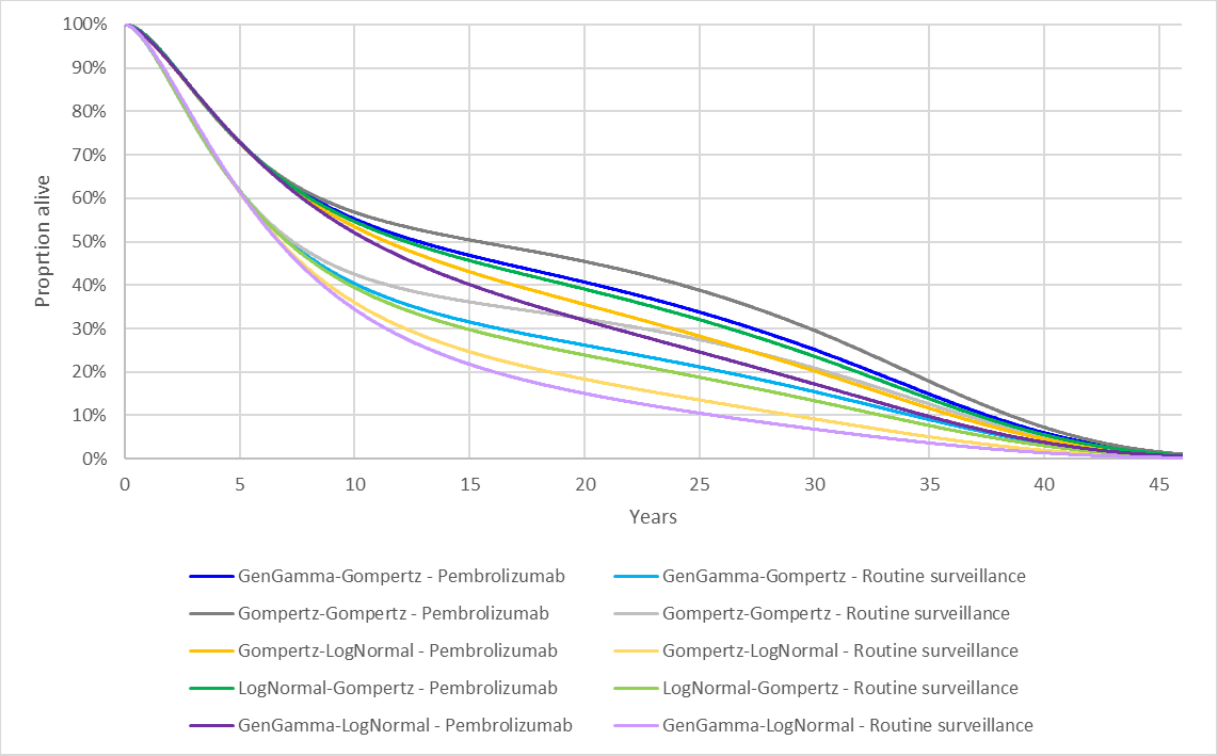
Table 21: Validation of base case modelled projections vs. published data, for OS

Source	OS by year from baseline									
	1	2	3	4	5	6	7	8	9	10
Routine surveillance arm – OS										
COMBI-AD placebo [30, 31, 34]	94%	83%	77%	-	-	-	-	-	-	-
TA553 ERG report, composite [1]	95%	79%	69%	62%	56%	50%	47%	45%	43%	40%
EORTC-18071 placebo [18, 36]	89%	76%	66%	61%	54%	53%	51%	-	-	-
AJCCv8 [26]	97%	83%	79%	75%	72%	71%	69%	67%	67%	67%
SEER 2000-2017 [27]	94%	83%	75%	70%	66%	63%	61%	60%	58%	57%
TA553 projections [1]	95%	86%	75%	64%	55%	47%	40%	35%	30%	26%
Gompertz- Gompertz	*95%*	*86%*	*77%*	*69%*	*62%*	*56%*	*51%*	*48%*	*45%*	*43%*
Generalised gamma – Gompertz‡	***95%***	***87%***	***77%***	***69%***	***62%***	***56%***	***51%***	***47%***	***43%***	***40%‡***
Lognormal – Gompertz	*95%*	*87%*	*77%*	*69%*	*62%*	*55%*	*50%*	*46%*	*42%*	*39%*
Gompertz – Lognormal	*95%*	*87%*	*78%*	*69%*	*61%*	*55%*	*49%*	*44%*	*40%*	*36%*
Generalised gamma - Lognormal	*95%*	*87%*	*78%*	*70%*	*62%*	*54%*	*48%*	*43%*	*38%*	*34%*
Pembrolizumab – OS										
CheckMate238 nivolumab [30, 31, 34]	96%	88%	82%	78%	-	-	-	-	-	-
Pembrolizumab SACT [25]	95%	90%†	-	-	-	-	-	-	-	-
EORTC-18071 ipilimumab [18, 36]	93%	82%	73%	67%	65%	62%	60%	-	-	-
TA553 projections [1]	96%	89%	82%	75%	68%	63%	58%	54%	51%	48%
Gompertz- Gompertz	*97%*	*91%*	*85%*	*78%*	*73%*	*68%*	*64%*	*61%*	*59%*	*57%*
Generalised gamma - Gompertz	***97%***	***91%***	***85%***	***79%***	***73%***	***68%***	***64%***	***61%***	***58%***	***55%***
Lognormal – Gompertz	*97%*	*91%*	*85%*	*79%*	*73%*	*68%*	*64%*	*60%*	*57%*	*55%*
Gompertz – Lognormal	*97%*	*91%*	*85%*	*79%*	*73%*	*68%*	*63%*	*60%*	*56%*	*53%*
Generalised gamma - Lognormal	*97%*	*91%*	*85%*	*79%*	*73%*	*68%*	*63%*	*59%*	*55%*	*52%*

Abbreviations: AJCC, American Joint Committee on Cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.
Bold font indicates curve used for base case analysis; Underlined font indicates value was digitised from published figure.
† 18 month follow-up; ‡ 10 year OS estimate without adjuvant treatment reported within Blueteq form used by clinicians for CDF applications for adjuvant melanoma treatment.

As OS data from KEYNOTE-054 are immature and therefore not available due to reasons explained previously, additional effort was made to validate the long-term OS projections with external sources. The different trajectories of the five key parametric functions explored are illustrated in Figure 13.

Figure 13: Predicted OS for key parametric functions over lifetime horizon



As an additional validation step, for each combination of parametric functions explored, the OS projections up to 10 years were visually assessed by plotting them on the same figure as the validation sources (Figure 14–Figure 18).

For routine surveillance, OS projections estimated by the parametric functions explored in the CEA show that early on, OS is higher than seen in the validation sources but this is consistent with the higher RFS and DMFS observed in KEYNOTE-054 vs EORTC-18071. In addition, the 3-year OS estimates for routine surveillance are aligned with the OS results observed for the placebo arm of the COMBI-AD trial. From 7 years onwards, OS predictions for routine surveillance are closely aligned with the composite curve previously provided by the ERG, particularly for the Generalised gamma – Gompertz, Gompertz – Gompertz, and Lognormal – Gompertz combinations. This suggests that long-term predictions for routine surveillance are reasonable when estimated with these functions.

Gompertz – Lognormal and Generalised gamma – Lognormal both fall below this composite curve after 7 years, and therefore provide more pessimistic extrapolations. Further, the composite curve developed by the ERG in TA553 (based on SEER 2010) aligns well with the OS reported for placebo in EORTC-18071, providing confidence that these sources are appropriate for validating the modelled OS projections. Note however that there was heavy censoring after 5 years in the EORTC-18071 trial therefore the plateau seen in the OS figure may be exaggerated due to small patient numbers.

For the active treatment arm, the projected OS for pembrolizumab matches very well with the OS data observed with nivolumab in Checkmate238 over approximately 5 years. Survival with pembrolizumab in the SACT dataset was slightly below the OS observed in CheckMate238 and in the estimates produced by the parametric functions (18 month OS was 90%, 92% and 94% in the SACT, CheckMate238 and parametric functions, respectively). This could be explained by the higher baseline age in the SACT cohort compared with the trials (64 years versus 54 years) and the lower proportion of patients with an ECOG performance score of 0 in the SACT cohort vs KEYNOTE-054 (69% vs 94.4%). OS estimates for pembrolizumab are significantly greater than for ipilimumab over 7 years in EORTC-18071, however this is expected given the higher RFS and DMFS observed for pembrolizumab in KEYNOTE-054 which is supported by the results observed in CheckMate238 (comparing adjuvant nivolumab versus an active comparator [adjuvant ipilimumab]).

Clinical experts were consulted with regards to the long-term extrapolations for both pembrolizumab and routine surveillance. They advised that Generalised gamma – Gompertz and Lognormal – Gompertz both provided very reasonable, if slightly conservative, predictions of OS. Gompertz – Gompertz was also deemed plausible and was a more optimistic projection, however the very long-term estimates (30 and 40 years) may be high. Gompertz – Lognormal and Generalised gamma – Lognormal were generally felt to be pessimistic. In addition, one clinical expert advised that the Blueteq form used by clinicians for CDF applications for adjuvant melanoma treatment states that 40% of patients are expected to be alive at 10 years without treatment [14].

Figure 14–Figure 18 present the OS extrapolation validations over a 10 year time horizon for the selected base-case model (Figure 14) and for alternative plausible parametric models (Figures 15 – 18).

Figure 14: OS versus external sources – Generalised gamma – Gompertz (used in updated base case)

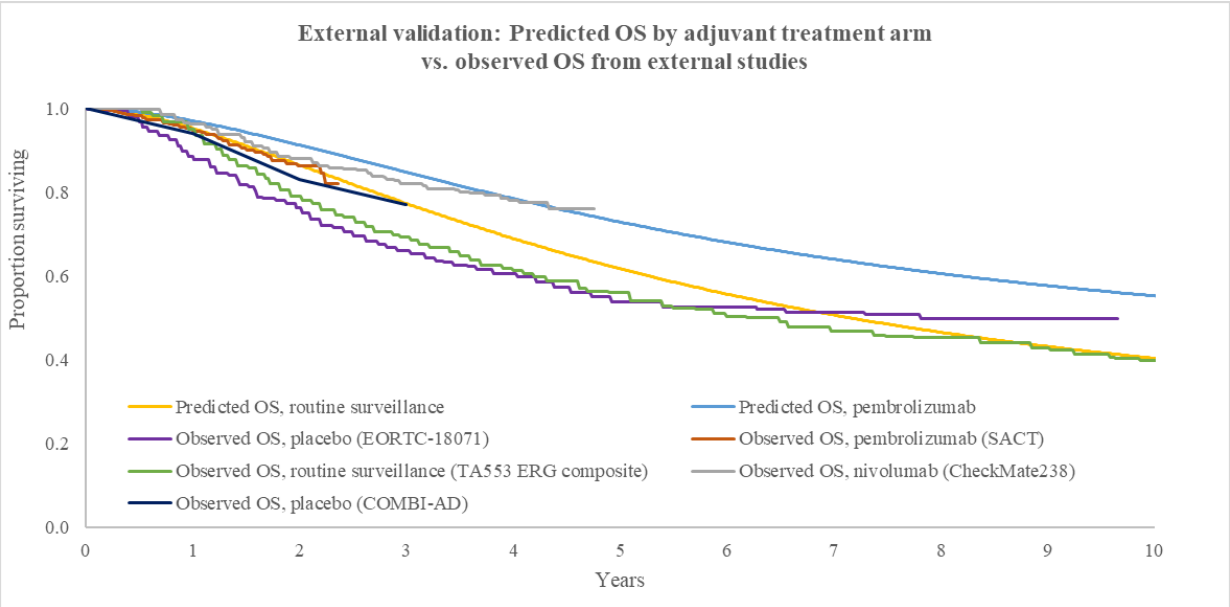


Figure 15: OS versus external sources - Gompertz – Gompertz (scenario analysis 1a)

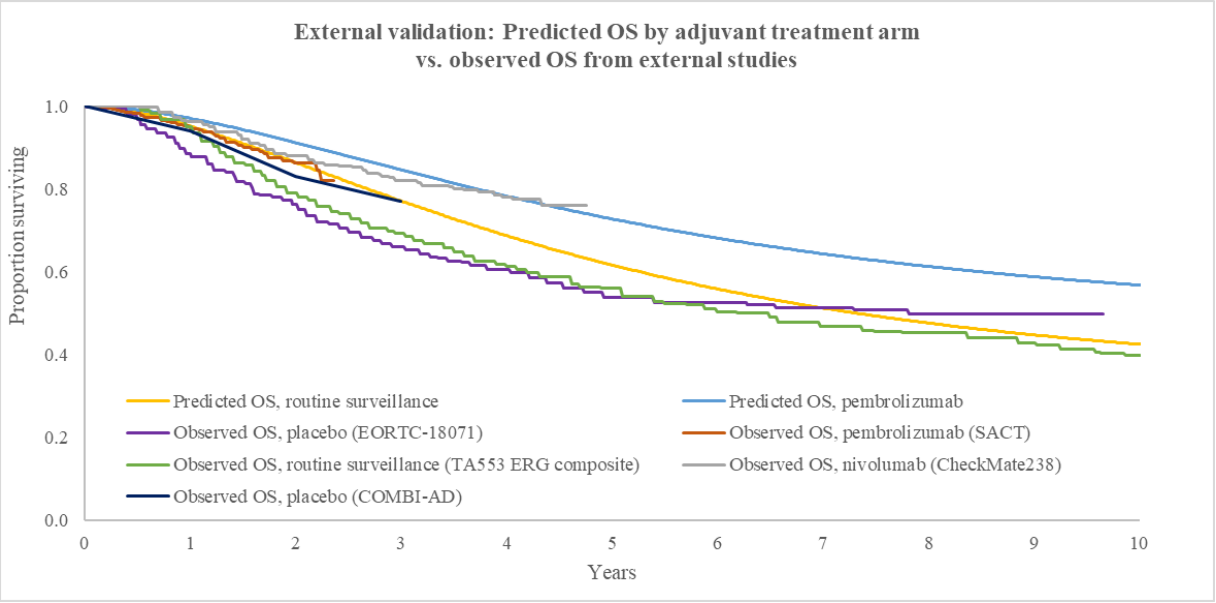


Figure 16: OS versus external sources – Lognormal – Gompertz (scenario analysis 1b)

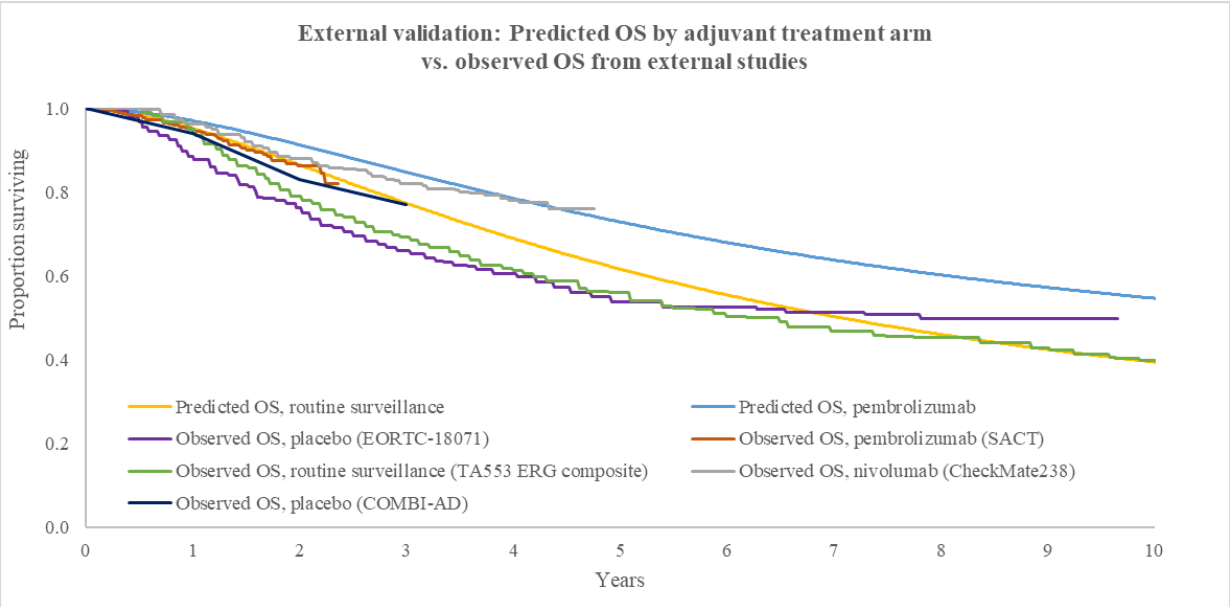


Figure 17: OS versus external sources – Gompertz – Lognormal (exploratory option)

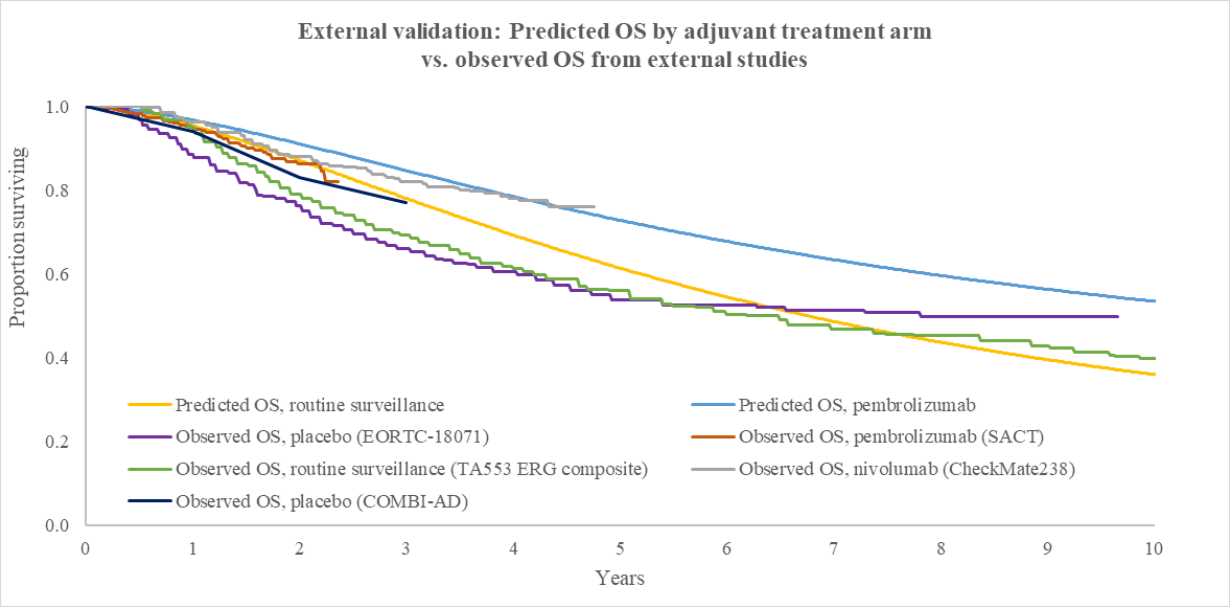
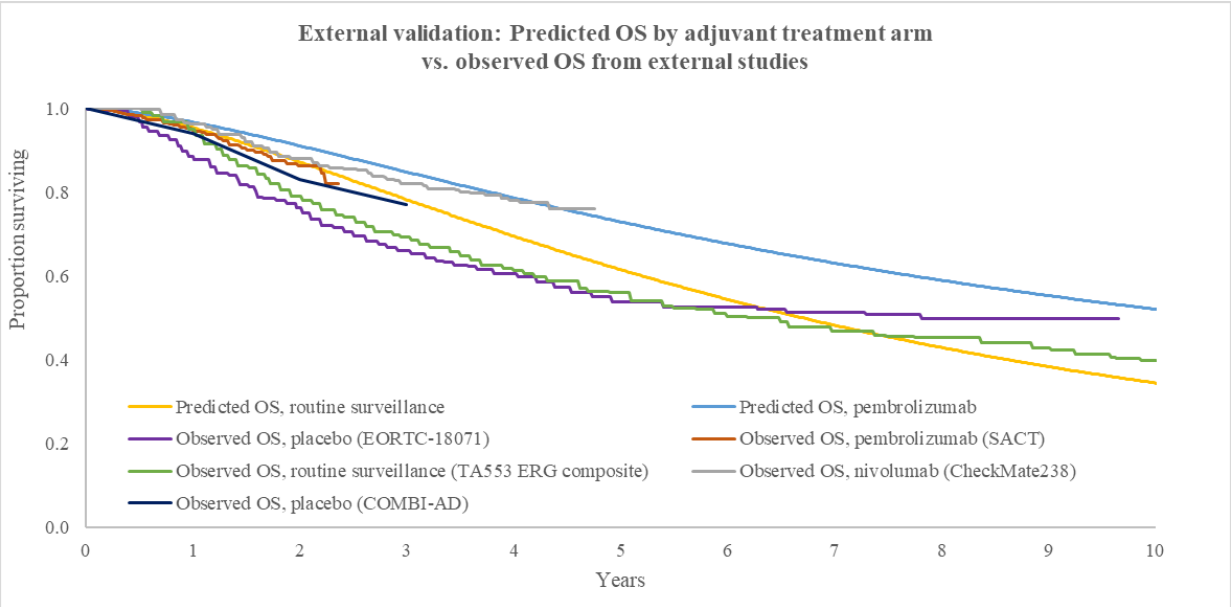


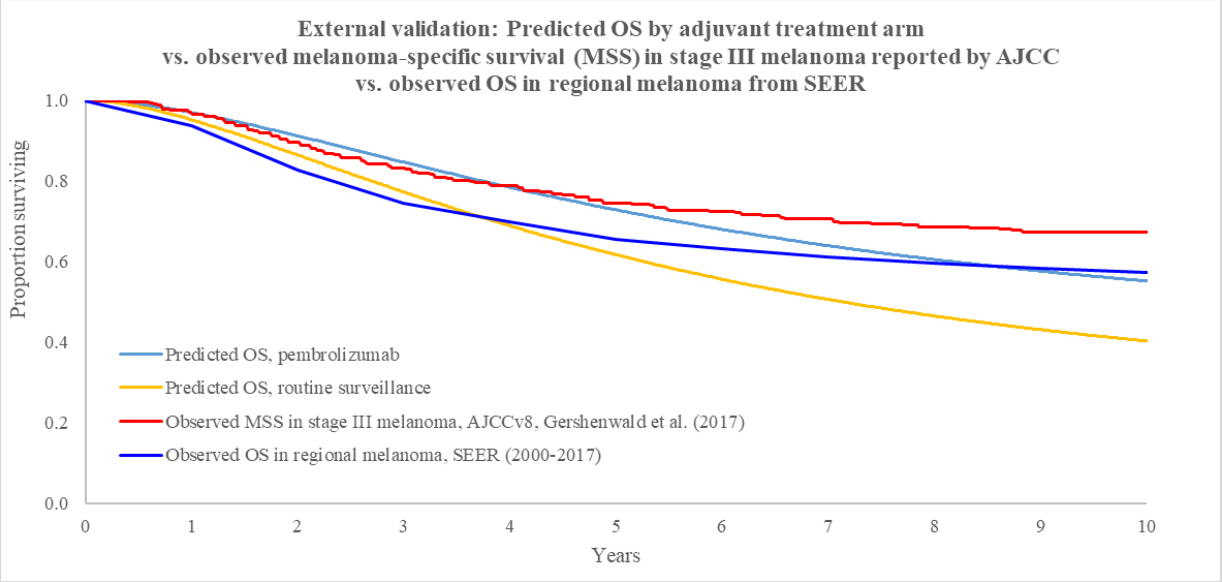
Figure 18: OS versus external sources – Generalised gamma – Lognormal (exploratory option)



Despite the limitations of external datasets with regards to generalisability to the population under consideration (KEYNOTE-054), OS projections for routine surveillance were also compared with real world survival data from SEER and the AJCC v8 staging manual (Figure 19). However, several limitations are associated with each of the datasets which limit their use as validation sources. These are described in more detail below.

Due to lack of access to individual patient-level data from these sources, no further adjustments could be explored as part of the validation process. However, as discussed previously, the key curves considered for use for routine surveillance align very well with those reported by the ERG within the TA553 ERG report (Figure 14–Figure 18).

Figure 19: OS versus external sources (SEER and AJCCv8) - Generalised gamma – Gompertz (used in updated base case)



As noted above, the ten-year survival data from some of these sources are higher than the projections explored in the CEA and the OS observed in both the EORTC-18071 trial and in the ERG's composite curve from TA553.

This can be explained based on the following considerations:

- KEYNOTE-054 did not include stage IIIA patients with <1mm metastases in the lymph nodes. Patients with <1 mm metastases in the lymph nodes have significantly better OS than patients who have ≥1 mm metastases in the lymph nodes [37]. The SEER and AJCC reflect real-world practice and are likely to include patients with <1 mm metastases, thus increasing the OS for stage III patients overall.

- The AJCC study presents melanoma-specific survival, whereas the projections in the CEA relate to overall survival (i.e. accounting for all-cause mortality, rather than melanoma-specific mortality).

- Patients included in the SEER and AJCC datasets reflect those of a large melanoma database and supplemented by data from contemporary clinical trials. It is plausible that this is pushing up the OS by not fully reflective standard of care.

- In both these datasets, survival is estimated from the point of diagnosis of stage III melanoma. By comparison, in KEYNOTE-054 outcomes are assessed after complete resection and treatment initiation therefore there will be a lag between diagnosis and

treatment initiation that is not captured in KEYNOTE-054, thus reducing survival times compared with the patients included in the AJCC and SEER datasets.

- Survival in AJCC (and likely also SEER) reflects data only for those patients for whom all relevant covariates for were known, which may further distort the survival results towards patients with better survival

- In KEYNOTE-054, a non-negligible proportion of patients were unevaluable using the 8th edition classification from AJCC, so there may be differences in the patient characteristics in terms of staging. In addition, baseline demographic characteristics in the validation datasets are not available, so there may be additional differences in the patient cohorts.

- Data in SEER are grouped by stage at diagnosis, but staging is denoted as 'Regional', therefore it is unclear how this corresponds to AJCC staging and thus how applicable it is to the patient cohort under consideration.

- Data from both SEER and AJCC are significantly higher than the OS observed in the EORTC-18071 trial, indicating that they are not representative of the cohort under consideration for the current indication.

It should also be noted that the CEA estimates OS using exponential functions as a highly conservative approach given observed OS data are unavailable from KEYNOTE-054. This may partially contribute to some deviation in OS projections from external sources but this approach was deemed more robust to avoid imposing additional assumptions within the economic model.

In conclusion, based on all of these considerations, the Generalised gamma for RF → LR and Gompertz for RF → DM combination of parametric functions appeared to provide the best balance between goodness-of-fit with the observed data for RFS and DMFS and plausible long-term extrapolations in each treatment arm. This combination was ranked second in the observational arm in terms of MSE and MSE remained low in the pembrolizumab arm.

The long-term OS projections are supported by findings in external trials and by expert clinical opinion and are preferred to those generated by the Gompertz – Gompertz parametric functions since the 30 and 40 year projections are more conservative. Gompertz – Gompertz and Lognormal – Gompertz were tested in scenario analyses to explore more optimistic and pessimistic projections, respectively.

Whilst external datasets for long term validation were also explored, all of these have associated limitations and therefore cannot be leveraged to optimise model projections further. However, based on the internal and external validation process conducted as well as the clinical expert opinion sought, the choice of parametric functions used for RF→LR and RF→ DM in the base-case (Generalised gamma and Gompertz, respectively) results in plausible OS extrapolations for both pembrolizumab and routine surveillance compared with recent trials in the adjuvant melanoma setting. Therefore long term projections can be considered robust for decision making purposes.

A.15.3 *Transition probabilities*

Table 22 and Table 23 present the ranking of all 36 combinations of parametric functions from smallest to largest mean squared error (MSE) for routine surveillance and pembrolizumab, respectively. Long-term predictions of RFS, DMFS, and OS are also presented for each of these different scenarios. Note that OS projections are a function of all transitions in the model and are therefore dependent on the selection of parametric functions used to extrapolate for RF → LR and RF → DM and the distribution of subsequent treatments used for the first line metastatic setting.

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 RFS MSE	Rank by DMFS MSE	Parametric functions		MSE for RFS	MSE for DMFS	Predicted RFS (%)					Predicted DMFS (%)					Predicted OS (%)				
		RF → LR	RF → DM			4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	1	Gompertz	Gompertz	0.0001265	0.0005782	41	38	37	32	21	45	39	37	32	21	69	51	43	32	21
2	2	Generalized gamma	Gompertz	0.0002943	0.0005824	40	35	32	24	15	45	37	33	25	15	69	51	40	26	15
3	4	Log-normal	Gompertz	0.0003913	0.0006201	39	33	30	21	12	45	36	32	22	13	69	50	39	24	13
4	7	Gompertz	Log-normal	0.0004385	0.0012984	39	31	26	16	8	44	32	27	16	8	69	49	36	18	9
5	5	Log-logistic	Gompertz	0.0004705	0.0006363	39	32	29	20	11	45	36	31	21	11	69	50	39	22	12
6	12	Gompertz	Generalized gamma	0.0005274	0.0015131	39	30	25	14	7	44	31	25	14	7	69	48	35	17	8
7	3	Weibull	Gompertz	0.0005365	0.0006196	39	32	28	17	9	45	36	30	19	9	69	50	39	21	10
8	17	Gompertz	Log-logistic	0.0006375	0.0017830	38	29	23	14	7	43	30	24	14	7	69	47	34	16	8
9	8	Generalized gamma	Log-normal	0.0008662	0.0013620	38	28	23	12	6	44	31	24	13	6	70	48	34	15	7
10	24	Gompertz	Weibull	0.0008869	0.0021207	38	27	20	8	3	43	28	21	8	3	70	47	32	11	4
11	13	Generalized gamma	Generalized gamma	0.0009941	0.0015730	38	27	21	11	5	44	30	23	11	5	70	48	34	14	6
12	9	Log-normal	Log-normal	0.0010340	0.0014265	38	27	21	11	5	44	30	23	11	5	70	48	34	14	6
13	18	Generalized gamma	Log-logistic	0.0011173	0.0018145	37	26	20	10	5	43	29	21	11	5	69	47	32	13	6
14	10	Log-logistic	Log-normal	0.0011577	0.0014551	37	26	20	10	4	44	30	22	10	5	70	48	33	13	5
15	14	Log-normal	Generalized gamma	0.0011867	0.0016409	37	26	20	10	4	44	29	22	10	4	70	47	33	13	5
16	11	Weibull	Log-normal	0.0012957	0.0014557	38	26	20	9	4	44	30	22	9	4	70	48	33	12	5
17	16	Log-logistic	Generalized gamma	0.0013221	0.0016702	37	26	19	9	4	44	29	21	9	4	70	47	33	12	5
18	20	Log-normal	Log-logistic	0.0013412	0.0018819	36	25	19	9	4	43	28	20	9	4	69	47	32	12	5
19	15	Weibull	Generalized gamma	0.0014636	0.0016676	37	25	19	8	3	44	29	21	8	3	70	47	32	11	4
20	22	Log-logistic	Log-logistic	0.0014910	0.0019095	36	24	18	8	4	43	28	20	9	4	69	46	32	11	4
21	25	Generalized gamma	Weibull	0.0014921	0.0022051	37	25	17	6	2	43	27	19	6	2	70	47	31	9	3
22	21	Weibull	Log-logistic	0.0016151	0.0018931	36	24	18	7	3	43	28	20	8	3	69	47	31	11	4
23	6	Exponential	Gompertz	0.0017128	0.0008304	36	25	18	5	1	45	32	23	7	2	69	49	34	10	3

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE for RFS	MSE for DMFS	Predicted RFS (%)					Predicted DMFS (%)					Predicted OS (%)				
		RF → LR	RF → DM			4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs
24	27	Log-normal	Weibull	0.0017305	0.0022884	36	24	16	6	2	43	27	18	6	2	70	46	31	9	2
25	28	Log-logistic	Weibull	0.0018939	0.0023234	36	23	16	5	1	43	26	17	5	2	70	46	30	8	2
26	29	Weibull	Weibull	0.0020725	0.0023286	36	23	15	5	1	43	26	17	5	1	70	46	30	8	2
27	19	Exponential	Log-normal	0.0029289	0.0018456	35	20	13	3	0	44	27	17	4	1	70	47	30	6	1
28	31	Gompertz	Exponential	0.0029651	0.0055732	35	19	11	1	0	40	21	11	1	0	70	43	25	4	0
29	23	Exponential	Generalized gamma	0.0032301	0.0020750	34	20	12	2	0	44	26	16	3	1	70	46	29	6	1
30	26	Exponential	Log-logistic	0.0034998	0.0022776	34	19	11	2	0	43	25	15	3	1	70	46	29	6	1
31	32	Generalized gamma	Exponential	0.0039944	0.0056779	34	18	9	1	0	40	20	10	1	0	70	43	25	3	0
32	30	Exponential	Weibull	0.0041130	0.0028413	34	18	10	1	0	43	24	13	2	0	70	45	28	4	1
33	33	Log-normal	Exponential	0.0044605	0.0057988	33	17	9	1	0	40	20	10	1	0	70	43	25	3	0
34	34	Log-logistic	Exponential	0.0047185	0.0058361	33	16	8	1	0	40	19	10	1	0	70	43	24	3	0
35	35	Weibull	Exponential	0.0049911	0.0058438	33	16	8	1	0	40	19	9	1	0	70	43	24	3	0
36	36	Exponential	Exponential	0.0084691	0.0066488	31	13	5	0	0	40	18	8	0	0	71	43	23	2	0

Abbreviations: DM, distant metastatic; DMFS, distant metastasis-free survival; LR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.

Updated from original submission: Company submission B.3.3.1 (Table 22, p60-61)

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

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE for RFS	MSE for DMFS	Predicted RFS (%)					Predicted DMFS (%)					Predicted OS (%)				
		RF → LR	RF → DM			4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	4	Generalized gamma	Log-normal	0.0001644	0.0002012	58	49	43	29	16	61	51	44	29	16	79	63	52	32	17
2	3	Log-normal	Log-normal	0.0001789	0.0001938	58	48	42	28	15	61	50	43	28	15	79	63	52	31	16
3	8	Generalized gamma	Generalized gamma	0.0001873	0.0002127	58	48	41	26	14	61	49	42	26	14	79	62	51	29	15
4	2	Log-logistic	Log-normal	0.0001993	0.0001888	58	48	41	26	14	61	50	42	27	14	79	63	51	30	15

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE for RFS	MSE for DMFS	Predicted RFS (%)					Predicted DMFS (%)					Predicted OS (%)				
		RF → LR	RF → DM			4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs
5	12	Generalized gamma	Log-logistic	0.0002036	0.0002272	57	47	40	26	13	61	49	41	26	14	79	62	50	29	15
6	13	Gompertz	Log-normal	0.0002090	0.0002357	58	51	46	33	19	61	52	46	34	19	79	63	53	36	20
7	19	Gompertz	Generalized gamma	0.0002091	0.0002519	58	50	44	30	16	61	50	44	30	16	79	63	52	32	17
8	1	Weibull	Log-normal	0.0002153	0.0001879	58	47	40	25	13	62	50	42	26	13	79	63	51	29	14
9	20	Gompertz	Log-logistic	0.0002175	0.0002691	58	49	43	29	16	61	50	44	29	16	79	63	52	32	17
10	7	Log-normal	Generalized gamma	0.0002224	0.0002110	57	47	40	25	13	61	49	41	25	13	79	62	50	28	14
11	21	Gompertz	Weibull	0.0002253	0.0002747	58	48	41	25	12	60	49	41	25	12	79	62	50	28	14
12	14	Generalized gamma	Weibull	0.0002357	0.0002384	57	46	38	22	10	61	48	39	22	10	79	62	49	25	12
13	11	Log-normal	Log-logistic	0.0002463	0.0002272	57	46	39	24	13	61	48	40	25	13	79	62	50	28	14
14	6	Log-logistic	Generalized gamma	0.0002570	0.0002083	57	46	39	23	12	61	48	40	24	12	79	62	50	27	13
15	27	Generalized gamma	Gompertz	0.0002654	0.0003305	58	52	49	39	25	61	54	50	40	25	79	64	55	41	25
16	5	Weibull	Generalized gamma	0.0002772	0.0002071	57	46	38	22	11	61	48	40	23	11	79	62	50	26	12
17	10	Log-logistic	Log-logistic	0.0002859	0.0002252	57	46	38	23	12	61	48	40	23	12	79	62	49	27	13
18	15	Log-normal	Weibull	0.0002872	0.0002436	57	45	37	21	9	61	47	38	21	9	79	62	49	24	11
19	26	Log-normal	Gompertz	0.0002935	0.0003171	58	51	47	37	23	61	53	49	38	23	79	64	55	39	24
20	9	Weibull	Log-logistic	0.0003073	0.0002236	57	46	38	22	11	61	48	39	23	11	79	62	49	26	12
21	23	Log-logistic	Gompertz	0.0003142	0.0003050	58	51	46	35	21	61	53	48	36	21	79	64	54	38	22
22	22	Weibull	Gompertz	0.0003250	0.0002991	58	50	46	34	20	61	53	48	35	20	79	64	54	37	21
23	16	Log-logistic	Weibull	0.0003348	0.0002453	57	45	37	19	9	61	47	38	20	9	79	62	48	24	10
24	17	Weibull	Weibull	0.0003611	0.0002456	57	45	36	19	8	61	47	38	19	8	79	62	48	23	10
25	29	Gompertz	Gompertz	0.0003738	0.0003917	58	54	53	45	30	61	55	53	45	30	78	64	57	45	30
26	18	Exponential	Log-normal	0.0008069	0.0002477	56	42	32	13	4	62	46	35	15	5	79	62	47	19	6
27	25	Exponential	Generalized gamma	0.0010179	0.0003076	56	41	30	12	4	61	45	34	13	4	80	61	46	17	6
28	24	Exponential	Gompertz	0.0010209	0.0003064	56	44	36	18	7	62	49	40	20	7	79	63	50	24	9
29	33	Gompertz	Exponential	0.0010890	0.0012371	56	41	30	10	2	58	41	30	10	2	79	59	43	14	4

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE for RFS	MSE for DMFS	Predicted RFS (%)					Predicted DMFS (%)					Predicted OS (%)				
		RF → LR	RF → DM			4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	7 yrs	10 yrs	20 yrs	30 yrs
30	28	Exponential	Log-logistic	0.0010999	0.0003362	55	40	30	12	4	61	45	33	13	4	80	61	46	17	5
31	30	Exponential	Weibull	0.0012239	0.0004024	55	39	28	10	3	61	44	32	11	3	80	61	45	15	4
32	31	Generalized gamma	Exponential	0.0012289	0.0011849	55	39	27	8	2	59	40	28	9	2	80	59	42	13	3
33	32	Log-normal	Exponential	0.0014060	0.0012307	55	38	27	8	2	59	40	28	8	2	80	59	42	12	3
34	34	Log-logistic	Exponential	0.0015392	0.0012524	55	38	26	8	2	59	40	27	8	2	80	59	42	12	3
35	35	Weibull	Exponential	0.0016010	0.0012581	55	38	26	7	2	59	40	27	8	2	80	59	42	12	3
36	36	Exponential	Exponential	0.0034412	0.0017459	53	33	20	4	1	59	37	23	4	1	80	58	39	8	1

Abbreviations: DM, distant metastatic; DMFS, distant metastasis-free survival; LR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.

Updated from original submission: Company submission B.3.3.1 (Table 21, p59-60).

Parameter estimates for transitions starting from the RF state are presented in Table 24 for each of the possible parametric models. Cause-specific hazards for transitions from the LR state are shown in Table 25.

Table 24: Parametric models for transitions starting from the recurrence-free state, separately fitted to each arm of the KEYNOTE-054 trial – Company submission Appendix L, Table 1

Distribution	Parameter	Parameter estimates for pembrolizumab			Parameter estimates for routine surveillance		
		RF → LR	RF → DM	RF → Death	RF → LR	RF → DM	RF → Death
Exponential	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Log mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log standard deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	Location	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastatic; LR, locoregional recurrence; RF, recurrence-free.

Table 25 Cause-specific hazards of transitions starting from LR recurrence

Adjuvant regimen	LR → DM		LR → Death	
	Exponential rate	*SE*	*Exponential rate*	*SE*
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastatic; LR, locoregional recurrence; SE, standard error.
Sources: Analyses of patient-level KEYNOTE-054 trial data; Office for National Statistics. National life tables, England & Wales (2017-2019). Note: Within each cycle, the transition probability from LR recurrence → death is set equal to the maximum of the estimated probability based on parametric modelling and background mortality (Office of National Statistics, 2017-2019).

Parameters for the exponential models of OS and PFS with pembrolizumab in the advanced melanoma setting are shown in Table 26. HRs used to estimate the efficacy of other subsequent treatments in the advanced melanoma setting are presented in Table 27.

Table 26: Exponential models of OS and PFS with pembrolizumab in the advanced melanoma setting - Company submission Appendix L, Table 2

Advanced regimen	Exponential model of OS		Exponential model of PFS		Source
	Rate	*SE*	*Rate*	*SE*	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Patient-level KEYNOTE-006 data

Abbreviations: OS, overall survival; PFS, progression-free survival; SE, standard error.

Table 27 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 DM 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]
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastatic; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SE, standard error.
Source for HRs: MSD data on file [20]; Encorafenib + binimetinib values only: Dummer et al. (2018) [21].

A.15.4 *Subsequent treatment market shares*

Sources explored to inform market share distributions of subsequent treatments are presented in Table 28 and Table 29.

Clinical experts advised that the market shares from the SACT dataset were the most suitable published data available and were a good representation of UK clinical practice for the adjuvant pembrolizumab arm for first- and second line metastatic settings (therefore addressing a key uncertainty element within the original submission).

Based on clinical expert opinion, market research data from Ipsos Oncology Monitor were not considered to be fully reflective of UK practice as the use of nivolumab + ipilimumab was too low, and the use of *BRAF*-targeted agents was too high; although the market share of pembrolizumab seen in the Ipsos research ([redacted]%) was considered reasonable. Wilmington Specialist Share Data were also not considered to be reflective, as the use of nivolumab + ipilimumab was too low. The SACT market shares were adjusted to allow for pembrolizumab use based on Ipsos Oncology Monitor market research and were subsequently deemed by UK clinical experts to be a good representation of clinical practice for patients in the routine surveillance arm.

As such, market shares from the SACT dataset were used in the base case analysis for the pembrolizumab arm, and the SACT shares adjusted for pembrolizumab use seen in Ipsos were used for the routine surveillance arm. This approach makes the best use of real-world data and ensures consistency in the sources used to inform each treatment arm. The use of Ipsos Oncology Monitor market research data for the routine surveillance arm was explored in a scenario analysis.

Raw data from KEYNOTE-054 (Appendix A.15.12) did not account for individual agents received in combination regimens, therefore the use of combination regimens (such as nivolumab + ipilimumab or dabrafenib + trametinib) may be underestimated and may not reflect current UK practice. In addition, part 2 of the KEYNOTE-054 (investigating cross-over/rechallenge with pembrolizumab) may further limit the generalisability of these estimates in the UK clinical practice. Therefore, no cost-effectiveness analyses are presented using the actual KEYNOTE-054 subsequent treatment data.

Although clinical experts regarded the SACT dataset (and SACT dataset adjusted by Ipsos Oncology Monitor) to be suitably reflective of UK clinical practice, some further adjustments were recommended to approximate an even better representation of UK practice for each adjuvant treatment arm (Table 30). In particular, the clinicians stated that the proportion of

patients assumed to have no active therapy at second line in the routine surveillance arm was too high, and estimated that this would be closer to 30%; the value used for the base case ([redacted]%, based on the ratio of first-line to second line patients in Ipsos Oncology Monitor) was felt to be appropriate for patients in the pembrolizumab arm. These adjusted datasets are explored in additional scenario analyses. An overview of the assumptions used in each of these additional KOL-adjusted scenarios is provided in Table 31.

Table 28 Market share sources explored for first-line advanced melanoma setting

Treatment regimen	Adjuvant pembrolizumab			Routine surveillance		
	SACT 1L [25]	*Adjusted Ipsos Oncology Monitor 1L, April 2021 [29]†*	*SACT 1L [25], adjusted for pembrolizumab rechallenge‡*	*Unadjusted Ipsos Oncology Monitor 1L, April 2021 [29]*	*Wilmington Specialist Share Data [38]*	*SACT 1L [25], adjusted by Ipsos Oncology Monitor 1L, April 2021 [29]$*
Pembrolizumab	0.00%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	19.33%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	2.67%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	55.33%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	0.00%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	0.00%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	14.00%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encorafenib + Binimetinib	8.67%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Abbreviations: 1L, first line; SACT, Systemic Anti-Cancer Therapy.

† Pembrolizumab market share set to 0% to prevent rechallenge and proportionally redistributed across other non-targeted therapies (ipilimumab, nivolumab, and nivolumab + ipilimumab);

‡ Pembrolizumab market share set to 5% to reflect rechallenge that may be observed in some patients. Market shares of ipilimumab and nivolumab + ipilimumab proportionally adjusted to account for pembrolizumab usage.

$ Pembrolizumab market share sourced from Ipsos Oncology Monitor [29] as pembrolizumab rechallenge was not observed in the SACT dataset but would be expected in practice for patients who on routine surveillance in the adjuvant setting. Market shares of other non-targeted therapies (ipilimumab, nivolumab, and nivolumab + ipilimumab) were proportionally adjusted to account for pembrolizumab usage.

Table 29 Market share sources explored for second-line advanced melanoma setting

Treatment regimen	Pembrolizumab		Routine surveillance	
Source	***SACT 2L [25]***	***Adjusted Ipsos Oncology Monitor 2L, April 2021 [29]†***	***Unadjusted Ipsos Oncology Monitor 2L, April 2021 [29]***	***SACT 2L [25], adjusted by Ipsos Oncology Monitor 2L, April 2021 [29]‡***
Pembrolizumab	0%	[redacted]	[redacted]	[redacted]
Ipilimumab	0.95%	[redacted]	[redacted]	[redacted]
Nivolumab	26.54%	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	2.84%	[redacted]	[redacted]	[redacted]
Vemurafenib	0.00%	[redacted]	[redacted]	[redacted]
Dabrafenib	0.00%	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	0.95%	[redacted]	[redacted]	[redacted]
Encorafenib + Binimetinib	6.64%	[redacted]	[redacted]	[redacted]
No active treatment	62.08%††	[redacted]	[redacted]	[redacted]
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Abbreviations: 2L, second line; SACT, Systemic Anti-Cancer Therapy.

† Pembrolizumab market share set to 0% to prevent rechallenge and proportionally redistributed across other non-targeted therapies (ipilimumab, nivolumab, and nivolumab + ipilimumab);

‡ Pembrolizumab market share sourced from Ipsos Oncology Monitor [29] as pembrolizumab rechallenge was not observed in the SACT dataset but would be expected in practice for patients who on routine surveillance in the adjuvant setting. Market shares of other non-targeted therapies (ipilimumab, nivolumab, and nivolumab + ipilimumab) were proportionally adjusted to account for pembrolizumab usage.

†† The proportion of patients assumed to receive no active treatment at second-line was estimated as the ratio between the number of patients on first vs second line regimens from the latest Ipsos market research [26].

Table 30: Summary of first line market shares adjusted to reflect clinical expert opinion

Adjustment	Adjuvant pembrolizumab		Routine surveillance	
	1L	*2L*	*1L*	*2L*
	SACT 1L, KOL adjustments: • Dabrafenib +Trametinib set to [redacted]% (aligned with Wilmington Specialist Share Data) • Nivolumab and pembrolizumab set to [redacted]% each to represent IO rechallenge • Ipilimumab and ipilimumab + nivolumab proportionally redistributed accordingly	Ipsos Oncology Monitor 2L, KOL adjustments: • Pembrolizumab set to [redacted]%, redistributed from nivolumab to represent rechallenge	SACT 1L, adjusted by Ipsos Oncology Monitor 2L, April 2021. KOL adjustments: • [redacted]% share removed from ipilimumab and added to nivolumab	SACT 2L adjusted by Ipsos Oncology Monitor 2L, April 2021. KOL adjustments: • No active treatment decreased to [redacted]% • Ipilimumab increased to [redacted]% • Dabrafenib + trametinib increased to [redacted]% • Encorafenib + binimetinib increased to [redacted]%
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Encorafenib + Binimetinib	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]	[redacted]
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Abbreviations: 1L, first line; 2L, second line; IO, immuno-oncology; KOL, key opinion leader; SACT, Systemic Anti-Cancer Therapy

Table 31: Description of scenarios explored based on market shares of subsequent treatments

Subsequent treatment scenario	Pembrolizumab		Routine surveillance	
	1L	2L	1L	2L
Base-case	SACT 1L	SACT 2L	SACT 1L, adjusted by Ipsos Oncology Monitor 1L	SACT 2L, adjusted by Ipsos Oncology Monitor 2L
Alternative published data: Ipsos Oncology Monitor for routine surveillance arm only	SACT 1L	SACT 2L	Ipsos Oncology Monitor 1L	Ipsos Oncology Monitor 2L
KOL scenario 1: 1L & 2L adjusted (combined)	SACT 1L, KOL adjustments: • Dabrafenib +Trametinib set to [redacted]% • Nivolumab and pembrolizumab set to [redacted]% each • Ipilimumab and ipilimumab + nivolumab proportionally redistributed	Ipsos Oncology Monitor 2L, KOL adjustments: • Pembrolizumab set to [redacted]%, redistributed from nivolumab	SACT 1L, adjusted by Ipsos Oncology Monitor 2L, April 2021. KOL adjustments: • [redacted]% share added to nivolumab and removed from ipilimumab	SACT 2L, adjusted by Ipsos Oncology Monitor 2L. KOL adjustments: • No active treatment set to [redacted]% • Ipilimumab increased to [redacted]% • Dabrafenib + trametinib increased to [redacted]% • Encorafenib + binimetinib increased to [redacted]%
KOL scenario 2: 2L only adjusted	SACT 1L	Ipsos Oncology Monitor 2L, KOL adjustments: • Pembrolizumab set to [redacted]%, redistributed from nivolumab	SACT 1L, adjusted by Ipsos Oncology Monitor 1L	SACT 2L adjusted by Ipsos Oncology Monitor 2L, April 2021. KOL adjustments: • No active treatment set to [redacted]% • Ipilimumab increased to [redacted]% • Dabrafenib + trametinib increased to [redacted]% • Encorafenib + binimetinib increased to [redacted]%

Subsequent treatment scenario	Pembrolizumab		Routine surveillance	
	1L	2L	1L	2L
KOL scenario 2: 1L only adjusted	SACT 1L, KOL adjustments: • Dabrafenib + Trametinib set to [redacted]% • Nivolumab and pembrolizumab set to [redacted]% each • Ipilimumab and ipilimumab + nivolumab proportionally redistributed	SACT 2L	SACT 1L, adjusted by Ipsos Oncology Monitor 2L, April 2021. KOL adjustments: • [redacted]% share added to nivolumab and removed from ipilimumab	SACT 2L, adjusted by Ipsos Oncology Monitor 1L
Pembrolizumab rechallenge permitted	SACT 1L, adjusted to allow pembrolizumab rechallenge: • Pembrolizumab set to [redacted]% • Ipilimumab and ipilimumab + nivolumab proportionally redistributed	SACT 2L	SACT 1L, adjusted by Ipsos Oncology Monitor 1L	SACT 2L, adjusted by Ipsos Oncology Monitor 2L

Abbreviations: 1L, first line; 2L, second line; KOL, key opinion leader; SACT, Systemic Anti-Cancer Therapy.

A.15.5 *Updated model inputs*

Adverse events

The incidence and mean duration of drug-related adverse events (AEs) were updated based on the latest available data from KEYNOTE-054 IA2 (Table 32).

Table 32: Incidence and duration of modelled AEs, as reported in the KEYNOTE-054 trial

Type of AE	Grades	Pembrolizumab n = 509	Routine surveillance (placebo) n = 502	Mean duration of AE (weeks)
		n (%)	n (%)	
Diarrhoea	2+	[redacted]	[redacted]	[redacted]
Pneumonitis	1+	[redacted]	[redacted]	[redacted]
Fatigue	3+	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	3+	[redacted]	[redacted]	[redacted]
Arthralgia	3+	[redacted]	[redacted]	[redacted]
Headache	3+	[redacted]	[redacted]	[redacted]
Dyspnoea	3+	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
Updated from original submission: Company submission B.3.3.3 (Table 29, p81).

Healthcare resource use

The proportion of patients who entered the LR recurrence state who then underwent salvage surgery was updated based on the latest available data from KEYNOTE-054 IA2 (Table 33).

Table 33: 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]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	

Abbreviations: CT, computed tomography; LR, locoregional; MRI, magnetic resonance imaging.
Updated from original submission: Company submission B.3.5.2 (Table 38, p91).

Health state utilities

The regression analysis of EQ-5D data from KEYNOTE-054 was updated based on the IA2 data cut-off using the same methods as in the original submission. The resulting utility estimates were used for the RF, LR recurrence and pre-progression DM health states, and an updated disutility of grade 3+ AEs was also applied (Table 34).

Table 34: Health state utilities

Health state	Utilities		Source
	Value	SE	
Recurrence-free (without toxicity)	[redacted]	[redacted]	KEYNOTE-054 [4]
Locoregional recurrence	[redacted]	[redacted]	
Distant metastases (pre-progression)	[redacted]	[redacted]	
Distant metastases (post-progression)	0.590	(0.020)	Beusterien et al, 2009 [40]
Disutility of grade 3+ AEs	[redacted]	[redacted]	KEYNOTE-054 [4]

Abbreviations: AE, adverse event; SE, standard error.
Updated from original submission: Company submission B.3.4.5 (Table 31, p84).

Drug acquisition costs

The current list price of pembrolizumab is £2,630 per 100 mg vial. A patient access scheme (PAS) is in place for patients with melanoma which has been applied for pembrolizumab in the adjuvant and metastatic setting. Competitor discounts available to the NHS have not been applied into the model. Encorafenib and binimetinib were added as a subsequent therapy option, and drug acquisition costs, based on list prices, were sourced from MIMS [41] (Table 35). Dosing schedules for each drug are presented in Table 36. The relative dose intensity (RDI) of pembrolizumab was updated based on data from KEYNOTE-054 IA2 and set to [redacted]%.

Table 35: Treatment cost per pack/vial

Treatment	Pack size/vial volume	Cost per pack/vial	Source
Pembrolizumab	100mg vial	£2,630	MIMS 2021: 100mg
Nivolumab	100mg vial 40mg vial	£1,097 £439	MIMS 2021: 10mg/ml, 10-ml vial MIMS 2021: 10mg/ml, 4-ml vial
Ipilimumab	5mg/ml vial concentration 10ml (50mg) vial 40ml (200mg) vial	 £3,750 £15,000	 MIMS 2021: 5mg/ml, 10-ml vial MIMS 2021: 5mg/ml, 40-ml vial
Vemurafenib	240mg 56-tab pack	£1,750	MIMS 2021: 240mg 56-tab pack
Dabrafenib	50 mg, 28-cap pack 75 mg, 28-cap pack	£933.33 £1,400	MIMS 2021: 50 mg, 28-cap pack MIMS 2021: 75 mg, 28-cap pack
Trametinib	2mg tablet, 30-tab pack 2mg tablet, 30-tab pack	£4,800 £1,120	MIMS 2021: 2 mg, 30-tab pack MIMS 2021: 2 mg, 7-tab pack
Encorafenib	75mg capsule, 42-cap pack	£1,400	MIMS 2021: 75mg, 42-cap pack
Binimetinib	15mg tablet, 84-tab pack	£2,240	MIMS 2021: 15mg, 84-tab pack

Updated from original submission: Company submission B3.5.3 (Table 42, p93)

Table 36: Drug doses for each treatment given in the advanced setting

Treatment	Dose	Frequency	Source
Pembrolizumab	200mg 400mg	3-weekly 6-weekly	Pembrolizumab SmPC
Nivolumab	240mg	2-weekly	NICE TA684
Ipilimumab	3mg/kg	3-weekly	NICE TA319
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
Encorafenib plus binimetinib	Encorafenib: 450mg Binimetinib: 45mg	Daily Twice daily	NICE TA562

Updated from original submission: Company submission B3.5.3 (Table 41, p93)

Drug administration costs

All drug administration costs were updated using the 2019/20 NHS Reference Costs [42], using the same Healthcare Resource Group (HRG) codes as in the original submission, and Personal Social Services Research Unit (PSSRU) 2020 [43] (Table 37).

Table 37: NHS reference costs and PSSRU costs – administration of treatments

Type	Source	Unit Price
Deliver simple parenteral chemotherapy at first attendance	NHS Reference Costs 2019/20 SB12Z-Total HRG	£281.28
Deliver more complex Parenteral Chemotherapy at first attendance	NHS Reference Costs 2019/20 SB13Z-Total HRG	£475.67
Deliver exclusively oral chemotherapy	NHS Reference Costs 2019/20 SB11Z-Total HRG	£210.79
Cost of 12 minutes of pharmacist time (subsequent administration of oral drugs)	PSSRU (2020); Hospital based scientific and professional staff – Band 6 (Pharmacist)	£9.60

Updated from original submission: Company submission B3.5.3 (Table 45, p96)

Healthcare resource use costs

The unit costs of healthcare resources were updated from the NHS Reference Costs 2019/20 [42] and the PSSRU 2020 [43] (Table 38). The frequency of use of healthcare resources in each health state remained unchanged from the original submission. Costs associated with terminal care, sourced from Georghiou and Bardsley (2014) [44], were inflated to 2020 using the Consumer Price Index (CPI) for Health from the Office for National Statistics (ONS) [45] (Table 39).

Table 38: Unit costs of health care resources

Resource use element	Unit cost (£)	Sources
Salvage surgery		
Surgical resection	2,843.79	NHS Reference Costs 2019/20 - Total HRG activity for JC41Z (major skin procedures)
Lymphadenectomy	2,499.72	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for WH54A and WH54B
Skin lesion resection	532.22	NHS Reference Costs 2019/20 - Total HRG activity for JC42C (intermediate skin procedures)
Outpatient visits		
Medical oncologist	192.90	NHS Reference Costs 2019/20 - Total outpatient attendances for 370 (medical oncology)
Radiation oncologist	144.47	NHS Reference Costs 2019/20 - Total outpatient attendances for 800 (clinical oncology, previously radiotherapy)
General practitioner	33.00	PSSRU 2020 without qualifications, including direct care staff
Palliative care, physician outpatient visit	118.75	NHS Reference Costs 2019/20 - Total HRG activity for SD04A (medical specialist palliative care attendance, 19 years and over)

Resource use element	Unit cost (£)	Sources
Psychologist	110.78	PSSRU 2020 per hour client contact (adjusted for ratio of direct to indirect time), assumes 1 hour
Plastic surgeon	117.32	NHS Reference Costs 2019/20 - Total outpatient attendances for 160 (plastic surgery)
Dermatologist	121.03	NHS Reference Costs 2019/20 - Total outpatient attendances for 330 (dermatology)
Cancer specialist nurse	91.24	NHS Reference Costs 2019/20 - Total HRG activity (Other Currencies Data) for N10AF (specialist nursing, cancer related, face to face)
Inpatient stays		
Oncology/general ward	2,176.65	NHS Reference Costs 2019/20 - Elective inpatients for JC42C (intermediate skin disorders, 19 years and over)
Palliative care unit – inpatient	365.73	NHS Reference Costs 2019/20 - Total HRG activity for SD01A (inpatient specialist palliative care, 19 years and over)
Home care		
Palliative care physician	189.00	PSSRU 2020 medical specialist palliative care attendance
Palliative care nurse	115.59	NHS Reference Costs 2019/20 - Community health services for N21AF (specialist nursing, palliative/respite care, adult, face to face)
Home aide visits	103.00	PSSRU 2020 - Outpatient Non-medical Specialist Palliative Care Attendance
Laboratory tests		
Complete blood count	2.58	NHS Reference Costs 2019/20 - Directly accessed pathology services for DAPS05 (haematology)
Complete metabolic panel	1.22	NHS Reference Costs 2019/20 - Directly accessed pathology services for DAPS04 (clinical biochemistry)
Lactate dehydrogenase	1.22	NHS Reference Costs 2019/20 - Directly accessed pathology services for DAPS04 (clinical biochemistry)
Radiologic exams		
CT scan of abdomen/pelvis	78.89	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
CT scan of chest	78.89	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
MRI of brain	147.19	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z
CT scan of brain	78.89	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
PET/CT scan	147.19	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z
Bone scintigraphy	304.30	NHS Reference Costs 2019/20 - Total HRG activity for RN16A (nuclear bone scan of other phases, 19 years and over)
Echography	87.37	NHS Reference Costs 2019/20 - Total HRG activity for RD51A (simple echocardiogram, 19 years and over)
Chest x-ray	121.74	NHS Reference Costs 2019/20 - Total HRG activity for RD30Z (contrast fluoroscopy procedures with duration of less than 20 minutes)

Updated from original submission: Company submission B3.5.3 (Table 48, p100)

Table 39: Supportive and terminal care costs

Terminal care cost	Cost	Source
District nurse	£345.51	Georghiou & Bardsley (2014)[44] inflated to 2020 prices
Nursing and residential care	£1,242.83	
Hospice care – inpatient	£683.55	
Hospice care – final 3 months of life	£5,592.72	
Marie Curie nursing service	£621.41	
Total	**£8,486.01**	

Updated from original submission: Company submission B3.5.4 (Table 50, p103)

Adverse event costs

As per the original submission, adverse event costs were mostly derived from TA319 [46], or updated using NHS Reference Costs 2019/20 [42], PSSRU 2020 [43] or eMIT [47] where appropriate. Costs were inflated to 2020 using the Office for National Statistics ONS CPI for Health [45] (Table 40).

Table 40: 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	805.64	Oxford Outcomes data reported in TA319, inflated to 2020 GBP
Hyperthyroidism	473.72	2013	557.96	Oxford Outcomes data reported in TA319 (endocrine disorders), inflated to 2020 GBP
Fatigue	173.89	2013	204.81	Oxford Outcomes data reported in TA319, inflated to 2020 GBP
Alanine aminotransferase increased	0.00	2017	0.00	Assumption of zero cost for laboratory abnormalities
Arthralgia	204.06	2020	204.06	NHS Reference Costs 2019/20 - Consultant-led outpatient attendances for 191 (pain management)
Headache	0.00	2017	0.00	Assumption based on TA319
Dyspnoea	0.00	2017	0.00	Assumption based on TA319
Pneumonitis	1,484.80	2020	1,484.80	Bronchoscopy (19 years and over): £1,401.67, regular day and night admissions (DZ69A, NHS reference costs 2019/20). Weekly OP appointments with a GP: 9.22 minutes of patient contact, excluding direct staff costs and without qualifications £28. Average across both arms is 2.93 weeks = £82.04 (PSSRU 2020). Four weeks of steroids: fluticasone propionate, 50 microgram per inhalation, 150

Type of adverse event	Cost per event (£)			Source for cost
	Original cost values	Original reporting year	Inflation adjusted costs (£)	
				inhalations=£2.73 (based on 100mg (i.e. 2 inhalations) per day for 30 days, 60/150*£2.73=£1.09) (eMIT March 2021). Updated from TA417

Updated from original submission: Company submission B3.5.4 (Table 49, p102)

A.15.6 *Summary of updates to model originally submitted to NICE*

A summary of all changes made to the model originally submitted to NICE is presented in Table 41. Additional details on the scenario relating to costs of crossover/rechallenge are provided in this Appendix.

Table 41: Summary of all model changes

#	Summary	Model tab(s)
1	Updated the following clinical inputs based on the clinical study report and supplemental results tables from the second interim analysis of the KEYNOTE-054 trial: • Risks and mean duration of drug-related grade 2+ diarrhoea • Risks and mean durations of drug-related grade 3+ AEs • Risks and mean duration of drug-related all-grade pneumonitis • Plot points for pembrolizumab time on treatment Kaplan-Meier curve • Plot points for recurrence-free survival (RFS) Kaplan-Meier curve in each arm • Plot points for distant metastases-free survival (DMFS) Kaplan-Meier curve in each arm (Note: The presentation of DMFS Kaplan-Meier curves from KEYNOTE-054 is a new addition to the model based on the second interim analysis of KEYNOTE-054. DMFS was not part of the pre-specified first interim analyses of KEYNOTE-054, and thus was not available at the time of the original submission) • Pembrolizumab mean relative dose intensity • Percentages of patients who underwent salvage surgery in the locoregional recurrence state among those who entered the locoregional recurrence state • AE-related disutility based on regression analysis of EQ-5D data • Health state utilities based on regression analyses of EQ-5D data	• 'Raw - AEs' • 'Raw - AEs' • 'Raw - AEs' • 'Raw_KN054 KM curves' • 'Raw_KN054 KM curves' • "Raw_KN054 KM curves'; • 'Effectiveness'" • 'Raw - Drug costs' • 'Raw - HCRU' • 'Raw - AEs' • 'Raw - Utilities'
2	Updated the following inputs based on publicly available data sources: • All unit costs from MIMS, NHS Reference Costs, or PSSRU • Inflation index • National mortality rates by age and gender	• 'Raw - Drug costs', 'Raw - AEs', 'Raw - HCRU' • 'Raw - UK CPI' • 'Raw - Life tables'

#	Summary	Model tab(s)
3	Re-ran the competing-risk survival analyses of patient-level data from the KEYNOTE-054 trial to obtain updated transition probabilities starting from the recurrence-free state (i.e., RF→LR, RF→DM, and RF→Death). (The statistical approaches for estimating these parameters remained the same as in the originally submitted model.) The following model inputs were updated accordingly: • Parameter estimates for the cause-specific hazards of RF→LR, RF→DM, and RF→Death in each arm under different survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalized gamma) • Plot points for the cumulative incidences of RF→LR, RF→DM, and RF→Death in each arm • Based on a series of internal and external validations (detailed in Appendix A.15.2), the base-case parametric functions have been changed to generalized gamma for RF→LR and Gompertz for RF→DM (originally, Gompertz for RF→LR and generalized gamma for RF→DM)	• 'Raw_Param Estimates' • 'Raw_KN054 KM curves' • Base-case parametric functions were changed via the relevant dropdown menus in 'Specifications'
4	Given the new availability of DMFS outcomes from the second interim analysis of KEYNOTE-054, additional competing-risk survival analyses of patient-level KEYNOTE-054 data were conducted to fit exponential distributions for each transition starting from the locoregional recurrence state (i.e., LR→DM and LR→Death). (In the original submission, these transition probabilities were estimated using real-world data from the Flatiron electronic medical record database.) The cost-effectiveness model was updated as follows to incorporate these newly available transition probability inputs from KEYNOTE-054: • Added dropdown menu in the Effectiveness tab to allow users to choose from the following two sources for transition probabilities starting from the LR state: KEYNOTE-054 (new base case) or Flatiron (former base case, now a scenario analysis) • Added a new tab ("Raw - LR Parameters Estimates") to store the exponential rates and corresponding standard errors from both of these sources • Updated DSA/scenario analyses to include a new scenario analysis in which Flatiron is used as the data source for these transition probabilities	• 'Effectiveness' (the same dropdown is also in the 'Specifications' tab) • 'Raw_Param Estimates_LR' • 'DSA Set-up', 'Tornado Setup', 'DSA Results'

#	Summary	Model tab(s)
5	To allow for additional scenario analyses related to transition probabilities from the LR state, exponential models for transitions starting from LR were also separately fitted for patients in each arm of KEYNOTE-054 who entered the LR state before or after a specified cut-off point. (Several different cut-off points were tested.) The rationale for this approach is that patients who experience earlier LR may have higher risks of distant metastases or death; thus, differentiating transition probabilities by timing of LR may yield closer fit with observed DMFS in KEYNOTE-054. The cost-effectiveness model was updated as follows to implement these scenario analyses: • Added dropdown menu in the Effectiveness tab to allow users to choose from several different cut-off points for differentiating the transitions from LR based on timing of LR (base case setting: no cut-off point). (Note: This dropdown menu is only applicable when KEYNOTE-054, rather than Flatiron, is the selected source for transition probabilities starting from LR.) • Stored the exponential rates and corresponding standard errors for each cut-off point into the "Raw - LR Parameters Estimates" tab • Revised the Markov traces such that, when transition probabilities from LR are differentiated by timing of LR, patients who enter the LR state before vs. after the user-selected cut-off point are separately tracked. This allows the Markov model to apply different LR→DM and LR→Death transition probabilities to patients who entered the LR state before vs. after the cut-off • Updated DSA/scenario analyses to include a new scenario analysis in which a 5-month cut-off (rather than no cut-off) is used for these transition probabilities • Updated PSA to accommodate the model option in which transition probabilities from the LR state are differentiated by timing of LR (i.e., so that the PSA can be run when this option is selected)	• 'Effectiveness' (the same dropdown is also in the 'Specifications' tab) • 'Raw - LR Parameter Estimates' • "TP_AdjReg1', 'TP_AdjReg2' • 'Trace_AdjReg1', 'Trace_AdjReg2'" • 'DSA Set-up', 'Tornado Setup', 'DSA Results' • 'PSA Setup'

#	Summary	Model tab(s)
6	Because LR→DM and LR→Death transition probabilities in KEYNOTE-054 were affected by the trial's crossover/rechallenge protocol, the model was updated with the functionality to either include or exclude the costs of pembrolizumab crossover/rechallenge among those who experience LR recurrence. (In the base case, crossover/rechallenge costs in the LR state are excluded to obtain a conservative base-case ICER). The model was updated as follows to allow for the scenario analysis in which crossover/rechallenge costs in the LR state are included: • Added dropdown menu to either exclude/include costs of pembrolizumab crossover/rechallenge in the LR state • Added new tables to calculate the drug and administration costs per infusion of pembrolizumab crossover/rechallenge. Also added a new table to store the percentages of patients in the watchful waiting arm who receive crossover and patients in the pembrolizumab arm who receive rechallenge among those who entered the LR state in each arm. (These percentages are as observed in KEYNOTE-054.) • Added new tables to store the maximum duration of crossover/rechallenge (2 years, per protocol) and the mean duration (as observed in KEYNOTE-054). • Added new calculation tab ('ToT_LR Adjuvant') to calculate the mean cost per crossover/rechallenge regimen. This mean regimen cost is multiplied by the percentage receiving crossover/rechallenge in each arm among those who enter the LR state. Updated trace tabs such that crossover/rechallenge costs (when included) are applied as a lump sum among patients newly entering the LR state in each weekly cycle • Updated DSA/scenario analyses to include a new scenario analysis in which rechallenge/crossover costs are included	• Drug & Admin Costs' (the same dropdown is also in the 'Specifications' tab) • Drug & Admin Costs'; 'Raw - Drug Costs' • 'Tx Duration' • 'ToT_LR Adjuvant', 'Drug & Admin Costs', 'Trace_AdjReg1', 'Trace_AdjReg2' • 'DSA Set-up', 'Tornado Setup', 'DSA Results'

#	Summary	Model tab(s)
7	Updates to the set of options regarding the market shares of 1L and 2L subsequent treatments among patients who develop distant metastases: • Added new dropdown menus to allow the user to select from different sources/assumptions regarding the market shares of: 1L and 2L subsequent treatments in the watchful waiting arm and among IO-eligible patients in the pembrolizumab arm. The market shares under each source option are stored in the 'Raw - Drug Costs' tab • Changed base-case market share assumptions to the following: o All patients in the pembrolizumab arm are assumed to be in the "IO-eligible" group (but not eligible for pembrolizumab), and their 1L/2L market shares are based on SACT data. In the watchful waiting arm, 1L/2L market shares are also based on SACT (but with adjustments based on Ipsos market research data to account for the expectation that some of these patients will receive pembrolizumab as a subsequent treatment). In the original submission, all patients in the pembrolizumab arm were assumed to be ineligible for subsequent IOs, and market shares in the watchful waiting arm were based on Ipsos data • Updated list of subsequent treatment options to also include encorafenib + binimetinib • Updated DSA/scenario analyses to include new market share scenarios	• Drug & Admin Costs' (the same dropdowns are also in the 'Specifications' tab), 'Raw - Drug Costs' • Drug & Admin Costs'; 'Raw - Drug Costs' • "<Central Data Control>', 'Effectiveness', 'Tx Duration', 'Drug & Admin Costs', 'Raw - Drug Costs', 'ToT_AdvReg', 'PSA Setup' • 'DSA Set-up', 'Tornado Setup', 'DSA Results'
8	Added new figures to externally validate the model's OS projections against different external data sources	• Effectiveness', 'Raw - External KM curves', 'Raw - AJCC KM curves'
9	Implemented new dropdown option to assume a pembrolizumab dosing schedule of either 200 mg Q3W (base case) or 400 mg Q6W (alternative assumption), in both adjuvant and advanced settings to reflect changes to the SmPC • Added a new scenario analysis to the DSA that assumes 400 mg Q6W dosing of pembrolizumab in both the adjuvant and advanced melanoma settings • Dosing schedule of pembrolizumab in the advanced melanoma setting has been updated to a fixed dosing schedule (i.e., either 200 mg Q3W or 400 mg Q6W, per the user's selection), rather than weight-based dosing	• 'Specifications' • 'DSA Set-up', 'Tornado Setup', 'DSA Results' • Raw - Drug Costs'

#	Summary	Model tab(s)
10	In the current base-case analysis, and in the originally submitted model, the efficacy of pembrolizumab as a treatment for advanced melanoma was based on all-comers data from KEYNOTE-006, a trial that enrolled a mix of patients who were previously untreated or who had received a prior line of therapy. However, because these efficacy parameters are used as estimates of first-line pembrolizumab efficacy, it would be more precise to use data from the previously untreated subgroup of KEYNOTE-006. A new dropdown menu has therefore been added that allows the user to select the source for efficacy of pembrolizumab as a treatment for advanced melanoma: KEYNOTE-006 (all-comers) or KEYNOTE-006 (1L subgroup) • Added a new scenario analysis to the DSA that uses KEYNOTE-006 (1L subgroup) as the selected source for efficacy of pembrolizumab as a treatment of advanced melanoma	• 'Effectiveness' • 'DSA Set-up', 'Tornado Setup', 'DSA Results'
11	Further modifications to the DSA: • To align with NICE's Guide to the Methods of Technology Appraisal (paragraph 5.6.3 at https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#discounting), the original high/low DSAs on the annual discount rate were replaced with a scenario analysis using rates of 1.5% for both costs and effectiveness	• 'DSA Set-up', 'Tornado Setup', 'DSA Results'

Costs of crossover/rechallenge in locoregional recurrence

The DMFS analysis of KEYNOTE-054 was not adjusted to account for crossover or rechallenge with pembrolizumab after LR recurrence that was permitted in part 2 of the trial. As such, the transition probabilities starting from the LR state were calculated based on a dataset that included [redacted] patients in the routine surveillance arm who had a LR recurrence and crossed over to receive pembrolizumab, and [redacted] patients in the pembrolizumab arm who had a LR recurrence and were rechallenged with pembrolizumab. In the base-case analysis, the model does not incorporate the costs of adjuvant pembrolizumab rechallenge/crossover within the LR state. The exclusion of crossover/rechallenge costs without adjustment for efficacy represents a conservative base-case approach: Among those who experienced LR recurrence, fewer patients in the pembrolizumab arm received rechallenge than patients in the placebo arm received crossover (Table 42).

Table 42: Utilization of crossover/rechallenge among patients entering the locoregional recurrence state in each adjuvant treatment arm

	Proportion of patients using pembrolizumab crossover/rechallenge following LR recurrence, by adjuvant treatment arm
Pembrolizumab	[redacted]
Routine surveillance	[redacted]

Source: KEYNOTE-054 [4].
Numerator represents the number of patients who crossed over/were rechallenged; denominator represents the number of patients with LR recurrence.

Therefore, a scenario analysis was conducted to explore the impact of including the cost of crossover/rechallenge to better represent the efficacy observed in the trial (Appendix A.15.1).

The average cost of crossover/rechallenge was calculated and applied as a one-time cost at the time of entry into the LR recurrence state. The average cost of a crossover/rechallenge regimen was calculated based on the same unit drug price, mean RDI, and unit cost of administration as that of adjuvant pembrolizumab in the RF state. The defined dosing schedule was consistent with the KEYNOTE-054 crossover/rechallenge protocol.

For the subset of patients who receive pembrolizumab crossover/rechallenge after LR recurrence in each arm (Table 42), the mean time on treatment for the crossover/rechallenge regimen was based on the observed mean time on treatment among patients in KEYNOTE-054 who initiated crossover/rechallenge within the LR recurrence state ([redacted] days). The weekly exponential rate of discontinuation (Table 43) was accordingly

calculated based on this mean time on treatment and the protocol-defined maximum duration of crossover/rechallenge (i.e. 2 years).

Table 43: Pembrolizumab crossover/rechallenge dosing and time on treatment in the locoregional recurrence state

Regimen	Dosing schedule description	Maximum ToT (weeks)	Weekly exponential rate of discontinuation
Pembrolizumab	200 mg IV Q3W, up to 2 years	104	[redacted]

Abbreviations: Q3W, every 3 weeks; ToT, time on treatment.
Sources: KEYNOTE-054 protocol (for maximum ToT); KEYNOTE-054 CSR and supplementary tables (for discontinuation rate).

A.15.7 *Recurrent Free Survival by PD-L1 status*

Table 44: RFS for PD-L1 positive (ITT)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median RFS, months (95% CI)†	RFS rate at month 42, % (95% CI)†	HR (95% CI)‡
Pembrolizumab	428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	425	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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.

(Database Cutoff Date: 03APR2020).

Table 45: RFS for PD-L1 negative (ITT)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median RFS, months (95% CI)†	RFS rate at month 42, % (95% CI)†	HR (95% CI)‡
Pembrolizumab	59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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.

(Database Cutoff Date: 03APR2020).

A.15.8 *Recurrent Free Survival overtime*

Table 46: RFS over time

	Pembrolizumab (N=514)	**Placebo (N=505)**
RFS rate at 6 Months in % (95% CI)†	81.8 (78.2, 84.9)	72.5 (68.4, 76.2)
RFS rate at 12 Months in % (95% CI)†	75.3 (71.3, 78.8)	60.0 (55.5, 64.1)
RFS rate at 18 Months in % (95% CI)†	71.4 (67.3, 75.2)	52.9 (48.4, 57.2)
RFS rate at 24 Months in % (95% CI)†	68.0 (63.7, 71.9)	46.9 (42.4, 51.2)
RFS rate at 30 Months in % (95% CI)†	65.1 (60.8, 69.1)	44.6 (40.2, 48.9)
RFS rate at 36 Months in % (95% CI)†	63.7 (59.3, 67.7)	43.5 (39.1, 47.9)
RFS rate at 42 Months in % (95% CI)†	59.8 (55.3, 64.1)	41.4 (37.0, 45.8)
RFS rate at 48 Months in % (95% CI)†	57.0 (51.9, 61.7)	41.4 (37.0, 45.8)
RFS rate at 54 Months in % (95% CI)†	55.0 (48.8, 60.8)	Not reached
RFS rate at 60 Months in % (95% CI)†	Not reached	

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: 03APR2020).

A.15.9 *Distant Metastases Free Survival over time*

Table 47: DMFS over time

	Pembrolizumab (N=514)	**Placebo (N=505)**
DMFS rate at 6 Months in % (95% CI)†	87.7 (84.5, 90.3)	80.6 (76.8, 83.8)
DMFS rate at 12 Months in % (95% CI)†	82.8 (79.2, 85.8)	69.8 (65.5, 73.6)
DMFS rate at 18 Months in % (95% CI)†	78.3 (74.4, 81.7)	62.7 (58.3, 66.8)
DMFS rate at 24 Months in % (95% CI)†	73.5 (69.4, 77.2)	56.0 (51.5, 60.3)
DMFS rate at 30 Months in % (95% CI)†	70.3 (66.1, 74.2)	53.5 (48.9, 57.8)
DMFS rate at 36 Months in % (95% CI)†	68.2 (63.9, 72.1)	51.5 (47.0, 55.9)
DMFS rate at 42 Months in % (95% CI)†	65.3 (60.9, 69.5)	49.4 (44.8, 53.8)

Distant metastasis-free survival is defined as the time between the date of randomization and the date of first distant metastasis or date of death (whatever the cause), whichever occurs first.
† From the product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 03APR2020).

A.15.10 *Recurrent Free Survival – subgroups*

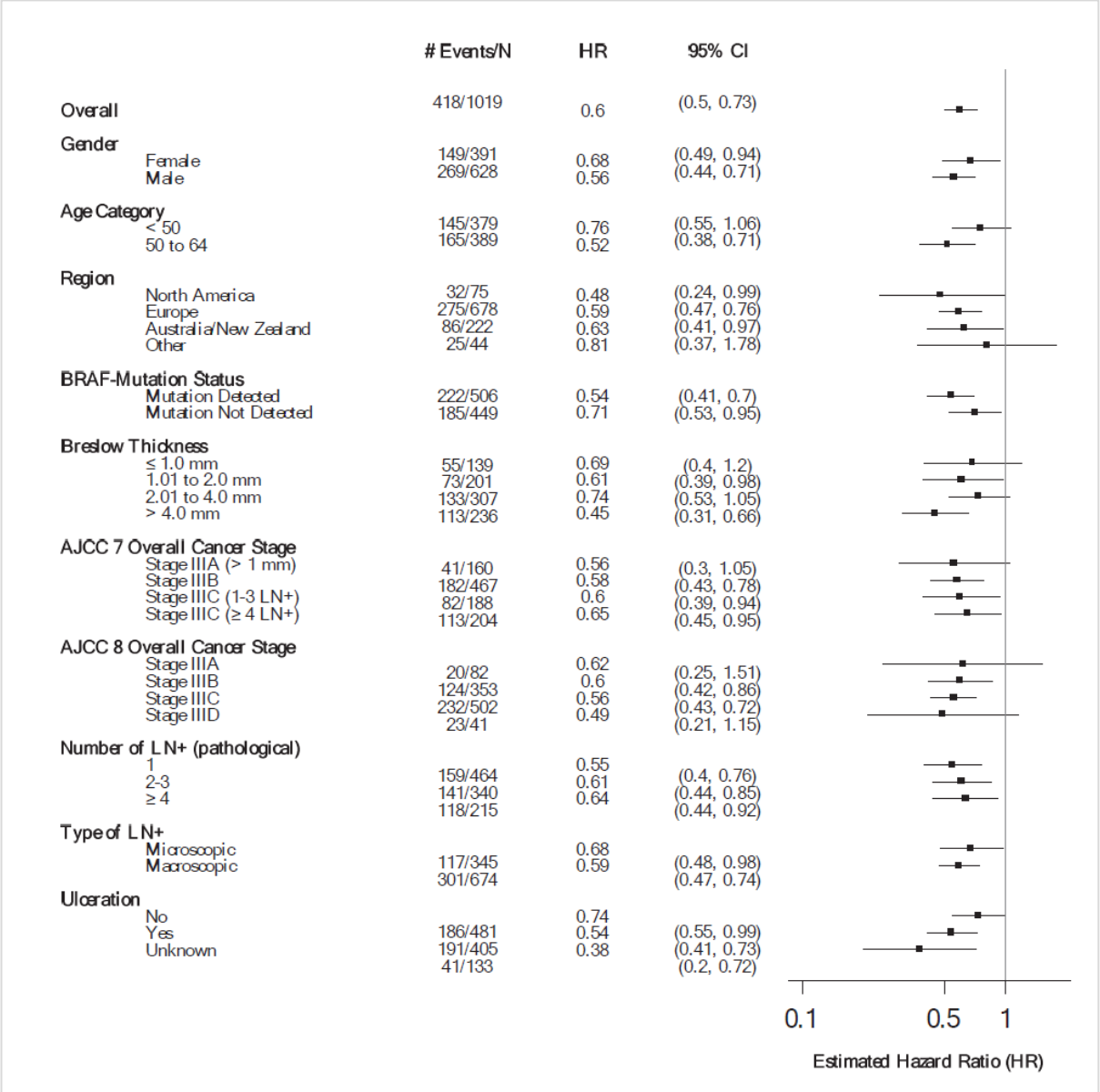
Figure 20: Forest plot of RFS HR by subgroup factors

[redacted]

Database cut-off date 3rd April 2020

A.15.11 *Distant Metastases Free Survival - subgroups*

Figure 21: Forest plot of DMFS HR by subgroup factors (ITT)



A.15.12 *Subsequent treatments after DM in KEYNOTE-054*

Table 48 First line treatments after distant metastasis in KEYNOTE-054

Regimen	Subsequent treatments by adjuvant treatment arm, N (%)	
	Pembrolizumab ([redacted])	Routine surveillance ([redacted])
Pembrolizumab	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
Encorafenib	[redacted]	[redacted]
Binimetinib	[redacted]	[redacted]
Trametinib	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Cobimetinib	[redacted]	[redacted]
Dabrafenib + vemurafenib	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
T-VEC	[redacted]	[redacted]
Other	[redacted]	[redacted]

Available data from KEYNOTE-054 do not take into account whether treatments were received in combination regimens, therefore columns sum to greater than the number of patients receiving first-line treatment and the number of patients receiving combination regimens may be underestimated.

Table 49 Second line treatments after distant metastasis in KEYNOTE-054

Regimen	Subsequent treatments by adjuvant treatment arm, N (%)	
	Pembrolizumab ([redacted])	Routine surveillance ([redacted])
Pembrolizumab	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
Encorafenib	[redacted]	[redacted]
Binimetinib	[redacted]	[redacted]
Trametinib	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]

Regimen	Subsequent treatments by adjuvant treatment arm, N (%)	
	Pembrolizumab ([redacted])	Routine surveillance ([redacted])
Cobimetinib	[redacted]	[redacted]
Dabrafenib + vemurafenib	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
T-VEC	[redacted]	[redacted]
Other	[redacted]	[redacted]

Available data from KEYNOTE-054 do not take into account whether treatments were received in combination regimens, therefore columns sum to greater than the number of patients receiving second-line treatment and the number of patients receiving combination regimens may be underestimated.

A.15.13 *Comparison of patient characteristic in KEYNOTE-054 and SACT dataset*

Table 50: Comparison of patient characteristics in KEYNOTE-054 and SACT dataset

		KEYNOTE-054 – Pembrolizumab (n=514)		**SACT cohort (n=1,324)**	
		N	**%**	**N**	**%**
Sex	Male	324	63.0%	772	58%
	Female	190	37.0%	552	42%
Age	Median	54		64	
	<50	193	37.5%	231	17.4%
	≥50	321	62.5%	1,093	82.6%
ECOG performance status	0	485	94.4%	909	69%
	1	29	5.6%	299	23%
	2	0	-	2	<1%
	3	0	-	0	0%
	4	0	-	0	0%
	Missing	0	-	114	9%
Stage (AJCC 8th edition)	IIIA	42	8.2%	152	11%
	IIIB	163	31.7%	415	31%
	IIIC	267	51.9%	683	52%
	IIID	20	3.9%	74	6%
	Unknown	22	4.3%		
***BRAF* Mutation**	V600 mutation negative	234	45.5%	1,073	81%
	V600 mutation positive	244	47.5%	251	19%
	Unknown	36	7.0%		

A.15.14 *Overall survival discussion*

At the time of the 2018 NICE dossier submission (TA553), analyses of OS by treatment arm for the KEYNOTE-054 ITT and trial-specified subgroups were requested by the European Medicine Agency (EMA) for regulatory approval. This analysis (based on data cut off 2-Oct-2017) with [redacted] OS events was provided as an "administrative" look as it was not pre-specified and was premature, representing only [redacted]% of the of the total [redacted] target OS events. Death events per treatment arm were subsequently provided to NICE during the clarification stage of the submission. Following this initial EMA request, MSD has not received any further regulatory agency requests for OS events by KEYNOTE-054 trial arm.

An evaluation of OS by treatment arm (i.e., not at a protocol-specified analysis) for the present NICE dossier would be an unplanned assessment of efficacy and would jeopardise KEYNOTE-054 trial integrity due to the need to unblind team members. Therefore, such unplanned efficacy analysis should be avoided unless there is a concern for patient safety.

The cumulative number of deaths in KEYNOTE-054 is accruing more slowly than anticipated. The trial protocol originally estimated that the [redacted] OS events required for final OS analysis would accrue approximately [redacted] years from start of trial accrual. With a first patient entry in August 2015, [redacted] events would be projected to be reached in August[redacted]. However, the total number of OS events through 3 April 2020 (DMFS analysis) is [redacted] representing only [redacted]% of the total [redacted] target events. The OS analysis is event driven and final analysis expected to occur in [redacted] based on current projections. However, due to slow event accrual, these projections carry a large uncertainty.

This slow rate of OS event accrual can be attributed to several reasons [5]. KEYNOTE-054 was designed with a crossover element where patients randomised to placebo could crossover to active treatment with pembrolizumab following recurrence. KEYNOTE-054 is the only adjuvant melanoma trial with this study design feature. Further, the effectiveness of subsequent systemic treatments for advanced melanoma following recurrence impacts accrual of OS events.

MSD conducted an evaluation of progression/recurrence-free survival 2 (PRFS2) based on the recent DMFS interim analysis data cut-off, per an EMA request. Within KEYNOTE-054 PRFS2 is defined as the time between the date of randomization and the earliest of the following:

- date of 1st disease progression per RECIST 1.1 beyond the initial unresectable disease recurrence (e.g. unresectable distant metastases);

- date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (e.g. local regional recurrences or resectable distant metastases);
- death

For patients who remained alive and whose disease had not recurred, or disease had recurred but subsequent disease progression or recurrence had not occurred, PRFS2 was censored on the date of last visit/contact with disease assessments or date of last follow up (presented below).

Pembrolizumab provided [redacted]

Figure 22: Kaplan-Meier Estimates of Progression/Recurrence-Free Survival 2 (ITT Population)

[redacted]

Table 51: Analysis of Progression/Recurrence-free Survival 2 ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS2† (Months) (95% CI)	PFS2 Rate at Month 42 in %† (95% CI)	Pembrolizumab vs. Placebo Hazard Ratio‡ (95% CI)‡
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression/Recurrence-free survival 2 is defined as time from randomization to the date of 1st disease progression per RECIST 1.1 after the initial unresectable disease recurrence, date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence, or date of 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.
(Database Cutoff Date: 03APR2020).

Source: [P054V02MK3475: adam-adsl; adtte]

Table 52: Progression/Recurrence-free Survival 2 Rate Over Time (ITT Population)

	Pembrolizumab (N=514)	Placebo (N=505)
PFS2 rate at 6 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 12 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 18 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 24 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 30 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 36 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 42 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 48 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 54 Months in % (95% CI)†	[redacted]	[redacted]
PFS2 rate at 60 Months in % (95% CI)†	[redacted]	[redacted]
Progression/Recurrence-Progression/Recurrence-free survival 2 is defined as time from randomization to the date of 1st disease progression per RECIST 1.1 after the initial unresectable disease recurrence, date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence, or date of death (whatever the cause), whichever occurs first. † From the product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 03APR2020).		

Source: [P054V02MK3475: adam-adsl; adtte]

A.15.15 *RFS analysis: Proportional hazards assessment*

The proportional hazards assumptions were not formally tested in KEYNOTE-054. Experience of immunotherapy studies (especially with immune check-point inhibitors) suggests a potential for an initial delay in the effect of the intervention, and true proportional hazards is not present. In the updated analysis at IA2 (3rd April 2020), the Cox proportional hazards model in the longer follow-up data is of descriptive nature since there is no further hypothesis testing on RFS (the RFS primary endpoint was met at IA1). At IA1, the log-rank test and Cox proportional hazards model analysis provide the greatest power to detect differences in the hazard functions associated with treatments when the hazard function differences are proportional. However, they are also valid tests for testing the null hypothesis that “the hazard functions for the treatments being compared are the same”, versus the alternative “that they are different”. Due to longer follow-up duration and losses to follow-up in the IA2 data-cut (3rd April 2020), the HR is expected to vary over the follow-up period, and tests of proportional hazards yielding high P-values may be underpowered and unreliable. It is therefore not necessary to test for proportional hazards. In addition, there is no convincing evidence that alternative methods of analysis for accommodating nonproportional hazards provide more accurate results or improve the development of oncologic therapies [48]. The convenient summary HR should therefore be interpreted as a weighted average of the true HRs over the entire follow-up period.

A.15.16 *Changes to base case assumptions versus original submission*

Table 53: Deterministic results - Impact of changes to base case assumptions versus original submission†

#	Description	Details	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
0	Replication of analysis from original submission	-	-3,988	2.73	3.18	Dominant
1	Incorporating key efficacy data from KEYNOTE-054 IA2	Key efficacy data from KEYNOTE-054: • RFS KM curve • DMFS KM curve • Parameter estimates for cause-specific hazards of RF→LR and RF→DM and RF→Death in each arm • Cumulative incidence of RF→LR and RF→DM and RF→Death in each arm • Transition probabilities for LR→DM and LR→Death	[redacted]	[redacted]	[redacted]	£2,743
2	Updated survival extrapolations	As #1, plus parametric functions for RF→LR and RF→DM selected based on fit to updated key efficacy data from KEYNOTE-054 and plausibility of long-term extrapolations (Generalised gamma – Gompertz)	[redacted]	[redacted]	[redacted]	£3,595
3	Additional clinical inputs from KEYNOTE-054 IA2	As #2, plus the following data from KEYNOTE-054 IA2: • Risks and mean duration of drug-related AEs (grade 2+ diarrhoea, grade 3+ AE, all-grade pneumonitis)‡ • Pembrolizumab mean RDI • % of patients who underwent salvage surgery in LR recurrence state • AE-related disutility based on regression analysis of EQ-5D • Health state utilities based on regression analysis of EQ-5D	[redacted]	[redacted]	[redacted]	£3,622

#	Description	Details	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALY)
4	Latest available data sources	As #3, plus the following inputs updated from latest available sources: • All unit costs from MIMS, NHS Reference costs, PSSRU and confidential PAS discount for pembrolizumab • Inflation index (CPI), updated to 2020 • National mortality rates (ONS life tables) • Pembrolizumab dosing schedule in advanced setting changed to fixed dose (200 mg Q3W)	[redacted]	[redacted]	[redacted]	£[redacted]
5	Market share assumptions for subsequent therapies in the advanced setting	As #4, plus market share assumptions as described in A.8.2	[redacted]	[redacted]	[redacted]	£9,357

Abbreviations: AE, adverse event; CPI, Consumer Price Index; DM, distant metastatic; DMFS, distant metastasis-free survival; ICER, incremental cost-effectiveness ratio; LR, locoregional; LY, life year; NHS, National Health Service; ONS, Office for National Statistics; PSSRU, Personal Social Services Research Unit; Q3W, every 3 weeks; QALY, quality adjusted life year; RDI, relative dose intensity; RF, recurrence-free; RFS, recurrence-free survival.

† The impact of changes to the base case assumptions versus the original submission were explored using the version of the model developed for the current submission and then reverting inputs/settings to match those used in the original submission. Although care was taken to replicate the settings as far as possible, due to the nature of some of the model edits that were required to update the base case assumptions, there may be some minor discrepancies.

‡ Hyperthyroidism was removed from the model for the updated base case analysis, and it was not possible to add it back in for this version.

A.15.17 *SACT CDF report produced by Public Health England*

TA533
Pembrolizumab_mela

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553)

Clarification questions

August 2021

File name	Version	Contains confidential information	Date
ID3776 pembrolizumab clarification questions – Company response_[REDACTED]	1.0	No	25th August 2021

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Overall survival data

A1. It is reported in the NICE Appraisal Committee (AC) preferred assumption table (reported in the Terms of Engagement document (pp2-5) and in the Company Submission (CS, pp8-11)) that the AC concluded that the survival benefit [of pembrolizumab] cannot be confirmed in the absence of overall survival (OS) data from the KEYNOTE-054 trial.

The ERG notes that only [redacted]/[redacted] OS events have occurred in the trial, and the final OS analysis is projected to take place in [redacted]. Would it be possible to provide the proportion of OS events that has occurred in the pembrolizumab arm?

Furthermore, while it is acknowledged that the data has yet to reach maturity, please undertake an interim survival analysis of the OS data. We recognize there are several important caveats for this including but not limited to, increased uncertainty as there are less data than if mature, proportional hazards may not hold in the long term and that if parametric survival fitting is done the shape of the curve will then be determined just by short-term data. However, this is a key uncertainty, so the company should demonstrate to committee that it has explored the use of trial data to the fullest extent possible, bearing such limitations in mind.

As discussed in the submission dossier (p18-19), OS data are not available from the KEYNOTE-054 trial as insufficient death events had occurred at the latest data cut-off to enable analysis of OS to be performed.

The trial protocol stipulates that analysis of OS will be conducted when the pre-specified number of events has been reached (i.e. event-driven analysis), rather than at a specified time point. An early evaluation of OS by treatment arm (i.e. not at a protocol-specified analysis) for the present submission would be an unplanned assessment of efficacy and would jeopardise KEYNOTE-054 trial integrity due to the need to unblind team members. Therefore, to maintain study integrity such unplanned efficacy analysis should be avoided unless there is a concern for patient safety.

However, data on OS with adjuvant pembrolizumab in patients with high-risk resected melanoma are available from the SWOG-S1404 Phase III RCT [1]. SWOG-

1404 compares adjuvant pembrolizumab versus ipilimumab or high dose interferon (HDI) in completely resected stage III/IV melanoma patients. Although there are some small differences in disease staging, the baseline characteristics of the patients in this trial are closely aligned with those in KEYNOTE-054, therefore the results of this study provide a good indication of the OS that may be expected with adjuvant pembrolizumab in KEYNOTE-054. These OS data from SWOG-S1404 are used in question A5 to provide further validation of the modelled OS projections for pembrolizumab.

Recurrence-free survival

A2. The NICE AC preferred assumption table (reported in the Terms of Engagement document (pp2-5) and in the Company Submission (CS, pp8-11)), includes a request for the company to explore the most appropriate method to calculate the recurrence-free survival (RFS) hazard ratio. Further, the original ERG report included the following text:

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.

Please fulfil the NICE AC request. Please also confirm the validity of the PH assumption.

The descriptive extended RFS analysis (at 3rd April 2020 data cut-off) showed that pembrolizumab provided a sustained RFS benefit with 45.5 months of median follow-up when compared with placebo (see submission dossier for RFS landmark analysis). The hazard ratio (HR) was 0.59 (95% CI: 0.49, 0.70) in favour of pembrolizumab, with a 41% reduction in the risk of recurrence or death. The Cox proportional hazards model in the longer follow-up data is of descriptive nature and the HR should be interpreted as a weighted average of the HRs over the entire follow-up period.

Experience of immunotherapy studies (especially with immune check-point inhibitors) suggests a potential for an initial delay in the effect of the intervention, and therefore true proportional hazards assumptions may not hold. Additional analyses were conducted to explore this assumption further.

The validity of the proportional hazards assumption for RFS was tested based on the approach of Grambsch and Therneau (1994) [2]. The time-dependent log(hazard ratio) β(t) was calculated and then plotted against event time, and a smoothing factor based on global minimum Akaike Information Criterion (AIC) was used to visualize any departure of β(t) from the proportional hazards assumption, alongside its 95% confidence interval. Scaled Schoenfeld residuals were used to test whether the proportional hazards assumption holds.

The smoothed time-dependent log hazard ratio β(t) over time suggests a small degree of varying HRs over time (Figure 1). However, this is expected due to longer follow-up duration and losses to follow-up. A higher degree of uncertainty is observed after around week 36 when the number of participants at risk gets smaller. The test of proportionality based on scaled Schoenfeld residuals suggests that the departure from proportionality assumption is not statistically significant at the nominal 5% significance level [redacted].

Figure 1: Log Hazard Ratio β(t) and 95% Confidence Intervals of RFS Over Time

Additionally, Eggermont et al (2021) [3] reported no evidence of non-proportionality of hazard based on the approach of Lin, Wei and Ying (1993) [4]. The test was based on cumulative sums of Martingale residuals over time from the model used for inference in the main analysis.

We further explored how the HRs for RFS vary over time at selected timepoints. Apart from the short, delayed effect in the pembrolizumab group versus placebo shortly after randomization, the observed HR consistently favours pembrolizumab versus placebo at all subsequent timepoints (Table 1). The ITT HR is reached after around month 42 after randomization, until the end of follow-up.

Table 1: RFS HR over time from KEYNOTE-054, pembrolizumab vs placebo

Time from randomisation, months	RFS HR (95% CI)
3	[redacted]
6	[redacted]
9	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival.
Data cut-off 3rd April 2020.

Note that the cost-effectiveness model does not rely on the proportional hazards assumption for RFS or DMFS, as parametric models are independently fitted to patient level data from KEYNOTE-054.

Clinical Study Report

A3. Please provide a copy of the latest Clinical Study Report for the KEYNOTE-054 trial.

The Clinical Study Report from the latest data cut-off (3rd April 2020, interim analysis 2 [IA2]) is now provided in the attached documents.

Network meta-analysis

A4. It is noted in the company's economic model on the sheet titled, 'Raw – Adv Drug Efficacy,' Table 14 that the original network meta-analysis undertaken as part of this appraisal has been updated. However, it does not appear that the details of the NMA update were included in the company's submission.

Please provide the details for the NMA update. Specifically, please include the following:

- A methods section detailing both how KM curves were selected and which statistical methods were chosen for this NMA and why
- The network diagram
- The trials included in the network
- An explanation as to why the Columbus trial wasn't included in the network
- The source for every Kaplan-meier curve that was extracted and included in the NMA
- It does not appear that testing for PH has been done. If this is incorrect, please provide the results of such testing. If this is correct, please test the validity of the PH assumption for every Kaplan-meier curve included in the NMA.
- The NMA results
- The code used to perform the NMA

We would like to clarify that the NMA used to model PFS and OS in the advanced melanoma setting in the submitted model has not been updated since the original submission in 2018 (Company submission 2018, section B 3.3.1, p76-77) [5]. As such, the PFS and OS HR estimates vs pembrolizumab for all subsequent therapies previously included are unchanged from the original submission. The COLUMBUS trial (Dummer et al, 2018 [6]) was not included in the NMA as it had not been published at the time the NMA was conducted (2017), therefore the study's exclusion from the NMA was justified. NICE subsequently issued a positive recommendation for this technology (encorafenib + binimetinib) in January 2019 (TA562) [7]. Based

on TA562 and clinical expert feedback, it was appropriate to introduce the encorafenib + binimetinib combination within the CDF exit review to better reflect the true costs to the NHS of subsequent therapies for the BRAF mutant population (see details below).

As the NMA is unchanged from the original submission and the technical report for the NMA [8] was provided in the reference pack for the original submission, in the response below we have only included a summary of the overall methodology used in the NMA (conducted in 2017) to aid the ERG in its review. Full details on the methodology employed for the NMA are available in the original NMA report (resubmitted as part of this response [8]). Further details relating to the addition of encorafenib + binimetinib are also provided below.

Summary of NMA methods (conducted in 2017) [8]

Separate analyses were conducted for BRAF wild-type and BRAF-mutant positive populations. 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 + 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, as observed in KEYNOTE-006 [9]. The evidence networks are presented in Figure 2.

Figure 2: Evidence networks for OS and PFS – (A) BRAF wild-type; (B) BRAF-mutant positive (unchanged from original NICE submission [5])

Abbreviations: COBI, cobimetinib; DAB, dabrafenib; DTIC, dacarbazine; IPI, ipilimumab; NIV, nivolumab; PEM, pembrolizumab; VEM, vemurafenib.
Note that encorafenib + binimetinib is not included in the network as the COLUMBUS trial had not been published at the time the NMA was conducted (2017). The combination was incorporated into the model for the CDF review using a pragmatic comparison of HRs – please see details below.

Two approaches to NMA were explored: conventional HR methods based on the proportional hazards assumption to generate constant HRs (using fixed-effects models due to the sparse networks and minimal heterogeneity between trials); and alternative methods where hazard functions of the interventions in each trial were modelled using parametric and fractional polynomial models to estimate multidimensional treatment effects, thus resulting in time-varying HRs [10, 11]. Time-

varying hazards require fewer assumptions about the treatment effects, but proportional hazards models lead to simpler model interpretation.

For OS, the fit of the constant (proportional hazards) and time-varying models were comparable in the BRAF wild-type NMA and the constant HRs were more clinically plausible in the BRAF-mutant positive NMA. The time-varying HR model demonstrated that parallel hazards were present after the first few months, indicating that the proportional hazards assumption was appropriate. It was also necessary to consider the practical implications of incorporating the NMA results into the cost-effectiveness model, to avoid unnecessarily complex methodology for modelling the efficacy of subsequent treatments. As such, the constant HR NMA results were deemed the most suitable for use in the cost-effectiveness model.

Further details on the NMA methodology, including the code used to perform the 2017 NMA, are available in the technical report provided with this response [8].

Including encorafenib + binimetinib in the CDF review model

In the original appraisal, the committee concluded that the most appropriate assumptions about subsequent treatments should be explored to adequately reflect UK clinical practice. Encorafenib + binimetinib was recommended by NICE in 2019 (TA562) [7]. Clinical experts have advised that it has been an important therapy option during the COVID-19 pandemic due to a lower incidence of fever-related adverse events. Consequently, they recommended that the regimen should be included in the updated model to reflect current practice in the advanced melanoma setting to better reflect the true costs of metastatic disease for BRAF-mutant positive patients.

Since this is a CDF exit submission, we are limited to the extent of updates that can be presented and we therefore sought a pragmatic way of reflecting the changes in the treatment pathway. To enable the inclusion of encorafenib + binimetinib as a subsequent therapy for the CDF review submission, and as a pragmatic approach in the absence of an updated NMA, OS and PFS HRs for encorafenib + binimetinib vs pembrolizumab were calculated using the HRs for encorafenib + binimetinib vs vemurafenib from COLUMBUS and HRs for vemurafenib vs pembrolizumab from the 2017 NMA described above. We acknowledge that this approach does have

limitations, as the trial is not formally incorporated in the statistical analysis and therefore HRs for encorafenib + binimetinib are not adjusted to account for differences between COLUMBUS and the other trials in the network (and vice versa). However, it is a pragmatic approach, intended to allow the regimen to be included in the model and thus to reflect the true cost of subsequent therapies to the NHS. To reiterate, HRs for all other subsequent therapies remain unchanged from the original submission.

Although this minor addition was not explicitly specified within the Terms of Engagement, the committee did request that the most appropriate assumptions regarding subsequent therapies should be explored. Therefore, given the changes to the advanced melanoma pathway for BRAF-mutant positive patients and the committee's request to adequately explore relevant subsequent treatment options, we consider it to be relevant to the decision problem.

Section B: Clarification on cost-effectiveness data

Scenario analysis

A5. Please perform an exploratory cost-effectiveness analysis using the interim survival analysis of OS data from A1.

As discussed in question A1, OS data are not available from the KEYNOTE-054 trial, therefore it is not possible to conduct the requested scenario analysis.

However, we would like to take this opportunity to reiterate that the cost-effectiveness model does not apply any OS benefit for adjuvant pembrolizumab after patients have progressed to the DM health state, which is a conservative assumption. Instead, the transitions to death are based on the distribution of subsequent treatments for advanced melanoma in each treatment arm and modelled using PFS and OS estimates from KEYNOTE-006 and from the NMA conducted in 2017. Within the submission, we have provided extensive scenarios around these distributions, based on UK clinical expert input to resolve any uncertainty around these.

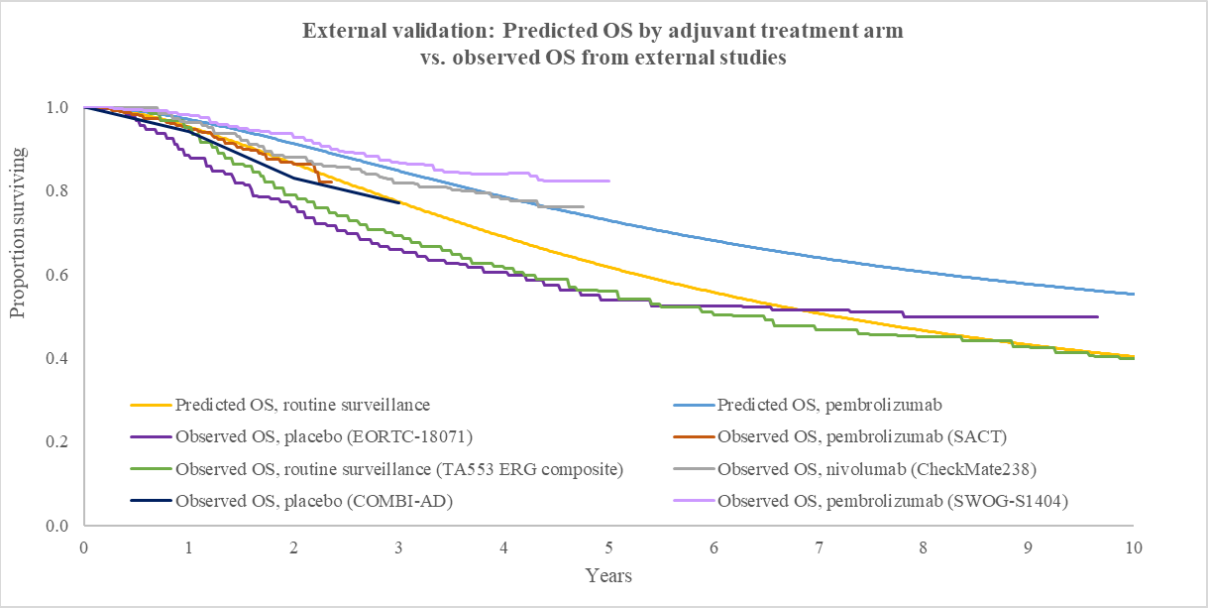
Further, data on OS with adjuvant pembrolizumab versus ipilimumab and high dose interferon in patients with high-risk resected melanoma are available from the

SWOG-S1404 Phase III RCT (NCT02506153) [1]. This study was included in the original submission as an ongoing trial; OS data have recently become available and can be used as additional validation for pembrolizumab OS projections.

Whilst there are some differences in disease staging, the baseline characteristics of the patients in this trial are broadly aligned with those in KEYNOTE-054, therefore the results of this study provide a good indication of the OS that may be expected with adjuvant pembrolizumab in KEYNOTE-054. We have therefore added this study to the model validation figure as part of our response.

The observed OS for pembrolizumab in SWOG-S1404 is very closely aligned with the OS projections predicted for pembrolizumab in the cost-effectiveness model over 3 years (Figure 3); after 3 years there was heavy censoring in the trial, which may exaggerate the plateau observed after this point. The data from this trial offer confidence that the model OS projections for pembrolizumab are reasonable and may even be conservative against the true OS for pembrolizumab.

Figure 3: Predicted OS vs external sources – base case analysis



Abbreviations: OS, overall survival.

In addition, the projected OS curves for pembrolizumab are comparable with the observed OS over approximately 5 years for nivolumab in CheckMate238, which provides further validation that the pembrolizumab projections presented in the submission are valid. It should also be noted that, in contrast to CheckMate238, the KEYNOTE-054 trial did not enrol any patients with stage IV melanoma, therefore it is

plausible that the OS for KEYNOTE-054 could be higher than that seen in CheckMate238.

We have previously provided extensive evidence to validate the projections for the routine surveillance arm (Company submission 2021, Appendix A.15.2, p65-69). Consideration of these recent data for pembrolizumab provides additional confidence that the model gives robust long-term predictions to inform decision making.

Section C: Textual clarification and additional points

No textual clarifications or additional points

References

1. Grossmann KF, Othus M, Patel SP, Tarhini AA, Sondak VK, Petrella TM, et al. Final analysis of overall survival (OS) and relapse-free-survival (RFS) in the intergroup S1404 phase III randomized trial comparing either high-dose interferon (HDI) or ipilimumab to pembrolizumab in patients with high-risk resected melanoma. Journal of Clinical Oncology. 2021;39(15_suppl):9501-.
2. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.
3. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(5):643-54.
4. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80(3):557-72.
5. NICE. TA553: Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence 2018 [Available from: https://www.nice.org.uk/guidance/ta553/history.
6. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603-15.
7. NICE. TA562: Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma. 2019 [Available from: https://www.nice.org.uk/guidance/TA562.
8. Merck Sharp & Dohme. Updated systematic literature review and network meta-analysis of pembrolizumab for the treatment of advanced melanoma: technical report - Data on file. 3rd August 2017.
9. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853-62.
10. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.
11. Jansen JP, Cope S. Meta-regression models to address heterogeneity and inconsistency in network meta-analysis of survival outcomes. BMC Med Res Methodol. 2012;12:152.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

(CDF review TA553) [ID3776]

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	[redacted]
2. Name of organisation	**Melanoma Focus**

3. Job title or position	[redacted]
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).	Melanoma Focus, a national UK charity is unique in its field, combining the functions of patient support and advocacy with the role of providing representation and up-to-date scientific information for UK healthcare professionals involved in melanoma. Melanoma Focus organises two professional meetings a year, creates guidelines on rare melanomas using NICE-accredited methodology and produces other consensus guidelines. Funding is from personal donations and fundraising activities, professional membership and sponsorship for various activities
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Melanoma Focus has received funding from MSD and other Pharma in the field of melanoma as sponsorship for meetings and a project. Funding has always been multiple Pharma supporting meetings/projects such as our Melanoma Helpline (emergency Covid funding).

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. 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.)	Adjuvant treatment of resected stage III melanoma patients – improvement in relapse-free survival and therefore overall survival is the main aim of treatment
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	To Reduce relative risk of relapse by 30%.

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?	There is certainly an unmet need as treatment of patients with resected melanoma at high risk of relapse as 40-60% of patients with resected stage III disease die from their melanoma within 5 years of their surgery.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Resected stage III patients are offered the opportunity of immunotherapy treatment with Pembrolizumab or Nivolumab using the Cancer Drugs Fund approval process. This is currently the only adjuvant t treatment for BRAF-wildtype tumours. For patients with BRAF-mutated stage 3 melanoma an alternative to immunotherapy would be dabrafenib and trametinib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines – are being updated.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Well defined.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Patients are currently offered this treatment. –so no change.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is used within current clinical practice
• How does healthcare resource use differ between the technology and current care?	Nil as currently used
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology is currently given within secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil –as already being used

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	After an overall median follow-up of 3 years, pembrolizumab (190 RFS events) compared with placebo (283 RFS events) resulted in prolonged RFS in the overall population (3-year RFS rate, 63.7% *v* 44.1% for pembrolizumab *v* placebo, respectively; HR, 0.56; 95% CI, 0.47 to 0.68). The impact of pembrolizumab on RFS was similar in subgroups, in particular according to AJCC-7 and AJCC-8 staging, and *BRAF* mutation status (HR, 0.51 [99% CI, 0.36 to 0.73] *v* 0.66 [99% CI, 0.46 to 0.95] for V600 *v* wild type. At an overall median follow-up of 42·3 months (IQR 40·5–45·9), 3·5-year distant metastasis-free survival was higher in the pembrolizumab group than in the placebo group in the ITT population (65·3% [95% CI 60·9–69·5] in the pembrolizumab group *vs* 49·4% [44·8–53·8] in the placebo group; HR 0·60 [95% CI 0·49–0·73]; p<0·0001). Recurrence-free survival remained longer in the pembrolizumab group 59·8% (95% CI 55·3–64·1) than the placebo group 41·4% (37·0–45·8) at this 3·5-year follow-up in the ITT population (HR 0·59 [95% CI 0·49–0·70])
• Do you expect the technology to increase length of life more than current care?	The professional body believe that adjuvant care with 1 year of pembrolizumab offers an increase in length of life compared to placebo (the previous standard of care in the UK). Since approved in the CDF, the risk benefit of adjuvant immunotherapies are discussed with patients.
• Do you expect the technology to increase health-related quality of life more than current care?	Health-related QOL was a prespecified exploratory endpoint, with global health/quality of life (GHQ) over 2 years measured by the EORTC QLQ-C30 as the primary analysis. Analyses were done in the intention-to-treat population. Median follow-up was 15·1 months (IQR 12·8–16·9) at the time of this analysis. HRQOL compliance was greater than 90% at baseline, greater than 70% during the first year, and greater than 60% thereafter for both groups. Because of low absolute compliance numbers at later follow-up, the analysis was truncated to week 84. Baseline GHQ scores were similar between groups (77·55 [SD 18·20] in the pembrolizumab group and 76·54 [17·81] in the placebo group) and remained stable over time. The difference in average GHQ score between the two groups over the 2 years was –2·2 points (95% CI –4·3 to –0·2). The difference in average score during treatment was –1·1 points (95% CI –3·2 to 0·9) and the difference in average score after treatment was –2·2 points (–4·8 to 0·4). These differences are within the 5-point clinical relevance threshold for the QLQ-C30 and are therefore clinically non-significant.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The absolute benefit to patients increases with the worsening prognosis of disease. Therefore patients with Stage IIIb-d disease have more to gain than those with stage IIIa.
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.)	There is significant experience in using pembrolizumab for numerous years in the metastatic setting and also in the adjuvant setting. Pembrolizumab can now be given 6-weekly (previously 3-weekly) which permits patients and the NHS to minimise the burden of treatments.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment is given for up to a year unless there is progression of disease or if the patients develops unacceptable toxicity.
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?	No
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	Melanoma is the 5th most common cancer and its incidence is related to age, however, unlike other cancers, there is a large increase in the younger working age groups (7-8 fold in the 15-24 year age group). There is a growing population of melanoma patients who are younger in age with the majority of their life ahead of them. Immunotherapies are innovative treatments that have revolutionised melanoma treatment over the last 5-10 years, initially in the metastatic setting and now in the adjuvant setting.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – but as mentioned - already being used via CDF.
• Does the use of the technology address any particular unmet need of the patient population?	Risk of relapse from 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?	The side effect profile of pembolizumab is well described and understood. The appropriate algorithms for managing such side effects are in place.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Keynote-054 reflected previous UK practice with no standard of care as control arm of the study. The CDF now allows for use of the drug.

• 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?	Overall survival is the most important outcome, however, takes 5-10 years to see such a benefit. Therefore, recurrence-free survival was a primary endpoint with distant metastasis-free survival, a secondary endpoint.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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?	
21. How do data on real-world experience compare with the trial data?	The experience if that the drug does reduce risk of relapse in keeping with the trial data.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
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.

- Pembrolizumab is a vital adjuvant treatment for patients with resected stage 3 melanoma
- The drug is currently used safely and appropriately in this indication via CDF funding.
- This is major step forward for patients with stage 3 melanoma
-
-

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Melanoma (resected, high risk) - pembrolizumab (adjuvant) (CDF Review of TA553) [ID3776]

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. [Please note that declarations of interests relevant to this topic are compulsory].

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 10 pages.

About you	
1.Your name	**Diane Cannon**

2. Name of organisation	Melanoma UK
3. Job title or position	Corporate Partnership Director Passionate aunty – my personal link to melanoma follows the death of my niece in 2014. Claire died at the young age of 38 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. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	No

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. 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?	Pre the pandemic Melanoma UK provided face-to-face opportunities to meet and discuss how patients and carers deal with their condition, but as a result of COVID we have had to rely heavily on our interaction taking place online, via ZOOM, through blogs, internet forums, our website and weekly patient calls every Thursday. Through our Melanoma UK Patient Registry we have been able to capture real time information on patient experience dealing with melanoma and the treatments available. These various platforms provide patients and carers a safe space to post their hopes for the short-, medium- and long-term future and share their fears with others. Melanoma UK try to help people to understand their condition as we are a very hands-on patient support group. For this submission we asked our patients via a survey through our various social media platforms and our registry database.

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?	**Personal (as a Carer)** As a carer I felt very overwhelmed because although I wasn't the patient, I was still 'living' with melanoma. I was the one who had to feed back to the family as my niece just didn't want to talk about her disease. I was uncertain every minute of the day and quickly realised that living with melanoma affects everyone differently. 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. Trying to keep positive when deep down I knew this disease could kill her. **Feedback (patients)** Our patients have unanimously stated that the stress of living with melanoma can be seen physically, mentally, and emotionally. It's not just the effects of the disease they are dealing with, it's also stress, depression, and anxiety. It can be confusing with some patients (and carers) and depends on 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.

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 on 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. There is a need for better sign posting for patients to care/help available especially the support the 3rd sector/patient organisations can offer.
8. Is there an unmet need for patients with this condition?	The principle unmet need of patients dealing with metastatic melanoma is the lack of adequate treatments and limited options available 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 (more so now following the pandemic), 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?	The HOPE that adjuvant therapy may reduce the risk of melanoma recurring following surgery. That it could improve a patient's overall condition and extend their life.
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 Might worsen their condition
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.	Patients with Stage III melanoma usually undergo surgery to remove the primary melanoma and the nearby lymph nodes. With pembrolizumab as adjuvant therapy after surgery, patients can reduce their risk of melanoma returning or improving recurrence-free survival (RFS).

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?	Melanoma UK is 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. We are keen to represent the patient voice today and the main unmet needs we hear from patients include uncertainty about their future, outcomes if melanoma were to spread, fears of melanoma returning The success of this treatment today could potentially improve/prolong a patient's life and although there is a commercial decision to be made, please 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.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • This treatment is vital for our patients. It gives them hope and confidence for their future	

- Patients and carers are at the center of everything we do, and this treatment could potentially improve their life
- There is more need for transformational drugs/treatments for melanoma sufferers
- With pembrolizumab as adjuvant therapy after surgery, patients can reduce their risk of melanoma returning or improving recurrence-free survival (RFS).

Thank you for your time.

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Public Health England

Protecting and improving the nation's health

Pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma – data review

Commissioned by NHS England and NHS Improvement

Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended the commissioning of pembrolizumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of pembrolizumab in the CDF population, during the managed access period. This report presents the results of the use of pembrolizumab in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 69% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 19 November 2018 and 18 November 2020, 1,440 applications for pembrolizumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 1,324 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

1,324 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 11.7 months [95% CI: 11.5, 11.8] (356 days) (N=1,324). 78% of patients were still receiving treatment at 6 months [95% CI: 75%,80%] and 41% of patients were still receiving treatment at 12 months [95% CI: 37%, 44%].

At data cut off, 53% (N=698) of patients were identified as no longer being on treatment. Of these 698 patients, 21% (N=147) of patients stopped treatment due to progression, 23% (N=159) of patients stopped treatment due to acute toxicity, 3% (N=21) of patients chose to end their treatment, 5% (N=34) of patients died not on treatment, <1% (N=1) of patients died on treatment, 17% (N=118) of patients completed treatment as prescribed, 3% (N=24) of patients stopped treatment due to COVID, <1% (N=1) of patients stopped due to other comorbidities and 28% (N=193) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median OS was not reached. OS at 6 months was 98% [95% CI: 97%, 99%], 12 months OS was 95% [95% CI: 93%, 96%] and OS at 18 months was 90% [95% CI: 88%, 92%].

A sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results for treatment duration and survival were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients prescribed pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with pembrolizumab for this indication.

Introduction

Melanoma (ICD-10: C43) accounts for 5% of all cancer diagnoses in England. In 2018, 14,824 patients were diagnosed with melanoma (males 7,474, females 7,350)[2].

- Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of stage III melanoma with lymph node involvement in adults who have had complete resection. It is recommended only if the conditions in the managed access agreement for pembrolizumab are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma [TA553].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of pembrolizumab (MSD) for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma [TA553] and published guidance for this indication in December 2018[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of pembrolizumab through the CDF for a period of 28 months, from November 2018 to March 2021.

During the CDF funding period, results from an ongoing clinical trial (KEYNOTE-054[7]) evaluating pembrolizumab in the licensed indication are likely to answer the main clinical

uncertainties raised by the NICE committee. Data collected from the KEYNOTE-054 clinical trial is primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for pembrolizumab, the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the KEYNOTE-054[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Overall survival** from the start of a patient's first treatment with pembrolizumab

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (MSD) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of pembrolizumab. It also detailed the eligibility criteria for patient access to pembrolizumab through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for pembrolizumab, approved through Blueteq® and followed up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and

key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Pembrolizumab clinical treatment criteria

- Patient has a confirmed histological diagnosis of malignant melanoma. Please indicate whether the melanoma is VRAF V600 mutation positive or not.
- Patient has melanoma which has been staged as stage III disease (according to the AJCC 8th edition) that has been completely resected either via sentinel lymph node biopsy (‘sentinel lymphadenectomy’) or when indicated via completion of a lymph node dissection and/or there has been complete resection of intransit metastases.
- Patient is treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received and BRAF V600 inhibbitors or MEK inhibitors or immunotherapy with any check point inhibitors.
- Clinician has discussed with the patient the benefits and toxicities of adjuvant pembrolizumab in stage III disease in relation to the risk of disease relapse if a routine surveillance policy is followed.
- Patient has an ECOG performance status of either 0 or 1.
- Pembrolizumab monotherapy will be continued for a maximum of 12 months (or a maximum of 18 cycles if given 3-weekly, or if the patients is stable and well, 9 cycles if given 6-weekly) from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent.
- A formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the first 9 weeks of treatment.
- Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle.
- Pembrolizumab is to be otherwise used as set out in its Summary of Product Characteristics.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for pembrolizumab for adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

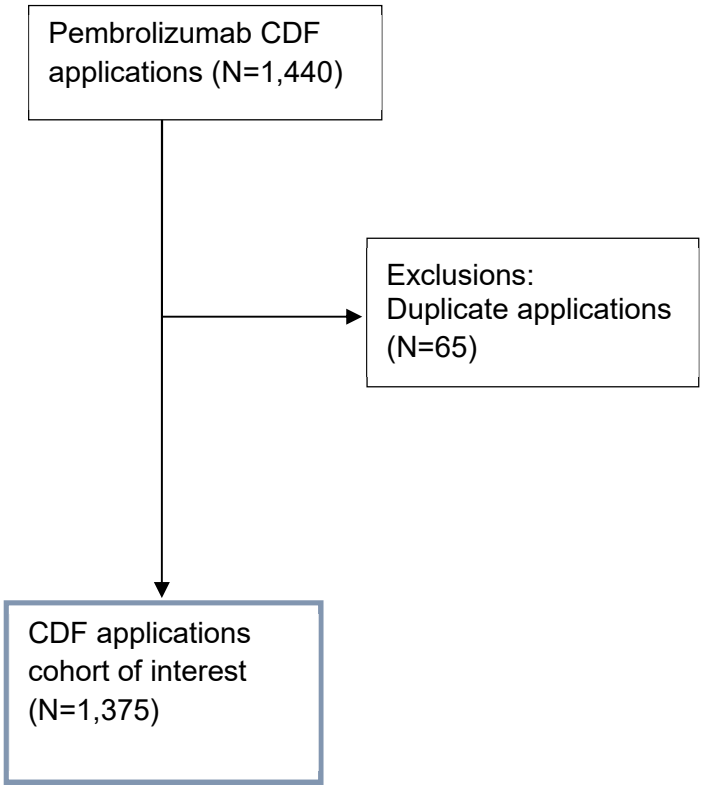
The analysis cohort is limited to the date pembrolizumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 19 November 2018 and 18 November 2020. A snapshot of SACT data was taken on 6 March 2021 and made available for analysis on 12 March 2021 and includes SACT activity up to the 30 November 2020. Tracing the patients' vital status was carried out on 28 April 2021 using the Personal Demographics Service (PDS)[1].

There were 1,440 applications for CDF funding for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma between 19 November 2018 and 18 November 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 1,375 unique patients.

No patients received pembrolizumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma between 19 November 2018 and 18 November 2020



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for pembrolizumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between

administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Pembrolizumab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that treatment administration has taken place on a specified date. A duration of 20-days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Pembrolizumab is a 21-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

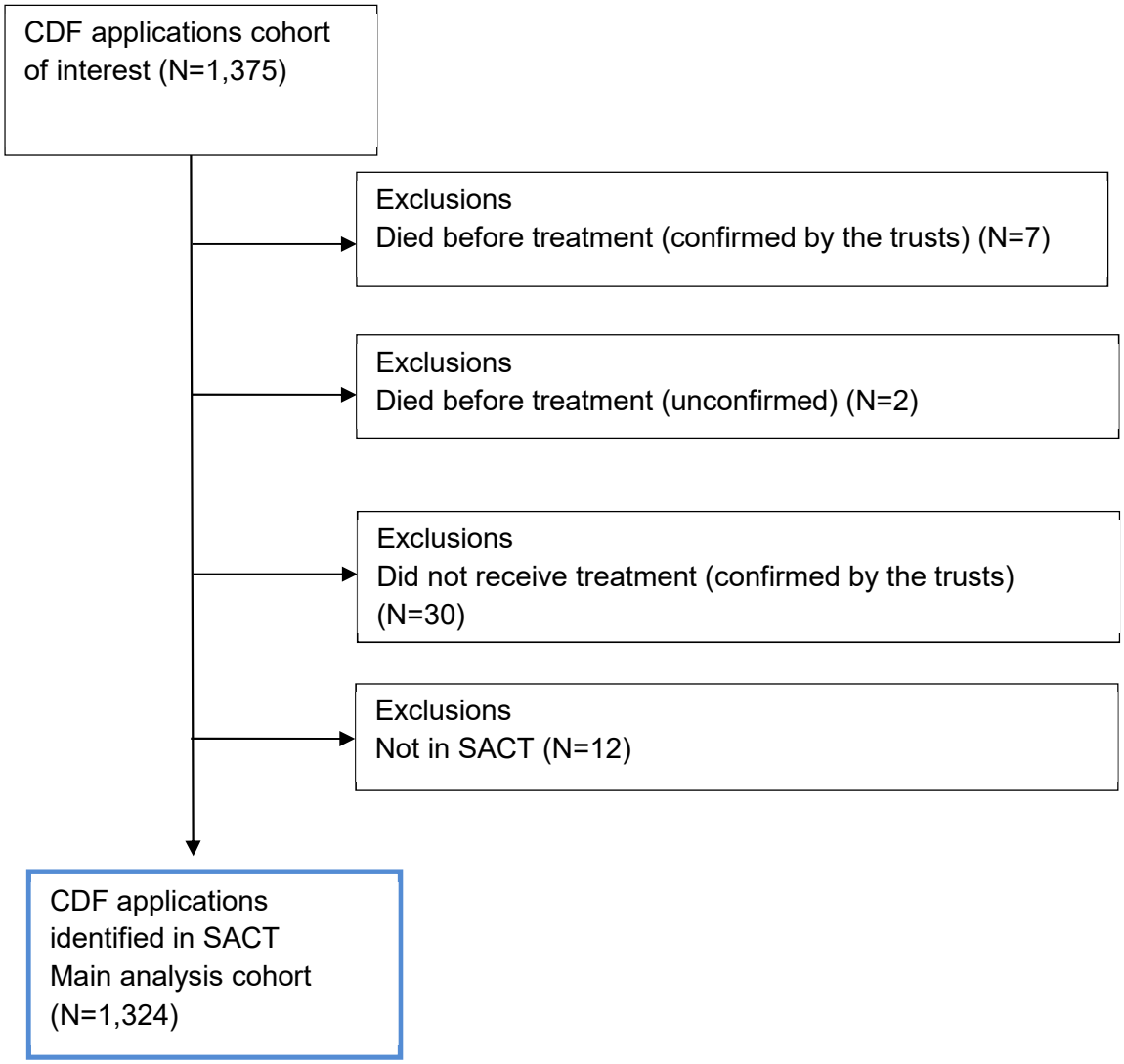
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 1,375 applications for CDF funding for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma, 30 patients did not receive treatment, nine patients died before treatment and 12 patients were missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma between 19 November 2018 and 18 November 2020



[a] Of the 30 patients that did not receive treatment, all were confirmed by the relevant trust by the PHE data liaison team. Of the nine patients that died before treatment, seven have been confirmed by the relevant trusts by the PHE data liaison team, two patients were followed up by the data liaison team but the relevant trust did not confirm if the patient died before treatment.

A maximum of 1,336 pembrolizumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 99% (1,324/1,336) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 91% complete.

Table 1. Completeness of key SACT data items for the pembrolizumab cohort (N=1,324)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	91%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with pembrolizumab in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 698 patients. Of these, 485 (69%) have an outcome summary recorded in the SACT dataset.

Table 2. Completeness of outcome summary for patients that have ended treatment (N=698)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	69%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq, all of which are 100% complete.

Table 3: Completeness of key Blueteq data items for the pembrolizumab cohort (N=1,324)

Variable	Completeness (%)
Melanoma BRAF mutation status	100%
Melanoma stage	100%

Patient characteristics

The median age of the 1,324 patients receiving pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma was 64 years. The median age in males and females was 66 and 62 years respectively.

Table 4. Patient characteristics (N=1,324)

Patient characteristics[b]			
		N	**%**
Sex	Male	772	58%
	Female	552	42%
Age	<40	98	7%
	40 to 49	133	10%
	50 to 59	280	21%
	60 to 69	322	24%
	70 to 79	415	31%
	80+	76	6%
Performance status	0	909	69%
	1	299	23%
	2	2	<1%
	3	0	0%
	4	0	0%
	Missing	114	9%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items, stage of diseae and melanoma BRAF mutation status.

Table 5: Distribution of key Blueteq data items (N=1,324)

Blueteq data items[c]

		N	%
Melanoma stage	Stage IIIA disease	152	11%
	Stage IIIB disease	415	31%
	Stage IIIC disease	683	52%
	Stage IIID disease	74	6%
Melanoma BRAF mutation status	BRAF V600 mutation negative	1,073	81%
	BRAF V600 mutation positive	251	19%

[c] Figures may not add to 100% due to rounding.

Time to subsequent treatments in SACT

153/1,324 (12%) unique patients treated with pembrolizumab in the CDF have subsequent therapies recorded in the SACT dataset, received after the patient's last pembrolizumab cycle. Table 6 reports regimens prescribed after pembrolizumab, as recorded in the SACT dataset. Some patients have more than one subsequent therapy, these regimens are are shown in Table 7.

The median time from a patient's last pembrolizumab cycle in SACT to their next treatment was 49 days[d].

The median time from a patient's first pembrolizumab cycle in SACT to their next treatment was 218 days.

Table 6: Distribution of first treatments prescribed after a patients last pembrolizumab cycle (N(Patients)=153) [e,f]

Regimen	Number of subsequent treatments
Ipilimumab + nivolumab	83
Ipilimumab	29
Dabrafenib + trametinib	21
Binimetinib + encorafenib	13
Nivolumab	4
Carboplatin + paclitaxel	1
Talimogene laherparepvec	1
Trial	1
Total number of subsequent treatments	**153**

[d] If a patient has > 1 subsequent regimen recorded in SACT, time to next treatment only includes regimen prescribed immediately after pembrolizumab.
[e] Some patients will have received more than one subsequent therapy. Table 6 lists therapies prescribed immediately after a patients last pembrolizumab cycle. Subsequent therapies could be related to a second primary tumour.
[f] These data have not been validated/confirmed with trusts or by the PHE data liaison team.

Table 7: Distribution of further lines of therapy following a patients last pembrolizumab cycle (N(Patients)=153) [g,h]

Regimen	Number of subsequent treatments
Nivolumab	28
Binimetinib + encorafenib	7
Ipilimumab + nivolumab	3
Carboplatin + paclitaxel	1
Cisplatin + dacarbazine	1
Cisplatin + dacarbazine + vinblastine	1
Dabrafenib + trametinib	1
Dacarbazine	1
Ipilimumab	1
Rituximab	1
Trial	1
Total number of subsequent treatments	**46**

[g] Some patients will have received more than one subsequent therapy. Table 7 lists further lines of therapies prescribed after a patients last pembrolizumab cycle in SACT. Subsequent therapies could be related to a second primary tumour.
[h] These data have not been validated/confirmed with trusts or by the PHE data liaison team.

Treatment duration

Of the 1,324 patients with CDF applications, 698 (53%) were identified as having completed treatment by 30 November 2020 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with pembrolizumab in at least three months (see Table 11). The median follow-up time in SACT was 7.7 months (234 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 24 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 25 months. SACT follow-up ends 30 November 2020.

Table 8: Breakdown by patients' treatment status[i,j,k]

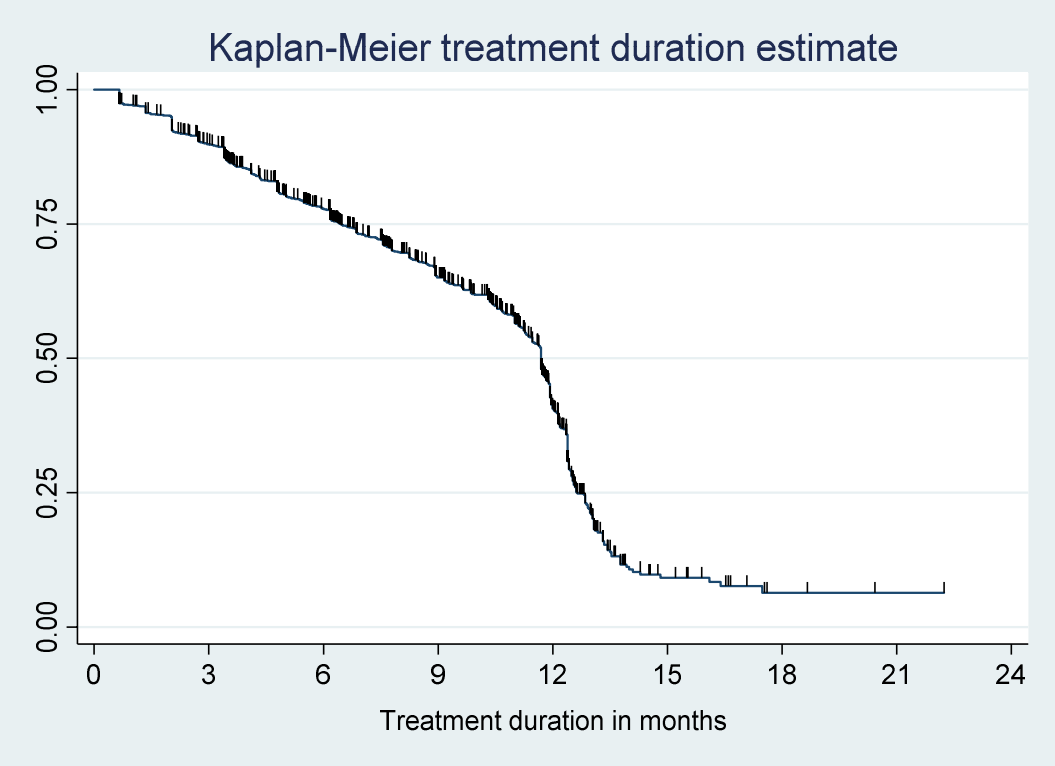
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	116	9%
Patient died – on treatment	1	<1%
Treatment stopped	581	44%
Treatment ongoing	626	47%
Total	**1,324**	**100%**

[i] Figures may not sum to 100% due to rounding.
[j] Table 11 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[k] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 11.7 months [95% CI: 11.5, 11.8] (356 days) (N=1,324).

78% of patients were still receiving treatment at 6 months [95% CI: 75%,80%] and 41% of patients were still receiving treatment at 12 months [95% CI: 37%, 44%].

Figure 3. Kaplan-Meier treatment duration (N=1,324)



Tables 9 and 10 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 24 months (730 days). SACT contains more follow-up for some patients.

Table 9. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Number at risk	1,324	1,112	842	574	230	16	3	1

Table 10 shows that for all patients who received treatment, 626 were still on treatment (censored) at the date of follow-up and 698 had ended treatment (events).

Table 10. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Censored	626	545	415	272	100	13	3	1
Events	698	567	427	302	130	3	0	0

Table 11 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 53% (N=698) of patients had ended treatment at 30 November 2020.

Table 11: Treatment outcomes for patients that have ended treatment (N=698)[l],[m]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – no treatment in at least 3 months	193	28%
Stopped treatment – acute toxicity	159	23%
Stopped treatment – progression of disease	147	21%
Stopped treatment – completed as prescribed	118	17%
Stopped treatment – died not on treatment[n]	34	5%
Stopped treatment – COVID	24	3%
Stopped treatment – patient choice	21	3%
Stopped treatment – died on treatment	1	<1%
Stopped treatment – comorbidty	1	<1%
Total	**698**	**100%**

[l] Figures may not sum to 100% due to rounding.
[m] Table 11 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[n] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 12: Treatment outcomes and treatment status for patients that have ended treatment (N=698)

Outcome[o]	Patient died [p] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – acute toxicity	11	148	
Stopped treatment – progression of disease	59	88	
Stopped treatment – completed as prescribed	7	111	
Stopped treatment – no treatment in at least 3 months		193	
Stopped treatment – died not on treatment	34		
Stopped treatment – COVID	2	22	
Stopped treatment – patient choice	3	18	
Stopped treatment – died on treatment			1
Stopped treatment – comorbidty		1	
Total	**116**	**581**	**1**

[o] Relates to outcomes submitted by the trust in table 11.
[p] Relates to treatment status in table 8 for those that have ended treatment.

Overall survival (OS)

Of the 1,324 patients with a treatment record in SACT, the minimum follow-up was 5.3 months (161 days) from the last CDF application. Patients were traced for their vital status on 28 April 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 15.7 months (477 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 28 April 2021. The median OS was not reached.

OS at 6 months was 98% [95% CI: 97%, 99%], 12 months OS was 95% [95% CI: 93%, 96%] and OS at 18 months was 90% [95% CI: 88%, 92%].

Figure 4. Kaplan-Meier survival plot (N=1,324)

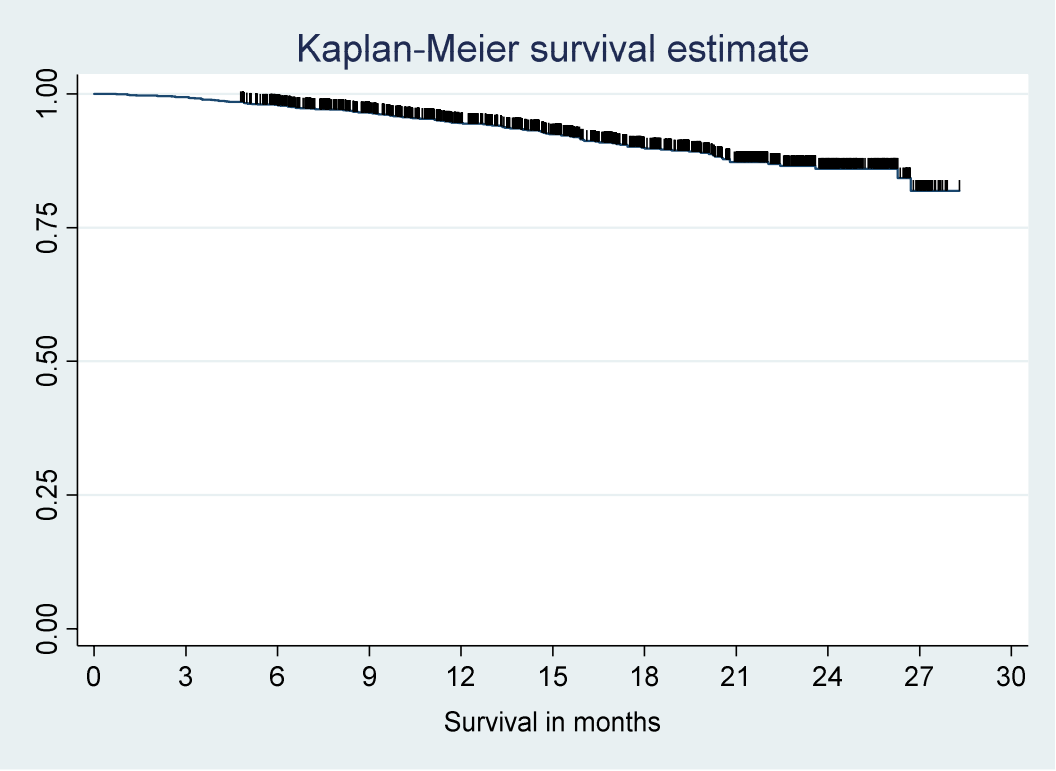


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 29 months (882 days), all patients were traced on 28 April 2021.

Table 13. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-30	3-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Number at risk	1,324	1,316	1,250	1,092	898	732	518	316	142

Table 14 shows that for all patients who received treatment, 1,207 were still alive (censored) at the date of follow-up and 117 had died (events).

Table 14. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-30	3-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Censored	1,207	1,207	1,160	1,019	846	698	501	311	140
Events	117	109	90	73	52	34	17	5	2

Sensitivity analyses

6-month SACT follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 19 November 2018 to 30 May 2020 and SACT activity was followed up to the 30 November 2020.

Following the exclusions above, 1,040 patients (79%) were included in these analyses. The median follow-up time in SACT was 9.9 months (301 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 11.7 months [95% CI: 11.3, 11.7] (356 days) (N=1,040).

Figure 5. Kaplan-Meier treatment duration plot (N=1,040)

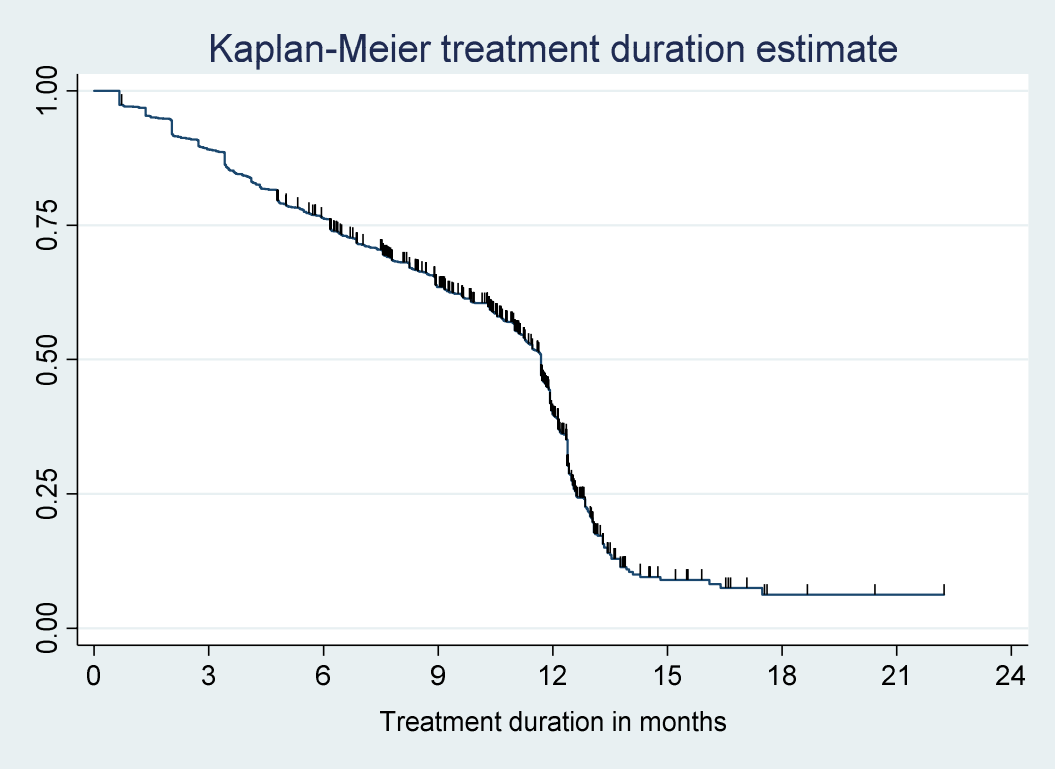


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 24 months (730 days).

Table 15. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Number at risk	1,040	926	781	571	230	16	3	1

Table 16 shows that for all patients who received treatment, 370 were still on treatment (censored) at the date of follow-up and 670 had ended treatment (events).

Table 16. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Censored	370	369	357	271	100	13	3	1
Events	670	557	424	300	130	3	0	0

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 19 November 2018 to 28 October 2020.

Following the exclusions above, 1,288 patients (97%) were included in these analyses. The median follow-up time in SACT was 16.3 months (496 days).

Figure 6 provides the Kaplan-Meier curve for OS, censored at 28 April 2021 The median OS was not reached.

Figure 6: Kaplan-Meier survival plot (N=1,288)

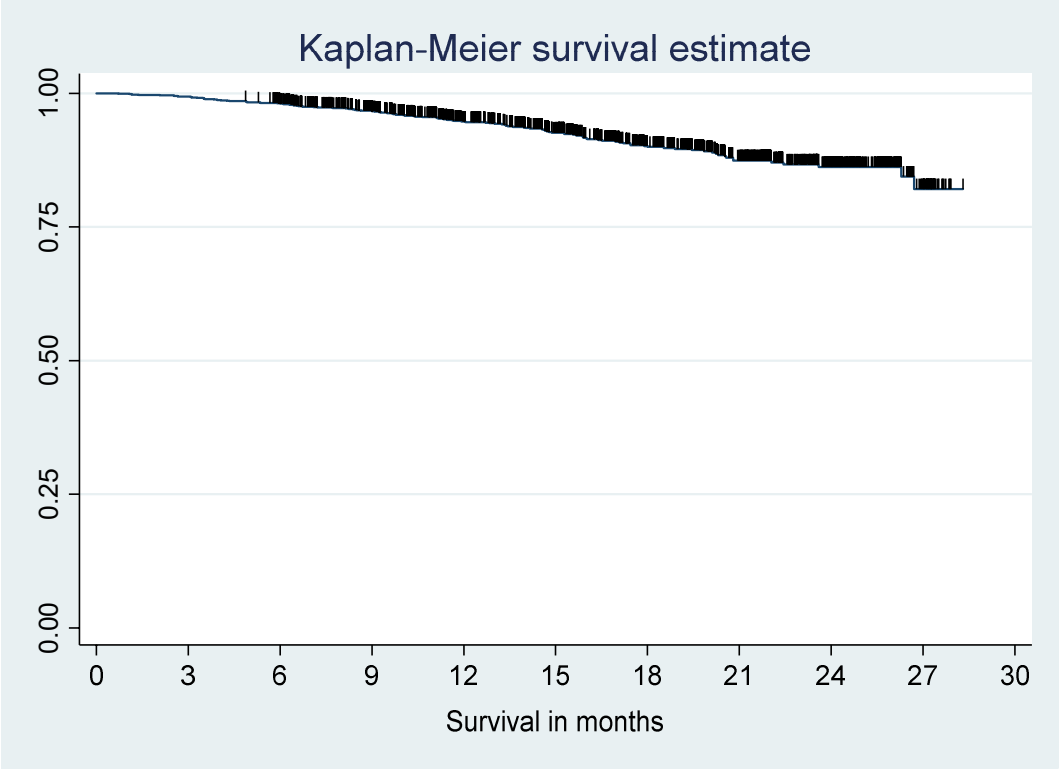


Table 17. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Number at risk	1,288	1,280	1,246	1,092	898	732	518	316	142	20

Table 18 shows that for all patients who received treatment, 1,174 were still alive (censored) at the date of follow-up and 114 had died (events).

Table 18. Number of patients at risk, those that have died pre-progression (events) and those that have died not on treatment or still alive but treatment has ended (censored) by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Censored	1,174	1,174	1,156	1,019	846	698	501	311	140	20
Events	114	106	90	73	52	34	17	5	2	0

Table 19. Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	1,324	1,040	1,288
Median treatment duration	11.7 months [95% CI: 11.5, 11.8] (365)	11.7 months [95% CI: 11.3, 11.7] (365)	
OS	Not reached		Not reached

Conclusions

1,336 patients received pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma [TA553] through the CDF in the reporting period (19 November 2018 and 18 November 2020). 1,324 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. An additional 30 patients with a CDF application did not receive treatment and nine patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 58% (N=772) of patients that received pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma were male, 42% (N=552) of patients were female. Most of the cohort were aged 50 years and over (83%, N=1,093) and 91% (N=1,208) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 53% (N=698) of patients were identified as no longer being on treatment. Of these 698 patients, 21% (N=147) of patients stopped treatment due to progression, 23% (N=159) of patients stopped treatment due to acute toxicity, 3% (N=21) of patients chose to end their treatment, 5% (N=34) of patients died not on treatment, <1% (N=1) of patients died on treatment, 17% (N=118) of patients completed treatment as prescribed, 3% (N=24) of patients stopped treatment due to COVID, <1% (N=1) of patients stopped due to other comorbidities and 28% (N=193) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration was 11.7 months [95% CI: 11.5, 11.8] (356 days) (N=1,324). 78% of patients were still receiving treatment at 6 months [95% CI: 75%,80%] and 41% of patients were still receiving treatment at 12 months [95% CI: 37%, 44%].

The median OS was not reached. OS at 6 months was 98% [95% CI: 97%, 99%], 12 months OS was 95% [95% CI: 93%, 96%] and OS at 18 months was 90% [95% CI: 88%, 92%].

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for treatment duration showed no difference (full cohort = 11.7 months; sensitivity analysis cohort = 11.7 months). The median OS was not reached for both the full and sensitivity cohort.

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Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID3776]

Cancer Drugs Fund Review of TA553

This report was commissioned by the NIHR Systematic Reviews Programme as project number 131840

Completed 6 September 2021

CONTAINS COMMERCIAL IN CONFIDENCE AND ACADEMIC 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 [ID3776] (Cancer Drugs Fund Review of TA553)
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Contributions of authors:

James Mahon	Critical appraisal of the economic 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
Rebecca Bresnahan	Critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AC	Appraisal Committee
AJCC	American Joint Committee on Cancer
CDF	Cancer Drugs Fund
CS	Company submission
DCA	Data collection agreement
DMFS	Distant metastasis-free survival
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERG	Evidence Review Group
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
MAA	Managed Access Scheme
OS	Overall survival
PAS	Patient Access Scheme
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
RFS	Recurrence-free survival
SACT	Systemic Anti-Cancer Therapy
SmPC	Summary of Product Characteristics
ToE	Terms of Engagement

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. A summary of the key issues is provided in Section 1.1. These issues are described in more detail in Section 1.2 (clinical issues) and Section 1.3 (economic issues). The ERG's reasons for not providing preferred cost effectiveness results are presented in Section 1.4 and a summary of the company's cost effectiveness results is presented in Section 1.5. Further details about the issues identified by the ERG are provided in the main body of the report.

All the issues outlined in this report represent the views of the ERG; they do not represent the opinion of NICE.

1.1 Overview of the ERG's key issues

Table A Summary of key issues

ID3776	Summary of issue	Report sections
Issue 1	Absence of any KEYNOTE-054 OS K-M data	Section 3.3
Issue 2	Company cost utility model does not generate reliable OS results for patients receiving pembrolizumab	Section 4.3
Issue 3	Company cost utility model does not generate reliable OS results for patients receiving routine surveillance	Section 4.3
Issue 4	The company assumption that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon is not supported by evidence	Section 4.4

DMFS=distant metastasis-free survival; ERG=Evidence Review Group; K-M=Kaplan-Meier; OS=overall survival; RFS=recurrence-free survival

1.2 Clinical effectiveness evidence: summary of the ERG's key issues

The ERG considers that it has not been possible for the company to provide evidence to allow a reliable comparison of the effectiveness of pembrolizumab versus routine surveillance on overall survival (OS).

Issue 1 There is no direct evidence to facilitate a comparison of the clinical effectiveness of pembrolizumab versus routine surveillance

Report section	3.3
Description of issue and why the ERG has identified it as important	The only OS data available from the KEYNOTE-054 trial are the number of participants who have died. As of data cut-off IA2 (April 2020), [redacted]
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Final OS data from the KEYNOTE-054 trial will be informative.

CI=confidence interval; IA2=interim analysis 2; K-M=Kaplan-Meier; OS=overall survival;SACT=Systemic Anti-Cancer Therapy

1.3 The cost effectiveness evidence: summary of the ERG's key issues

Issue 2 Company cost utility model does not generate reliable OS results for patients treated with pembrolizumab

Report section	4.3
Description of issue and why the ERG has identified it as important	For patients treated with pembrolizumab, over the first 18 months of the company model time horizon, the company model mortality rate estimate was [redacted]% lower than the rate experienced by patients treated with pembrolizumab and registed in the SACT database ([redacted]% versus [redacted]%). This shows that after 18 months (i.e., 3.3% of the 46 year model time horizon), the company model is already generating OS estimates that are higher than those for NHS patients.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The company model should be modified to reflect available SACT data. Longer follow-up of SACT data would demonstrate whether company model projections reflect the experience of NHS patients in the longer term.

SACT=Systemtic Anti-Cancer Therapy

Issue 3 Company cost utility model does not generate reliable OS results for patients receiving routine surveillance

Report section	4.3
Description of issue and why the ERG has identified it as important	A comparison of company model and Gershenwald/AJCC estimates shows that company model OS estimates are pessimistic compared with the Gershenwald/AJCC data and that the level of pessimism increases over time.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The company model should be modified to reflect available Gershenwald/AJCC data.

AE=adverse event; ERG=Evidence Review Group; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Issue 4 Company assumption that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon is not supported by evidence

Report section	4.4
Description of issue and why the ERG has identified it as important	The company has assumed that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon. Analyses undertaken by the ERG suggest that, for patients who receive a maximum of 12 months of treatment (KEYNOTE-054 trial protocol), RFS and DMFS benefits endure for a period of between 24 and 36 months from commencement of treatment.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Over-estimating the RFS and DMFS benefit for patients receiving pembrolizumab results in the company model generating cost effectiveness results that favour pembrolizumab.
What additional evidence or analyses might help to resolve this key issue?	Making changes to RFS and DMFS in isolation will not be informative and could lead to the generation of spurious cost effectiveness results.

DMFS=distant metastasis-free survival; ERG=Evidence Review Group; RFS=recurrence-free survival

1.4 Summary of ERG's preferred assumptions and resulting cost effectiveness results

The ERG considers that the company's estimated incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained are unreliable. Furthermore, in the absence of KEYNOTE-054 trial OS Kaplan-Meier (K-M) data and given the company model structure, the ERG has not been able to produce ICERs per QALY gained that are more reliable than those presented by the company.

1.5 Company cost effectiveness results

1.5.1 Company cost effectiveness results

The company's base case cost effectiveness results are presented in Table A. A list of the changes made by the company to the original company model is provided in the CDF Review CS (Table 41).

Table A Company model results for the comparison of pembrolizumab (PAS price) versus routine surveillance

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Cost effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	6.61	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Cost effectiveness analysis 2: As above incorporating updated clinical evidence (RFS and DMFS from KEYNOTE-054 IA2)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	7.73	[redacted]	[redacted]	[redacted]	[redacted]	£2,743
Cost effectiveness analysis 3: New company base case (RFS; DMFS; new survival extrapolations; subsequent treatments; cost inputs)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	9.02	[redacted]	[redacted]	[redacted]	[redacted]	£9,357

CDF=Cancer Drugs Fund; DMFS=distant metastasis-free survival; ICER=incremental cost effectiveness ratio; LYG=life years gained; RFS=recurrence-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: CDF Review CS, Table 13

2 BACKGROUND

2.1 Introduction

In December 2018, the National Institute for Health and Care Excellence (NICE) recommended pembrolizumab,[1] within the Cancer Drugs Fund (CDF), as an option for the adjuvant treatment of Stage III melanoma with lymph node involvement in adults who have had a complete resection, if the conditions in the Managed Access Agreement (MAA)[2] for pembrolizumab were followed.

This CDF Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement (ToE)[3] document issued by NICE. The ToE,[3] although not binding, outline NICE's expectations relating to the content of the company submission (CS) for the CDF review.

2.2 Pembrolizumab

Key facts:

- pembrolizumab is approved by the European Medicines Agency for the adjuvant treatment of adult patients with Stage III melanoma and lymph node involvement who have undergone complete resection
- no diagnostic test is required for this indication (i.e., it is available irrespective of tumour level of PD-L1/BRAF expression)
- pembrolizumab is administered as monotherapy at a dose of 200mg every 3 weeks via an intravenous infusion over 30 minutes
- pembrolizumab is available to the NHS at a (confidential) discounted price via a Patient Access Scheme (PAS).

2.3 Evidence sources

The two main sources of evidence for this review are the KEYNOTE-054[4] trial and Systemic Anti-Cancer Therapy (SACT)[5] data. The company considers that data from the latest data-cuts of these two sources provide sufficient evidence to address the NICE Appraisal Committee's main uncertainties (as detailed in the Data Collection Agreement).[2]

KEYNOTE-054 trial

The company's main source of clinical effectiveness evidence for this appraisal is the KEYNOTE-054 trial. This is a randomised, placebo-controlled, parallel-group, multi-centre, double-blind, Phase III trial assessing the clinical effectiveness of pembrolizumab versus placebo in patients who have undergone complete surgical resection of Stage III melanoma. The trial design is shown in Figure 1.

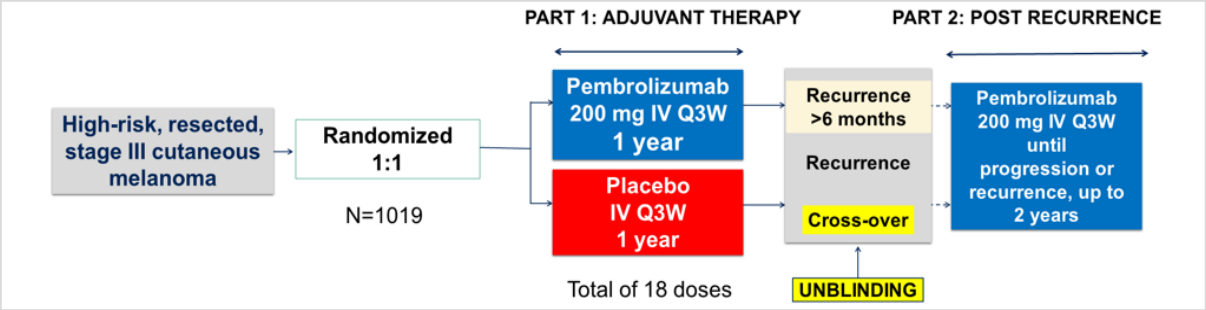

Figure 1 KEYNOTE-054 trial diagram

IV=intravenous; Q3W=once every 3 weeks
Source: Eggermont 2021[6]

The KEYNOTE-054 trial results presented in the CDF Review CS were generated using data from the latest data cut (3 April 2020, interim analysis 2 [IA2]). All efficacy analyses were conducted using the intention to treat (ITT) population.

SACT data

Public Health England (PHE) provided a report for NHS England which includes results from analyses of data collected from patients who received pembrolizumab via the CDF ([redacted] applications of interest between 19 November 2018 and 18 November 2020). This population comprises NHS patients with Stage III melanoma (according to the AJCC 8th edition)[7] that had been completely resected either via sentinel lymph node biopsy or, when indicated, via completion lymph node dissection. Patients (n=1324) received pembrolizumab monotherapy for up to 1 year.

Median treatment duration for patients with a SACT record was [redacted]. Reasons for patients no longer receiving pembrolizumab are provided in Table 1.

Table 1 Reasons for patients with a SACT record stopping treatment with pembrolizumab

	Pembrolizumab SACT data N=1324
Patients no longer on treatment at date of data cut-off	[redacted]

Source: Public Health England report[5]

Comparison of KEYNOTE-054 trial and SACT patient populations

The main differences between the two populations are:

- the median age of patients in the KEYNOTE-054 trial is lower than the median age of the SACT cohort (54 years versus [redacted] years respectively)
- a higher number of patients in the KEYNOTE-54 trial were assessed to have an ECOG performance status (PS) of 0 than in the the SACT cohort (94.4% versus [redacted]% respectively)
- the proportion of patients with a BRAF V600 positive mutation was higher in the KEYNOTE-054 trial than in the SACT cohort (47.5% versus [redacted]% respectively).

Clinical advice to the ERG is that these difference are to be expected.

3 THE CLINICAL DECISION PROBLEM

The NICE Appraisal Committee's preferred clinical assumptions (as set out in the ToE[3]) are presented in Table 2. Further information relating to each assumption is provided in the text following the table.

Table 2 ERG summary of NICE AC preferred clinical assumptions

Area	ERG summary of NICE Appraisal Committee's preferred assumptions
Population	Adults with completely resected Stage III melanoma at high risk of recurrence
Comparators	Pembrolizumab compared to routine surveillance.
Survival data	More mature recurrence-free survival, distant metastases-free survival and overall survival data from the KEYNOTE-054 trial are required
RFS hazard ratio analyses	Explore alternative methods to calculate the RFS hazard ratio.
Subsequent treatments	Explore the most appropriate assumptions about subsequent treatments using SACT data

AC=Appraisal Committee; CDF=Cancer Drugs Fund; ERG=Evidence Review Group; RFS=relapse-free survival; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2019[3]

3.1 Population

Box 1 NICE Appraisal Committee's preferred assumption: population

NICE preferred assumption	ERG comment
Adults with completely resected Stage III melanoma at high risk of recurrence	The company has provided appropriate data for the relevant population

ERG=Evidence Review Group
Source: NICE 2019[3]

The population described in the final scope[8] issued by NICE was adults with resected melanoma with high risk of recurrence. The key trial supporting the appraisal (KEYNOTE-054 trial) enrolled patients with Stage IIIA, Stage IIIB and Stage IIIC melanoma. NICE recommended[1] pembrolizumab as an option for treating Stage III melanoma with lymph node involvement in adults who had had a complete resection.

The ERG is satisfied that the patients recruited to the KEYNOTE-054 trial are broadly 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. However:

- clinical advice to the ERG is that approximately 20% of patients with Stage III melanoma treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than patients participating in the KEYNOTE-054 trial (ECOG PS 0: 94.4%; ECOG PS 1: 5.6%) or who contributed to the SACT dataset (only patients who had an ECOG PS of 0 or 1 were elegible to receive pembrolizumab)
- approximately four-fifths (83.3%) of patients enrolled in the KEYNOTE-054 trial were defined as having programmed death-ligand 1 (PD-L1) positive disease. However, 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 Comparators

Box 2 Appraisal Committee's preferred assumption: comparators

NICE preferred assumption	ERG comment
Pembrolizumab compared to routine surveillance	The company has provided appropriate data for the comparison of pembrolizumab versus placebo. Placebo is routinely used as a proxy for routine surveillance

ERG=Evidence Review Group
Source: NICE 2019[3]

The ERG is aware that the Summary of Product Characteristics[9] for pembrolizumab was amended in March 2019 following EMA approval to allow treatment to be administered at a dose of 200mg every 3 weeks or at a dose of 400mg every 6 weeks, across all monotherapy indications. The company has presented cost effectiveness results for 200mg every 3 weeks in the base case cost effectiveness analysis and for 400mg every 6 weeks in a scenario analysis.

3.3 Survival data

Box 3 NICE Appraisal Committee's preferred assumption: survival results

NICE preferred assumption	ERG comment
More mature RFS, DMFS and OS data are required	The company has provided updated KEYNOTE-054 trial RFS data and DMFS final analysis results. The company has not provided any KEYNOTE-054 trial OS K-M data

DMFS=distant metastasis-free survival; ERG=Evidence Review Group; K-M=Kaplan-Meier; OS=overall survival; RFS=recurrence-free survival
Source: NICE 2019[3]

3.3.1 Updated KEYNOTE-054 trial results: RFS, DMFS and OS

The company has provided recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) results from the pre-specified final analyses of the KEYNOTE-054 trial using the latest data-cut (3 April 2020, interim analysis 2 [IA2]). All efficacy analyses were carried out using the intention to treat (ITT) population. Results of these analyses are shown in Table 3.

The company has not been able to provide any KEYNOTE-054 trial OS Kaplan-Meier data. The company highlighted to NICE and the ERG (in the company engagement form) that KEYNOTE-054 trial OS data would not be available to inform this CDF Review.

The KEYNOTE-054 OS analysis is event driven and will only take place once [redacted] OS events have occurred. In the original CS, it was anticipated that this target would be reached in [redacted]; however, examination of IA2 OS data showed that only [redacted] target events ([redacted]) had occurred and the date of the final analysis was revised to [redacted]. During the original appraisal, the Appraisal Committee concluded that the survival benefit associated with pembrolizumab could not be confirmed without OS data from the KEYNOTE-054 trial.

Table 3 Original and extended data analysis results (ITT population)

Treatment Follow-up		Number of events (%)	Event rate/100 person-months	Median, months (95% CI)	Rate, % (95% CI)	HR (95% CI)
Recurrence-free survival*						
Original CS (18 months)	Pembrolizumab (n=514)	135 (26.3)	2.2	NR (NE to NE)	71.4 (66.8 to 75.4)	0.57 (0.43 to 0.74); p<0.0001
	Placebo (n=505)	216 (42.8)	3.9	20.4 (16.2 to NE)	53.2 (47.9 to 58.2)	–
CDF Review CS (42 months)	Pembrolizumab (n=514)	203 (39.5)	[redacted]	[redacted]	59.8 (55.3 to 64.1)	0.59 (0.49 to 0.70)
	Placebo (n=505)	288 (57.0)	[redacted]	[redacted]	41.4 (37.0 to 45.8)	–
Distant metastasis-free survival**						
Original CS (18 months)	[redacted]					
CDF Review CS (42 months)	Pembrolizumab (n=514)	173 (33.7)	1.1	Not reached (49.6 to –)	65.3 (60.9 to 69.5)	0.59 (0.49 to 0.70)†
	Placebo (n=505)	245 (48.5)	1.8	40.0 (27.7 to –)	49.4 (44.8 to 53.8)	-
Overall survival						
Original CS (18 months)	As of data cut-off (IA1, October 2017), [redacted]					
CDF Review CS (42 months)	As of data cut-off (IA2, April 2020), [redacted]					

* RFS is defined as time from randomisation to the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first

** Distant metastasis-free survival is defined as the time between the date of randomisation and the date of first distant metastasis or date of death (whatever the cause), whichever occurs first

† Company clarification response

CDF=Cancer Drugs Fund; CI=confidence interval; CS=company submission; DMFS=distant metastases-free survival; HR=hazard ratio; ITT=intention to treat; NE=not evaluable; NR=not reached; OS=overall survival

Source: Original CS (p20, p34, Table 13 and Table 14), CDF CS (Table 5 and Table 6)

3.3.2 SACT overall survival data

The SACT report includes OS data for [redacted] patients with a treatment record in the SACT dataset; the median follow up time (censor date [redacted]) for these patients was [redacted] months (minimum [redacted] months to maximum [redacted] months). As of the censor date, median OS had not been reached ([redacted] of the cohort who received pembrolizumab had died). Overall survival rates for the cohort are shown in Table 4.

Table 4 Pembrolizumab SACT data

Pembrolizumab SACT data [redacted]	
OS at 6 months	[redacted]
OS at 12 months	[redacted]
OS at 18 months	[redacted]

CI=confidence interval; OS=overall survival; SACT=Systemic Anti-Cancer Therapy
Source: CDF Review CS, Section A.6.2.1, Public Health England report[5]

3.4 Recurrence-free survival hazard ratio analyses

Box 4 NICE Appraisal Committee's preferred assumption: RFS HRs

NICE preferred assumption	ERG comment
Explore alternative methods to calculate the RFS hazard ratio	The ERG is satisfied that there is no evidence that KEYNOTE-054 trial RFS hazards are not proportional and considers that alternative approaches to estimating RFS HRs are not necessary

ERG=Evidence Review Group; HR=hazard ratio RFS=recurrence-free survival
Source: NICE 2019[3]

The hazard ratios (HRs) for RFS presented in the original CS were estimated using a Cox proportional hazards (PH) model. At the time of the original appraisal, the ERG considered that, although the company had not carried out any formal testing of the proportionality of KEYNOTE-054 trial RFS data, the PH assumption was unlikely to hold for RFS. The ERG highlighted that a HR estimated using a Cox PH model has no meaningful interpretation when the PH assumption is violated. Due to uncertainty around proportionality, the ToE[3] document included a request to explore methods of generating RFS HRs that do not rely on the assumption of PH.

In response to clarification question A2, the company explored the validity of the PH assumption for RFS based on the approach described by Grambsch[10] and concluded that the departure from the proportionality assumption was not statistically significant at the nominal 5% level. The company also highlighted that Eggermont[4] tested for proportionality and, based on the approach described by Lin,[11] reported no evidence of non-proportionality. The company also carried out an analysis to explore how RFS HRs varied over time at select time points.

Results from this analysis showed that whilst there was some instability over the first 42 months, HRs at 48 months were identical to those at 54 months (company clarification response, Table 1). The company advises that the Cox PHs model in the longer follow-up data is of a descriptive nature and the HR should be interpreted as a weighted average of the HRs over the entire follow-up period.

3.5 Subsequent treatments

Box 5 NICE Appraisal Committee's preferred assumption: subsequent treatments

NICE preferred assumption	ERG comment
Explore the most appropriate assumptions about subsequent treatments using SACT data	The company analyses are appropriate.

ERG=Evidence Review Group; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2019[3]

KEYNOTE-054 trial

Whilst subsequent treatment data were collected as part of the KEYNOTE-054 trial, the company highlights that these data are still immature and that categorisation of treatment regimens was not performed i.e., the trial did not account for individual agents received in combination regimens. The company also cautions that the KEYNOTE-054 trial design may limit the generalisability of subsequent treatment data; the trial was designed so that after 1 year (a total of 18 doses), patients in the placebo arm with a documented recurrence were permitted to crossover to receive pembrolizumab and patients in the pembrolizumab arm who experienced a recurrence after 6 months were eligible to be rechallenged with pembrolizumab.

SACT data

Of the [redacted] patients who had a SACT record, [redacted] had received one subsequent treatment and [redacted] had received more than one subsequent treatment (Table 5). After treatment with adjuvant pembrolizumab, over half of the patients received ipilimumab+nivolumab ([redacted]), with some patients receiving further treatment with ipilimumab monotherapy ([redacted]). These subsequent treatments are in line with with NICE recommendations[12] for the treatment of Stage IV melanoma, i.e., treatments include a mix of targeted therapies and immunotherapy agents (CDF Review CS, p22).

Table 5 SACT subsequent treatment data

Distribution of first treatments prescribed after a patient's last pembrolizumab cycle	Patients with subsequent treatments ([redacted])	%
[redacted]	[redacted]	[redacted]
Distribution of further lines of therapy following a patient's last pembrolizumab cycle (interpreted as 2nd line metastatic)	**Patients with subsequent treatments ([redacted])**	**%**
[redacted]	[redacted]	[redacted]

* Encorafenib+binimetinib was recommended by NICE in 2019 (TA562)[13] for patients with unresectable or metastatic *BRAF* mutation-positive melanoma
Source: CDF Review CS, Table 7 and Table 8

3.6 ERG clinical effectiveness conclusions

The ERG considers that the most important area of uncertainty is around the effect of adjuvant treatment with pembrolizumab on OS. Whilst SACT data are informative, the length of follow-up is short and the number of deaths is low. Uncertainty around OS cannot be resolved until after the final analysis of KEYNOTE-054 trial OS data and/or mature SACT data are available.

4 THE COST EFFECTIVENESS DECISION PROBLEM

The NICE Appraisal Committee's preferred economic assumptions (as set out in the ToE[3] document) are presented in Table 6. Further information relating to each assumption is provided in the text following the table.

Table 6 ERG summary of NICE AC preferred economic assumptions

Area	ERG Summary of NICE Appraisal Committee's preferred assumptions
RFS	The company should use more mature RFS data from the KEYNOTE-054 trial to inform the economic model
DMFS	The company should use more mature DMFS data from the KEYNOTE-054 trial to inform the economic model
OS	The company should use OS data from the KEYNOTE-054 trial to inform the economic model
Duration of treatment effect	The company should use more mature data from the KEYNOTE-054 trial to inform assumptions about the duration of treatment effect after stopping treatment
Subsequent treatments	The company should fully explore the most appropriate assumptions about subsequent treatments using data collected through SACT
NICE End of Life criteria	The Appraisal Committee considered that pembrolizumab, for this indication, does not meet the NICE End of Life criteria

AC=Appraisal Committee; DMFS=distant metastasis-free survival; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year; RFS=relapse-free survival; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2019[3]

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. However, concerns remain around the validity of company model OS estimates and the ERG considers that company model cost effectiveness results remain highly uncertain.

4.1 Relapse-free survival

Box 6 NICE Appraisal Committee's preferred assumption: relapse-free survival

NICE preferred assumption	ERG comment
Use more mature RFS data from the KEYNOTE-054 trial to inform the economic model	More mature RFS data have been included in the company model

ERG=Evidence Review Group; RFS=relapse-free survival
Source: NICE 2019[3]

4.2 Distant metastasis-free survival

Box 7 NICE Appraisal Committee's preferred assumption: distant metastasis-free survival

NICE preferred assumption	ERG comment
Use more mature DMFS data from the KEYNOTE-054 trial to inform the economic model	The company has now been able to populate the model with KEYNOTE-054 trial final analysis DMFS data

DMFS=distant metastasis-free survival; ERG=Evidence Review Group
Source: NICE 2019[3]

4.3 Overall survival

Box 8 NICE Appraisal Committee's preferred assumption: overall survival

NICE preferred assumption	ERG comment
Use OS data from the KEYNOTE-054 trial to inform the economic model	OS data from the KEYNOTE-054 trial were not available

ERG=Evidence Review Group; OS=overall survival
Source: NICE 2019[3]

The primary area of uncertainty in this CDF Review is the validity of the company model OS estimates. The company model structure is not designed to directly model OS Kaplan-Meier (K-M) data. Instead, OS estimates are generated indirectly as a function of all transition probabilities in the model (i.e., OS is a model output). In the absence of any KEYNOTE-054 trial results, it is not possible to determine whether the model reflects the OS experience of patients enrolled in the KEYNOTE-054 trial.

4.3.1 Validation of company model OS projections

In the absence of trial data the validity of the company model OS projections can be assessed using SACT[5] data and other published sources.

Pembrolizumab overall survival data

At 18 months, [redacted] of patients treated with pembrolizumab and registered in the SACT database had died and the company model mortality estimate was [redacted]%, i.e., over the first 18 months, the company model mortality rate estimate was [redacted]% lower than the rate experienced by NHS patients. This shows that after 18 months (i.e., 3.3% of the 46 year model time horizon), the company model is already generating OS estimates that are higher than those for NHS patients.

Routine surveillance overall survival data

The company used data from five sources (CDF Review CS, Table 21) to validate model routine surveillance arm OS estimates. The company considered that the 'ERG composite model',[1] the EORTC-18071 and COMBI-AD trials were useful sources to validate the model projections.

Of the data sources considered by the company, the ERG considers that the company analysis based on data presented by Gershenwald (Gershenwald/AJCC[7]) is the most appropriate as it includes the most up-to-date registry data of any of the data sources considered as well as data from trials considering immunotherapies that are now routinely used in NHS clinical practice. The company has raised several concerns about the applicability of their Gershenwald/AJCC[7] analysis and the ERG has addressed some of these concerns in Table 7.

Table 7 Selected company concerns and ERG comment relating to the use of Gershenwald/AJCC analysis to validate OS projections

Company concern	ERG comment
Only melanoma-specific survival	All-cause general population mortality estimates indicate that for patients aged 54-63 years (i.e., over the first 10 years of the model time horizon) all-cause mortality would only account for approximately 8% of deaths. In contrast, for patients in the routine surveillance arm, results from the company model indicate that [redacted]% of patients had died by 10 years. The majority of the mortality in the company model is, therefore, melanoma-specific
Included patients enrolled in clinical trials	The Gershenwald/AJCC[7] analysis is more appropriate than the out-of-date 'ERG composite analysis'[1] as the Geshenwald/AJCC[7] dataset includes patients enrolled in clinical trials of immunotherapies in the metatstatic setting

Source: CDF Review CS, pp70-71

A comparison of the company model with Gershenwald/AJCC[7] OS data is shown in Figure 2 and shows that the company model OS estimates for the routine surveillance arm are pessimistic compared wth the Gershenwald/AJCC[7] OS data and that the level of pessimism increases over time.

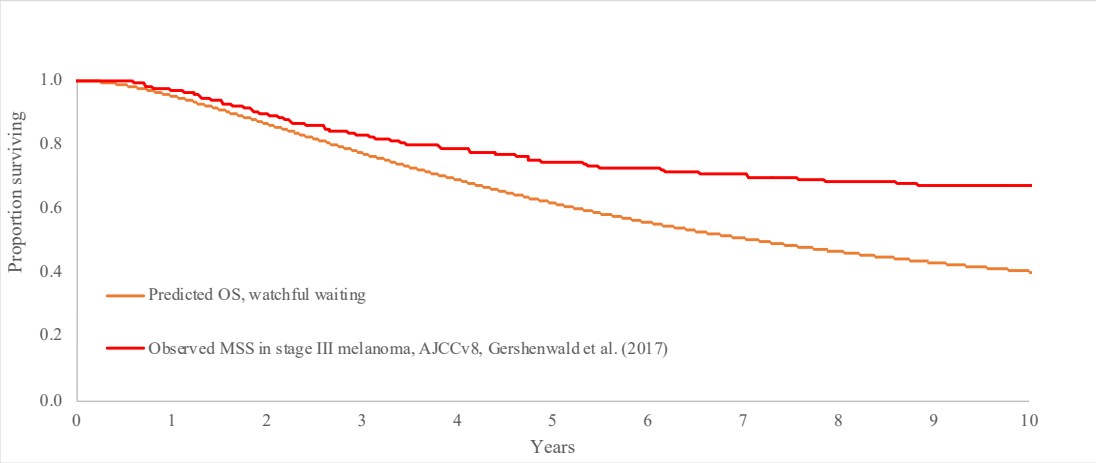

Figure 2 OS estimates for patients receiving routine surveillance (company model and Gershenwald/AJCC)

MSS=melanoma specifc survival; OS=overall survival
Source: Company model

A potential source of the company model routine surveillance arm pessimistic OS estimates are the implausibly low survival estimates generated in the DM health state. The company model estimate for the average survival of patients who are eligible for treatment with an immunotherapy in the metastatic setting ranges between [redacted] and [redacted] years ([redacted] and [redacted] weeks). Survival estimates were generated by the company (and ERG) to inform the the NICE appraisal of pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366[15]); the company base case and ERG survival estimates for patients treated with pembroliuzumab were [redacted] and [redacted] years respectively. The ERG therefore considers that the company's current estimates of survival for patients with Stage III melanoma in the advanced setting may be too low.

4.4 Duration of treatment effect

Box 9 NICE Appraisal Committee's preferred assumption: duration of treatment effect

NICE preferred assumption	ERG comment
Use more mature data from the KEYNOTE-054 trial to inform assumptions about the duration of treatment effect after stopping treatment	Additional RFS and DMFS KEYNOTE-054 trial data are available; however, the company has not performed any analysis of these data to explore the likely duration of treatment effect. The analyses undertaken by the ERG demonstrate that the effect of pembrolizumab on RFS and DMFS is unlikely to exend for a period longer than 36 months from treatment commencement

ERG=Evidence Review Group; DMFS=distant metastasis-free survival; RFS=recurrence-free survival
Source: NICE 2019[3]

The company has assumed that RFS and DMFS benefit endures for the whole model time horizon (46 years). Data presented in Table 8 and Table 9 show the risk (in 6-month time bands) of experiencing a first recurrence and a distant metastasis respectively. The KEYNOTE-054 trial RFS and DMFS K-M data show that the risks of first recurrence and distant metastasis respectively in the pembrolizumab arm were lower than the risks in the routine surveillance arm from time zero to month 36 but the risks in both arms were approximately equal from month 24 onwards. This suggests that, for patients who are permitted a maximum of 12 months of treatment (KEYNOTE-054 trial protocol), RFS benefit endures for a period of between 24 and 36 months from commencement of treatment. For DMFS, conclusions are complicated by KEYNOTE-054 trial patients being permitted to crossover to pembrolizumab after a local recurrence. However, the ERG considers that the DMFS K-M data suggest that the DMFS risk for pembrolizumab and routine suriveillance had equalised by 36 months. The ERG highlights that the uncertainty around OS means that it is not informative to make changes to the duration of treatment effect in isolation.

Over-estimating the RFS and DMFS benefit for patients receiving pembrolizumab results in the company model generating cost effectiveness results that are biased towards pembrolizumab.

Table 8 Risk of experiencing a first recurrence: KEYNOTE-054 trial and company model data

	Pembrolizumab		Routine surveillance	
Months	**Kaplan-Meier**	**Model**	**Kaplan-Meier**	**Model**
0-6	[redacted]	[redacted]	[redacted]	[redacted]
6-12	[redacted]	[redacted]	[redacted]	[redacted]
12-18	[redacted]	[redacted]	[redacted]	[redacted]
18-24	[redacted]	[redacted]	[redacted]	[redacted]
24-30	[redacted]	[redacted]	[redacted]	[redacted]
30-36	[redacted]	[redacted]	[redacted]	[redacted]
36-42	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG calculations based upon the percentage of people having a first recurrence between different time periods divided by the percentage of people at risk of having a first recurrence at the start of the period

Table 9 Risk of experiencing a distant metastasis: KEYNOTE-054 trial and company model data

	Pembrolizumab		Routine surveillance	
Months	**Kaplan-Meier**	**Model**	**Kaplan-Meier**	**Model**
0-6	[redacted]	[redacted]	[redacted]	[redacted]
6-12	[redacted]	[redacted]	[redacted]	[redacted]
12-18	[redacted]	[redacted]	[redacted]	[redacted]
18-24	[redacted]	[redacted]	[redacted]	[redacted]
24-30	[redacted]	[redacted]	[redacted]	[redacted]
30-36	[redacted]	[redacted]	[redacted]	[redacted]
36-42	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG calculations based upon the percentage of people having a distant metastasis between different time perionds divided by the percentage of people at risk of having a distant metastis at the start of the period

4.5 Subsequent treatments

Box 10 NICE Appraisal Committee's preferred assumption: subsequent treatments

NICE preferred assumption	ERG comment
Fully explore the most appropriate assumptions about subsequent treatments using data collected through SACT	The company has made use of the SACT data to generate estimates of the proportions of patients receiving different subsequent treatments; an appropriate adjustment was made to incorporate pembrolizumab as a subsequent therapy for patients in the routine surveillance arm The ERG notes that encorafenib+binemetanib was not a recommended subsequent treatment combination at the time of the original appraisal and the company has now included this treatment in their model based on advice from UK clinical experts

ERG=Evidence Review Group; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2019[3]

4.6 NICE End of Life criteria

Box 11 NICE Appraisal Committee's preferred assumption: NICE End of Life criteria

NICE preferred assumption	ERG comment
The Appraisal Committee considered that pembrolizumab, for this indication, does not meet the NICE End of Life criteria[16]	The company (appropriately) has not presented a case for pembrolizumab to be assessed against the NICE End of Life criteria

ERG=Evidence Review Group
Source: NICE 2019[3]

4.7 ERG cost effectiveness conclusions

The company has now been able to provide evidence to address the NICE Appraisal Committee concerns around the uncertainty associated with DMFS, duration of pembrolizumab treatment effect and subsequent therapies. The key area of uncertainty remains the absence of long-term OS data from the KEYNOTE-054 trial. Additional OS data are now available from the SACT database. The SACT data support the view that the company model pembrolizumab OS estimates remain implausible. Furthermore, a comparison of company model routine surveillance OS estimates with Gershenwald/AJCC[7] data shows that company model estimates routine surveillance arm may be too pessimistic.

Due to the way that the company model is constructed, it is not possible for the ERG to make modifications to generate more plausible OS estimates for patients receiving pembrolizumab and routine surveillance treatments. For example, the only way to generate more plausible estimates for the routine surveillance arm would be to reduce the mortality rate for patients in the DM health state; however, this would result in increased survival for patients in the pembrolizumab arm, where, in the ERG's opinion, survival is already over-estimated.

The ERG considers that the company's estimated ICERs per QALY gained are unreliable. The company model over-estimates OS for patients receiving pembrolizumab (by [redacted] over the first 18 months of the model time horizon compared with SACT data) and under-estimates OS for patients receiving routine surveillance (compared with Gershenwald/AJCC[7] data). This results in company ICERs per QALY gained being under-estimated (i.e., favouring pembrolizumab). As the ERG is not able to make modifications to the company model, the magnitude of the under-estimate cannot be quantified. The ERG is unable to produce ICERs per QALY gained that are more reliable than those presented by the company.

5 REFERENCES

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 17 September** using the below 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.

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

Issue 1 Absence of Overall Survival data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 8, Issue 1 – Final OS data from the KEYNOTE-054 trial will be informative	'Final OS data from the KEYNOTE-054 trial will be informative, **however these are not expected to be available until approximately [redacted]. The company has provided scientific rationale to explain why OS could not be provided.'**	MSD flagged to NICE in 2019 that OS data would not be available for the CDF Review and were advised to proceed to submit without OS data from KEYNOTE-054. The rationale for not being able to provide the OS information has been discussed in detail in the company submission document. The proposed amendments provide more context for the Appraisal Committee to consider during the Appraisal Process.	The confidential dates in the proposed amendment were not available to the ERG at the time the ERG report was submitted to NICE and, therefore, changes to the ERG report cannot be made. The ERG highlights that, [redacted]% of OS events need to have occurred before the KEYNOTE-054 trial OS data can be analysed. The company suggests that this proportion of deaths will not occur until [redacted] (i.e., [redacted]). However, the company model projects that [redacted]% of the population will be dead at the end of [redacted].
Page 15, box 3 – 'The company has not provided any KEYNOTE-054 trial OS K-M data'	'The company has not **been able to provide** any KEYNOTE-054 trial OS K-M data. **This was communicated to NICE by MSD in 2019**.'	MSD flagged to NICE in 2019 that OS data would not be available for the CDF Review and were advised to proceed to submit without OS data from KEYNOTE-054. In addition, the rationale for not being able to provide the OS information was discussed in detail in the company submission document.	Communications between NICE and the company in 2019 were not shared with the ERG. Therefore, suggested changes to the ERG report have not been made. However, the ERG is aware that the company highlighted to NICE and the ERG (in the company engagement form) that KEYNOTE-054 trial OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		The proposed wording is the same as the first sentence of the last paragraph on page 15.	data would not be available to inform this CDF Review. The following text has been added to the ERG report (p15): "The ERG is aware that the company highlighted to NICE and the ERG (in the company engagement form), that KEYNOTE-054 trial OS data would not be available to inform this CDF Review."
Page 15 – 'During the original appraisal, the Appraisal Committee concluded that the survival benefit associated with pembrolizumab could not be confirmed without OS data from the KEYNOTE-024 trial.'	'During the original appraisal, the Appraisal Committee concluded that the survival benefit associated with pembrolizumab could not be confirmed without OS data from the KEYNOTE-0**5**4 trial. **NICE were made aware in 2019 that OS data from KEYNOTE-054 would not be available in time for CDF Review**.'	Please correct the typographical error in the spelling of KEYNOTE-054. MSD flagged to NICE in 2019 that OS data would not be available for the CDF Review and were advised to proceed to submit without OS data from KEYNOTE-054. In addition, the rationale for not being able to provide the OS information was discussed in detail in the company submission document. To ensure the full context of the appraisal is evident, it should be captured in the report that NICE were aware that OS would not be available and MSD were advised to submit based on updated DMFS only. Please amend	Typographical error corrected. The ERG was not aware of discussions between the company and NICE that took place in 2019. The following additional text has been added to the ERG report (p15): "The ERG is aware that the company highlighted to NICE and the ERG (in the company engagement form) that KEYNOTE-054 trial OS data would not be available to inform this CDF Review."

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		the statement to provide additional context.	
Page 19 – 'Uncertainty around OS cannot be resolved until after the final analysis of KEYNOTE-054 trial OS data and/or mature SACT data are available'	'Uncertainty around OS cannot be **fully** resolved until after the final analysis of KEYNOTE-054 trial OS data. **However, the company presented data from KEYNOTE-053/SWOG-S1404 which provide additional evidence on the effectiveness of pembrolizumab in the adjuvant setting**."	MSD have highlighted in our response to clarification questions A1 and A5 the recent availability of OS data for pembrolizumab from the KEYNOTE-053/SWOG-S1404 Phase III RCT. The results of this trial provide a good indication of the OS results that could be expected with adjuvant pembrolizumab in KEYNOTE-054. These data provide robust evidence that reduce the uncertainty around the effect of adjuvant pembrolizumab on OS. Therefore, the sentence should be updated to reflect that evidence is available that contributes to partially resolving the uncertainty. In addition, mature SACT data will not resolve the remaining uncertainty given the differences in the characteristics of the patient cohorts between SACT and KEYNOTE-054 (BRAF mutation status, age and fitness), and further data collection within SACT is not possible under the current framework. Please amend the sentences to offer additional context around all the available evidence for OS with adjuvant pembrolizumab.	The ERG's statement is not factually inaccurate. No change required. The relevance of the KEYNOTE-053 trial/SWOG S1404 data are of limited relevance because they are only available as a presentation and therefore have not been peer reviewed. With the level of detail available it is not possible to make comparisons. The ERG highlights that KEYNOTE-053 trial results indicate that it is possible to have a statistically significant improvement in RFS but no statistically significant improvement in OS. The absence of KEYNOTE-054 trial OS data is of concern. An adjusted analysis of KEYNOTE-053 trial RFS and OS data could be informative. Longer-term data from the SACT dataset will help resolve uncertainty around OS for NHS patients treated with pembrolizumab. Only KEYNOTE-054 trial data can resolve

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
			uncertainty around the OS gain for pembrolizumab versus routine surveillance.
Page 21, Box 8 – 'OS data from the KEYNOTE-054 trial were not available'	'OS data from the KEYNOTE-054 trial were not available. **This was communicated to NICE by MSD in 2019**.'	MSD flagged to NICE in 2019 that OS data would not be available for the CDF Review and were advised to proceed to submit without OS data from KEYNOTE-054. In addition, the rationale for not being able to provide the OS information has been discussed in detail in the company submission document.	The ERG was not aware of discussions between the company and NICE that took place in 2019 and, therefore, no change can be made to the ERG report. The following additional text has been added to the ERG report (p15): "The ERG is aware that the company highlighted to NICE and the ERG (in the company engagement form) that KEYNOTE-054 trial OS data would not be available to inform this CDF Review."
Page 21 – 'Instead OS estimates are generated indirectly through 'RFS to death' events and 'DM to death' events'	'Instead, OS estimates are generated indirectly **as a function of all transition probabilities in the model (i.e. OS is a model output)**'	OS is estimated based on transitions to death from all model health states including 'LR to Death', not just 'RFS to death' and 'DM to death' (see CDF Review CS). Note that KEYNOTE-054 data are used to inform transitions to death from all health states, with the exception of 'DM to death'.	The ERG has made the suggested change.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 25 – 'The key area of uncertainty remains the absence of long-term OS data from the KEYNOTE-054 trial. Additional OS data are now available from the SACT database. The SACT data support the view that the company model pembrolizumab OS estimates remain implausible.'	Please add a note to highlight the key differences between SACT and KEYNOTE-054 datasets which explain deviations in model projections (see above). Please also include discussion of the KEYNOTE-053/SWOG-S1404 Phase III trial which provides observed OS estimates for pembrolizumab from a comparable patient cohort. Data from this trial can be used to validate the OS projections for pembrolizumab and they demonstrate that the OS projections in the model are closely aligned with trial data for pembrolizumab.	The lack of context around the SACT dataset can lead to misinterpretation of model projections. MSD have highlighted in our response to clarification questions A1 and A5 the recent availability of OS data for pembrolizumab from the KEYNOTE-053/SWOG-S1404 Phase III RCT. The results of this trial provide a good indication of the OS results that could be expected with adjuvant pembrolizumab in KEYNOTE-054, as the characteristics of the patient cohorts are highly comparable. The observed OS for pembrolizumab in KEYNOTE-053/SWOG-S1404 is very closely aligned with the OS projections predicted for pembrolizumab in the model over 3 years, supporting the validity of the projections for pembrolizumab. Please make the proposed changes to avoid misinterpretation of the evidence.	This is not a factual inaccuracy. No change required.

Issue 2 Unreliable OS estimates for Pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 8 – 'For patients treated with pembrolizumab, over the first 18 months of the company model time horizon, the company model mortality rate estimate was [redacted]% lower than the rate experienced by patients treated with pembrolizumab and registered in the SACT database ([redacted]% versus [redacted]%). This shows that after 18 months (i.e., 3.3% of the 46 year model time horizon), the company model is already generating OS estimates that are higher than those for NHS patients.'	'For patients treated with pembrolizumab, over the first 18 months of the company model time horizon, the company model mortality rate estimate was [redacted]% lower than the rate experienced by patients treated with pembrolizumab and registered in the SACT database ([redacted]% versus [redacted]%). This shows that after 18 months (i.e., 3.3% of the 46 year model time horizon), the company model is already generating OS estimates that are higher than those for NHS patients. **However, there are key differences in the characteristics of the patients in SACT vs KEYNOTE-054 which the company discussed in the submission and may in part explain this.'**	There are significantly fewer BRAF mutation positive patients (who have an additional treatment option and therefore better prognosis) in the SACT cohort than in KEYNOTE-054 (19% vs 47.5%). In addition, patients in the SACT cohort are older and less fit (64 vs 54 years and ECOG PS 0 69% vs 94.4%) than patients in KEYNOTE-054, therefore OS is expected to be lower for patients in SACT than the patients in the trial. Using only the SACT data to validate the OS projections for pembrolizumab is therefore biased against pembrolizumab. The differences in patient characteristics should be stated in this paragraph to ensure that the SACT data are taken in context with their limitations, and thus avoiding the misinterpretation of available evidence. Finally, the model applies conservative assumptions by not adjusting DMFS for patients who crossed over from placebo to adjuvant pembrolizumab after locoregional recurrence.	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 8 – 'The company model should be modified to reflect available SACT data.'	Please remove this statement as it is misleading.	This request is not feasible. Data on RFS and DMFS are not available from SACT, therefore it is not possible to conduct a competing risks analysis and include OS data from SACT in the model. In addition, this would require conducting a matching adjusted indirect comparison to ensure imbalances between populations are accounted for, which is not feasible given patient-level data from SACT are not available to MSD.	This is the ERG's opinion, not a factual inaccuracy. No change required.
Page 21 – 'At 18 months, 10% of patients treated with pembrolizumab and registered in the SACT database had died and the company model mortality estimate was 5.8%, i.e., over the first 18 months, the company model mortality rate estimate was 42% lower than the rate experienced by NHS patients. This shows that after 18 months (i.e., 3.3 % of the 46 year model time horizon), the company model is already generating OS estimates that are higher than those for NHS patients.'	Please include discussion of the KEYNOTE-053/SWOG-S1404 Phase III trial which provides observed OS estimates for pembrolizumab from a comparable patient cohort. Data from this trial (provided at the ERG clarification response stage) can be used to validate the OS projections for pembrolizumab and they demonstrate that the OS projections in the model are closely aligned with trial data for pembrolizumab. Please also include a sentence to note the differences between the SACT and KEYNOTE-054 patient cohorts, which are likely to impact observed OS (i.e.	This paragraph is misleading, as it only mentions the SACT dataset and therefore implies that the SACT data are the only source that can be used to validate the OS projections for pembrolizumab. This is not true. MSD have highlighted in our response to clarification questions A1 and A5 the recent availability of OS data for pembrolizumab from the KEYNOTE-053/SWOG-S1404 Phase III RCT which can also be used to validate the pembrolizumab projections. There are significantly fewer BRAF mutation positive patients (who have an additional treatment option and therefore better prognosis) in the SACT	Typographical error corrected. No other changes required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	BRAF mutations, age and ECOG status). Please also correct the spelling of pembrolizumab in the first sentence.	cohort than in KEYNOTE-054 (19% vs 47.5%). In addition, patients in the SACT cohort are older and less fit (64 vs 54 years and ECOG PS 0 69% vs 94.4%) than patients in KEYNOTE-054, therefore OS is expected to be lower for patients in SACT than the patients in the trial. Using only the SACT data to validate the OS projections for pembrolizumab is therefore biased against pembrolizumab. The differences in patient characteristics should be stated in this paragraph to ensure that the SACT data are taken in context with their limitations. Whilst there are some differences in disease staging, the baseline characteristics of the patients in KEYNOTE-053/SWOG-S1404 are broadly aligned with those in KEYNOTE-054. The results of this study therefore provide a good indication of the OS that may be expected with adjuvant pembrolizumab in KEYNOTE-054. The trial is a more appropriate validation source than SACT as the patient characteristics are more closely aligned and indicates that the modelled OS projections are valid.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 25 – 'For example, the only way to generate more plausible estimates for the routine surveillance arm would be to reduce the mortality rate for patients in the DM health state; however, this would result in increased survival for patients in the pembrolizumab arm, where survival is already over-estimated.'	'For example, the only way to generate more plausible estimates for the routine surveillance arm would be to reduce the mortality rate for patients in the DM health state; however, this would **also** result in increased survival for patients in the pembrolizumab arm.'	It is the ERG's opinion that survival with pembrolizumab is overestimated, not a statement of fact, and this opinion is not supported by the evidence from KEYNOTE-053/SWOG-S1404. This part of the statement should therefore be removed.	Text added to clarify that the statement is the ERG's opinion. "…; however, this would result in increased survival for patients in the pembrolizumab arm, where, **in the ERG's opinion**, survival is already over-estimated."
Page 25 – 'The company model over-estimates OS for patients receiving pembrolizumab (by [redacted]% over the first 18 months of the model time horizon compared with SACT data)'	Please also include discussion of the KEYNOTE-053/SWOG-S1404 Phase III trial which provides observed OS estimates for pembrolizumab from a comparable patient cohort. Data from this trial can be used to validate the OS projections for pembrolizumab and they demonstrate that the OS projections in the model are closely aligned with trial data for pembrolizumab. Please present where appropriate this dataset when discussing the model validation. Please also include a sentence to note the differences between the SACT and KEYNOTE-054 patient cohorts which are likely to impact observed OS (i.e. BRAF status, age and ECOG status).	This paragraph is misleading, as it does not mention the OS data for pembrolizumab from the KEYNOTE-053/SWOG-S1404 Phase III RCT which can also be used to validate the pembrolizumab projections. There are significantly fewer BRAF mutation positive patients (who have an additional treatment option and therefore better prognosis) in the SACT cohort than in KEYNOTE-054 (19% vs 47.5%). In addition, patients in the SACT cohort are older and less fit (64 vs 54 years and ECOG PS 0 69% vs 94.4%) than patients in KEYNOTE-054, therefore OS is expected to be lower for patients in SACT than the patients in the trial. The differences in patient characteristics should be stated in this	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		paragraph to ensure that the SACT data are taken in context with their limitations. The results of KEYNOTE-053/SWOG-S1404 provide a good indication of the OS that may be expected with adjuvant pembrolizumab in KEYNOTE-054. This trial is a more appropriate validation source than SACT as the patient characteristics are more closely aligned. Please make the suggested edits to reflect the totality of the evidence submitted.	

Issue 3 Unreliable OS estimates for Routine Surveillance

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 9 – 'The ERG considers that the company analysis of data presented by Gershenwald (Gershenwald/AJCC) is the most appropriate dataset to use to validate company model OS estimates for patients receiving routine surveillance. A comparison of company model and Gershenwald/AJCC estimates shows that company model OS estimates are pessimistic and that	'A comparison of company model and Gershenwald/AJCC estimates shows that company model OS estimates are pessimistic **compared with the Gershenwald/AJCC data** and that the level of pessimism increases over time. **However, the company's OS projections have been validated with UK clinical experts**'	It is the ERG's opinion that the modelled OS estimates are pessimistic, not a statement of fact. It should be clarified that the projections appear pessimistic versus the AJCC data (not necessarily pessimistic versus what is seen in clinical practice or versus other sources). The ERG does not provide any rationale to support their opinion that the Gershenwald/AJCC source is now the	For clarity, the text in the ERG report has been amended as follows: "A comparison of company model and Gershenwald/AJCC estimates shows that company model OS estimates are pessimistic **compared with the Gershenwald/AJCC data** and

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
the level of pessimism increases over time.'		most appropriate of the available sources to validate the model OS projections. Without discussing the merits of the other sources this summary is unbalanced and precludes a transparent assessment of the suitability of all sources. We have raised several concerns regarding the generalisability of the AJCC data to the patients included in the KEYNOTE-054 trial in the CDF Review CS which limits the credibility of the AJCC study as an appropriate validation source. In addition, the model OS projections have been validated by UK clinical experts who felt the projections were reasonable – this should also be stated for transparency.	that the level of pessimism increases over time."
Page 21 – 'The company considered that the 'ERG composite model' was the most informative.'	'The company considered that the 'ERG composite model', **and the EORTC-18071 and COMBI-AD trials were useful sources to validate the model projections.**' Please update the paragraph to reflect discussion of all the sources MSD considers relevant for validation to appropriately reflect our submission.	This statement does not reflect MSD's submission (CDF review CS, page 65-66). We have not stated which external source we consider to be most informative but have presented a comprehensive discussion comparing the routine surveillance OS projections against several external sources which all have merit. We have highlighted that the ERG composite curve aligns reasonably well with the observed OS from EORTC-	Additions (and deletions) to the ERG report have been made as follows: "The company considered that the 'ERG composite model', **and the EORTC-18071 and COMBI-AD trials were useful sources to validate the model projections.**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		18071, which offers some credibility to this curve as the characteristics of patients in this trial are comparable to those in KEYNOTE-054. However, we have also highlighted that the OS estimates for routine surveillance are closely aligned with the observed OS from the placebo arm of the COMBI-AD trial. Note that the 'ERG composite curve' was the primary source utilised by the ERG in TA553 to assess the validity of the OS projections in the model, despite the Gershenwald/AJCC study having been published in 2017 (prior to TA553). It is therefore appropriate to consider the 'ERG composite curve' in the CDF review to demonstrate how the estimates compare to the dataset previously used to benchmark the projections.	**Of the data sources considered by the company, the ERG** considers that the company analysis based on the data presented by Gershenwald (Gershenwald/AJCC[7]) is the most appropriate as it includes the most up-to-date registry data of any of the data sources considered as well as data from trials considering immunotherapies that are now routinely used in NHS clinical practice."
Page 22 – 'The company has raised concerns about the applicability of their Gershenwald/AJCC analysis and the ERG has addressed key concerns in Table 7.' 'Table 7 Company concerns and ERG comment relating to the	'The company has raised **several** concerns about the applicability of **the** Gershenwald/AJCC analysis and the ERG has addressed **some of these** concerns in Table 7.' 'Table 7 **Selected** company concerns and ERG comment relating to the **use of Gershenwald/AJCC analysis to validate OS projections'**	MSD has raised seven key concerns relating to the use of AJCC data to validate the OS projections. The current sentence is misleading as is it does not communicate the extent of the concerns raised by MSD and implies that all of the issues raised by MSD are addressed by the ERG in Table 7, which is not the case.	ERG report has been amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
company Gershenwald/AJCC analysis'		The table header should also be updated to reflect that only a selected subset of the concerns raised by MSD in relation to the use of AJCC data are addressed in the table, to ensure that the table is viewed in context. In addition, MSD have not raised concerns about our analysis of Gershenwald/AJCC data, but rather of the data source itself being an inappropriate source to validate the model projections. Please amend the sentence accordingly.	
Page 22 – Company concern: 'The analysis included patients with Stage IIIA disease' ERG comment: 'The company analysis based on data available from Gershenwald/AJCC is adjusted for the inclusion of patients with Stage IIIA disease'	Please remove this row from the table or update the row to reflect the concern presented in the company submission.	This row does not reflect the concern raised by MSD in the submission (CDF review CS, p70) which states: *"KEYNOTE-054 did not include stage IIIA patients with <1mm metastases in the lymph nodes. Patients with <1 mm metastases in the lymph nodes have significantly better OS than patients who have ≥1 mm metastases in the lymph nodes. The SEER and AJCC reflect real-world practice and are likely to include patients with <1 mm metastases, thus increasing the OS for stage III patients overall."* The issue raised by MSD related specifically to the exclusion from KEYNOTE-054 of patients with <1mm	Row removed as requested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		metastases in the lymph nodes. Approximately 50% of stage IIIA patients have been estimated to have <1mm metastases [1]. These patients have been shown to have significantly better survival than patients with ≥1 mm metastases in the lymph nodes, and therefore the AJCC OS estimates could be overestimating the survival of patients in KEYNOTE-054.	
Page 22 – 'All-cause general population mortality estimates indicate that for patients aged 56-65 years (i.e., over the first 10 years of the model time horizon) all-cause mortality would only account for approximately 8% of deaths. In contrast, for patients in the routine surveillance arm, results from the company model indicate that [redacted]% of patients had died by 10 years. The majority of the mortality in the company model is, therefore, melanoma-specific'	'All-cause general population mortality estimates indicate that for patients aged **54-63** years (i.e., over the first 10 years of the model time horizon)…' Please amend the remainder of the paragraph to clarify the meaning and update the 8% figure to reflect the correct age bracket under consideration in the model. Please change [redacted]% to [redacted]% to reflect the model.	The starting age in the model is 54 years, therefore the 10-year age range of the model cohort would be 54-63 years. This overall statement is not clear. We believe it is intending to state that the proportion of the general population who are alive at age 54 (i.e. start of model) who would be dead by age 63 due to all-cause mortality is 8%. However, please clarify. Further, the model shows that [redacted]% of patients had died by 10 years – please correct this. Please note that the model has not been developed to differentiate between melanoma-specific mortality and other causes of mortality, therefore it is not possible to determine the proportion of deaths in the model attributed to	The numbers in the ERG report have been changed as suggested. No other changes have been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		melanoma-specific causes. However, it remains true that the use of melanoma-specific mortality from AJCC will provide higher OS estimates than if all-cause mortality was considered (as is considered in the model).	
Page 22 – 'A comparison of the company model with Gershenwald/AJCC7 OS data is shown in Figure 2 and shows that the company model OS estimates for the routine surveillance arm are pessimistic and that the level of pessimism increases over time.'	'A comparison of the company model with Gershenwald/AJCC OS data is shown in Figure 2 and shows that the company model OS estimates for the routine surveillance arm are pessimistic **compared with the Gershenwald/AJCC data** and that the level of pessimism increases over time. **However, the company have raised concerns regarding the generalisability of the Gershenwald/AJCC data to the KEYNOTE-054 trial, and have validated the modelled OS projections with UK clinical experts and a number of alternative data sources.**'	It is the ERG's opinion that the OS projections are pessimistic, not a statement of fact. It should be clarified that the projections appear pessimistic versus the AJCC data (not necessarily pessimistic versus what is seen in clinical practice). We have raised several concerns regarding the generalisability of the AJCC data to the patients included in the KEYNOTE-054 trial in the CDF Review CS which limits the credibility of the AJCC study as an appropriate validation source. In addition, the model OS projections have been validated by UK clinical experts who felt the projections were reasonable – this should also be stated for transparency.	The ERG report has been changed as follows: "A comparison of the company model with Gershenwald/AJCC OS data is shown in Figure 2 and shows that the company model OS estimates for the routine surveillance arm are pessimistic **compared with the Gershenwald/AJCC data** and that the level of pessimism increases over time."
Page 22 – 'Of the other data sources considered by the company, the ERG considers that the company analysis based on data presented by Gershenwald	Please provide justification to explain why the Gershenwald/AJCC source is now considered the most appropriate.	MSD has presented several external sources that can be used to validate OS projections. We acknowledge that all these sources have some limitations but consider that they should all be presented and discussed for full	Justification for why the Gershenwald/AJCC source is considered the most appropriate is included in the ERG report on

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
(Gershenwald/AJCC7) is the most appropriate'… Figure 2 OS estimates for patients receiving routine surveillance (company model and Gershenwald/AJCC)	Please include in Figure 2 all sources presented by MSD to validate the modelled OS projections. Please add a footnote to the figure to define the abbreviations (MSS and OS) to ensure the results are taken in context. Please also highlight that the curves presented compare MSS vs Overall Survival (not necessarily melanoma-specific) and that these are not necessarily directly comparable.	transparency. This is not reflected anywhere in the relevant sections of the ERG report. The ERG does not provide any rationale to support their opinion that the Gershenwald/AJCC source is now the most appropriate of the available sources to validate the model OS projections. At the same time the ERG does not discuss the extended model validation conducted which includes their originally proposed composite OS curve based on SEER data (as well as the Gershenwald/AJCC *et al* 2017 study). Without discussing the merits of the other sources this summary is unbalanced and precludes a transparent assessment of the suitability of all sources identified by the reader. In addition to the concerns raised by MSD in the CDF Review CS, the Gershenwald/AJCC OS data may be considered implausible as the OS is significantly higher than all the other key sources available to validate the routine surveillance arm (EORTC-18071, ERG composite curve and COMBI-AD), and also higher than the OS observed with pembrolizumab in SACT. This will be clearly demonstrated when all sources are viewed on the same figure.	p22 (see ERG response to Issue 3). Footnotes to Figure 2 have been added as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		All sources should therefore be displayed and discussed for transparency.	
Page 23 – 'The company model estimate for the average survival of patients who are eligible for treatment with an immunotherapy in the metastatic setting ranges between [redacted] and [redacted] years ([redacted] and [redacted] weeks)'	'The company model estimate for the average survival of patients in the metastatic setting is [redacted] years ([redacted] weeks) in the adjuvant pembrolizumab arm.'	The base case model uses subsequent treatment distributions from the 'IO-eligible' category only, and assumes that all patients are eligible for immunotherapy (although the proportion of patients who will get immunotherapy in the metastatic setting is determined by the market share distributions). The calculations to convert weeks to years should be corrected to reflect the exact number of weeks in a year.	No change required.

Issue 4 RFS and DMFS treatment effect duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 23 – 'The KEYNOTE-054 trial RFS and DMFS K-M data show that the risks of first recurrence and distant metastasis respectively in the pembrolizumab arm were lower than the risks in the routine surveillance arm from time zero to month 36 and the risks in both	Please clarify the sentence.	This statement appears to be contradictory, as it implies that the risk of recurrence with pembrolizumab vs routine surveillance is both lower and equal from month 24 to month 36 which is implausible.	For clarity, the ERG report has been changed as follows: "The KEYNOTE-054 trial RFS and DMFS K-M data show that the risks of first recurrence and distant metastasis respectively in the pembrolizumab arm were lower than the risks in the routine

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
arms were approximately equal from month 24 onwards'			surveillance arm from time zero to month 36 **but** the risks in both arms were approximately equal from month 24 onwards"
Page 23 – 'This suggests that, for patients who are permitted a maximum of 12 months of treatment (KEYNOTE-054 trial protocol), RFS benefit endures for a period of between 24 and 36 months from commencement of treatment'	Please delete the sentence as it is misleading in the absence of scientific evidence.	Please note that most recurrences for stage III melanoma occur in the first 1–2 years post-surgical resection. After this point the rate of recurrence reduces significantly with very few recurrences occurring after 5 years of RFS [2]. Consequently, we would expect to observe very few recurrences after the recurrence rate plateaus. As such, the plateau observed in the RFS KM curves may not be indicative of loss of treatment benefit with pembrolizumab. The rate of recurrence in both arms is very low beyond this point and therefore the benefit cannot be observed in the data due to the sample size. Specifically, a much larger sample size would be needed to detect a benefit given the low event rate during later follow-up. However, it is clinically reasonable to consider that the benefit of pembrolizumab still persists with longer follow up after complete resection. Finally, scientific literature indicates that there is a durable separation of curves	This is the ERG's opinion. No change to the ERG report required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		for RFS, DMFS and OS from other adjuvant studies compared to observation with longer follow up [3, 4], which is also seen in KEYNOTE-054. Therefore, we consider this statement to be both factually incorrect and misleading given the available data.	
Page 23-24 – 'Data presented in **Error! Reference source not found.** and **Error! Reference source not found.** show the risk (in 6-month time bands) of experiencing a first recurrence and a distant metastasis respectively…' Table 8 and Table 9	Please provide an explanation on how the risk of recurrence over time has been estimated.	It is not clear how the ERG has calculated the risk of recurrence in these tables which means it is difficult to interpret and validate them.	Footnotes have been added to Table 8 and Table 9 as follows. Source: ERG calculations based upon the percentage of people having a first recurrence between different time periods divided by the percentage of people at risk of having a first recurrence at the start of the period Source: ERG calculations based upon the percentage of people having a distant metastasis between different time periods divided by the percentage of people at risk of having a distant metastasis at the start of the period
Page 24 – 'Over-estimating the RFS and DMFS benefit for patients receiving pembrolizumab results in the company model generating cost	Please ensure the statement is specific and also considers the conservative assumptions which bias against pembrolizumab.	This statement is overly broad and does not take into account the conservative assumptions that are utilised in the model that bias in favour of routine surveillance. Most notably, the model	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
effectiveness results that are biased towards pembrolizumab'		does not account for crossover from the placebo arm to adjuvant pembrolizumab in KEYNOTE-054 for patients who had a locoregional recurrence and does not apply the treatment costs associated with this crossover. As such, DMFS in the routine surveillance arm is likely to be overestimated and the relative benefit with adjuvant pembrolizumab underestimated.	

Issue 5 Other textual clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 8, 15, 16 The company expects the final OS analysis will take place in [redacted].	Please change the estimated date of final analysis to '[redacted]	The modelling used to estimate when the number of OS events required to conduct the OS analysis will be reached necessary for a final analysis has been revised to [redacted]. Please update the report to reflect the current estimates.	The confidential dates in the proposed amendment were not available to the ERG at the time the ERG report was submitted to NICE and, therefore, changes to the ERG report cannot be made.
Page 14 – clinical advice to the ERG is that approximately 20% of NHS patients are likely to be less fit (ECOG PS 2 or 3) than those participating in the KEYNOTE-054	Clinical advice to the ERG is that approximately 20**% of all stage III melanoma** NHS patients are likely to be less fit (ECOG PS 2 or 3) than those **who received pembrolizumab** in the KEYNOTE-054 trial (ECOG PS 0: 94.4%;	The percentage of patients in the SACT report with a PS status recorded as PS 0-1 was 99.8% (n=1,208).	The text has been amended as follows: "… clinical advice to the ERG is that approximately 20% of patients with Stage III

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
trial (ECOG PS 0: 94.4%; ECOG PS 1: 5.6%)	ECOG PS 1: 5.6%). **In line with the Blueteq registration form, only patients who have a PS of 0 or 1 can be prescribed pembrolizumab.**	The Blueteq form states only patients PS0-1 can be prescribed pembrolizumab [5]. Therefore, the SACT report and KEYNOTE-054 (100%) have a similar percentage of patients who are PS0-1. The 20% referenced is for all melanoma patients not those who had received pembrolizumab. The 94.4% and 5.6% figures are for those who received pembrolizumab in KEYNOTE-054 rather than the whole trial cohort.	melanoma treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than patients participating in the KEYNOTE-054 trial (ECOG PS 0: 94.4%; ECOG PS 1: 5.6%) or who contributed data to the SACT data set (only patients who had an ECOG PS of 0 or 1 were eligible to receive pembrolizumab)."
Page 15 – '…could not be confirmed without OS data from the KEYNOTE-024 trial.'	'…could not be confirmed without OS data from the KEYNOTE-**054** trial.'	This is a typo. The trial name should be KEYNOTE-054, not KEYNOTE-024.	Typographical error corrected.
Page 15 – Section 3.3.1 Updated KEYNOTE-054 trial results: RFS, DMFS and OS	Please include reference the PRFS2 data provided by MSD in the CDF Review CS which further demonstrates the clinical benefit of adjuvant pembrolizumab.	MSD have given rationale to explain why OS data are not available. Data on PRFS2 were also provided in the CDF Review CS as supplementary evidence in support of the benefit of adjuvant pembrolizumab in the absence of available OS data from KEYNOTE-054. This should be discussed in this section for a complete and transparent overview of the available evidence provided to support the submission.	This is not a factual inaccuracy. No change required to the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		Please note that PRFS2 data should be treated as Commercial in Confidence.	
Page 24 – 'The ERG notes that encorafenib+binemetanib was not a recommended subsequent treatment combination at the time of the original appraisal and the company has now included this treatment in their model'	'The ERG notes that encorafenib+binemetanib was not a recommended subsequent treatment combination at the time of the original appraisal and the company has now included this treatment in their model **based on advice from UK clinical experts'**	Encorafenib + binimetinib was included in the CDF review CS based on advice from UK clinical experts to ensure the costs of subsequent treatments appropriately reflect clinical practice. Note that if encorafenib + binimetinib is removed from the model and those patients are assumed to receive dabrafenib + trametinib instead, the ICER increases by approximately £100.	Text amended as suggested.
Page 25 – 'The ERG considers that the company's estimated ICERs per QALY gained are unreliable.'	Please revise the sentence to reflect the evidence presented, including the extensive scenario analyses conducted.	MSD have presented extensive scenario analyses and one-way sensitivity analyses to explore the reliability of the ICER. In all relevant scenarios, the ICER remained below the £30,000 WTP threshold. Therefore we consider this statement to be misleading.	The text represents the ERG's opinion. No change to the ERG report required.
Page 25 – 'The SACT data support the view that the company model pembrolizumab OS estimates remain implausible.'	Please revise the statement to reflect that model projections have been validated by UK clinical experts, and that there are key differences in the patient	MSD have presented extensive model validation and have highlighted key differences in the patient characteristics between SACT and KEYNOTE-054. In addition, the survival projections for both arms	This is not a factual inaccuracy. No change required to the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	characteristics between SACT and KEYNOTE-054.	have been validated by UK clinical experts. Please add this note to the cost effectiveness conclusion.	
Page 25 – 'being under-estimates'	Please change to 'being underestimated'.	Please correct the typographical error.	Typographical error corrected.

References

1. van der Ploeg AP, van Akkooi AC, Rutkowski P, Nowecki ZI, Michej W, Mitra A, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and Dewar topography criteria. J Clin Oncol. 2011;29(16):2206-14.
2. Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol. 2010;28(18):3042-7.
3. Dummer R, Hauschild A, Santinami M, Atkinson V, Mandalà M, Kirkwood JM, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. N Engl J Med. 2020;383(12):1139-48.
4. Eggermont AMM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. Eur J Cancer. 2019;119:1-10.
5. NHS England. National Cancer Drugs Fund list, version 1.187 2021 [Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 13 October 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Absence of any KEYNOTE-054 OS K-M data	**YES** **(New analyses on evidence already submitted at the ERG clarification question stage)**	As explained in the company submission, the overall survival (OS) endpoint analysis for KEYNOTE-054 is event driven. Patients are living longer than predicted, therefore deaths are accruing more slowly than anticipated. As such, the pre-specified number of death events required for analysis of OS has not been reached and is currently expected to occur in [redacted] based on the latest forecasting. MSD flagged to NICE in 2019 that OS data from KEYNOTE-054 would not be available for the Cancer Drugs Fund (CDF) Review and were advised to proceed and submit based on the latest distant metastases-free survival (DMFS) evidence only (final analysis), without OS data from KEYNOTE-054. It should also be noted that the OS data from KEYNOTE-054 are likely to be confounded by the crossover nature of the trial design. In the routine surveillance arm, [redacted] patients who had a LR recurrence crossed over to receive pembrolizumab, which is expected to improve survival in the routine surveillance arm. **<u>KEYNOTE-053/SWOG-S1404 data are highly relevant to decision-making</u>** MSD acknowledges that the absence of OS data from KEYNOTE-054 does present uncertainty. However, the availability of OS data for adjuvant pembrolizumab from the KEYNOTE-053/SWOG-S1404 Phase III randomised controlled trial (RCT) [1] helps to reduce this uncertainty. Despite small differences in staging (KEYNOTE-053/SWOG-S1404 enrolled some stage IV patients), the baseline characteristics are highly comparable between the two trials. Results from this trial [redacted] In the absence of data from KEYNOTE-054, the results from KEYNOTE-053/SWOG-S1404 should be considered highly relevant to this appraisal regardless of current publication status.

To supplement the KEYNOTE-053/SWOG-S1404 trial data presented at ASCO [1], MSD have provided additional evidence with this response that offers further detail on the recurrence-free survival (RFS) and OS results observed in KEYNOTE-053/SWOG-S1404 for the **stage III subgroup of patients who were pre-specified to have ipilimumab as control** ("Additional KEYNOTE-053/SWOG-S1404 analysis"), to assist with comparison of the KEYNOTE-054 trial results and reduce uncertainty. These data are based on the March 2021 data cut (3.5 years after the last patient was randomised) and comparison with the KEYNOTE-054 trial shows that:

- The baseline characteristics of the KEYNOTE-054 and KEYNOTE-053/SWOG-S1404 trial populations are highly comparable (Table 1), with the only deviation between the populations observed in BRAF mutation status. The high proportion of patients with 'Unknown' BRAF status in KEYNOTE-053/SWOG-S1404 reflects that BRAF mutation testing was not required by the study protocol. However, note that adjuvant pembrolizumab provides treatment benefit regardless of BRAF status.

Table 1: KEYNOTE-053/SWOG-S1404 baseline patient characteristics vs KEYNOTE-054 – stage III pre-specified ipilimumab control subgroup

Characteristic, n (%)	KEYNOTE-053/SWOG-S1404		KEYNOTE-054
	Ipilimumab	Pembrolizumab	
	(N=[redacted])	(N=[redacted])	(N=1,019)
Age			
Mean	[redacted]	[redacted]	53.7
Median	[redacted]	[redacted]	54.0
Min, Max	[redacted]	[redacted]	(19, 88)
Standard Deviation	[redacted]	[redacted]	13.9
<50 years	[redacted]	[redacted]	379 (37.2)
50 to <65 years	[redacted]	[redacted]	389 (38.2)
=>65 years	[redacted]	[redacted]	251 (24.6)

		Stage (AJCCv7)			
		Stage IIIA(N2a)	[redacted]	[redacted]	160 (15.7)
		Stage IIIB	[redacted]	[redacted]	467 (45.8)
		Stage IIIC	[redacted]	[redacted]	392 (38.4)
		PD-L1 Status			
		Indeterminate	[redacted]	[redacted]	50 (4.9)
		PD-L1+	[redacted]	[redacted]	853 (83.7)
		PD-L1-	[redacted]	[redacted]	116 (11.4)
		ECOG PS			
		PS0	[redacted]	[redacted]	960 (94.2)
		PS1	[redacted]	[redacted]	59 (5.8)
		BRAF Status			
		BRAF+	[redacted]	[redacted]	506 (49.7)
		BRAF-	[redacted]	[redacted]	449 (44.1)
		Unknown	[redacted]	[redacted]	64 (6.3)
		Sex			
		F	[redacted]	[redacted]	391 (38.4)
		M	[redacted]	[redacted]	628 (61.6)
		Ulceration			
		Yes	[redacted]	[redacted]	405 (39.7)
		No	[redacted]	[redacted]	481 (47.2)
		Unknown	[redacted]	[redacted]	133 (13.1)
		Number of positive lymph nodes			
		0	[redacted]	[redacted]	0
		1	[redacted]	[redacted]	464 (45.5)
		2 or 3	[redacted]	[redacted]	340 (33.4)

4 or more	[redacted]	[redacted]	215 (21.1)
Not Reported	[redacted]	[redacted]	0
Type of lymph node involvement			
Macroscopic	[redacted]	[redacted]	674 (66.1)
Microscopic	[redacted]	[redacted]	345 (33.9)
Not reported	[redacted]	[redacted]	0

- The observed RFS curve for pembrolizumab in KEYNOTE-053/SWOG-S1404 is very closely aligned with the RFS observed in KEYNOTE-054 (Figure 1).

Figure 1: Comparison of observed RFS with pembrolizumab from KEYNOTE-054 and KEYNOTE-053/SWOG-S1404, stage III pre-specified ipilimumab control subgroup

[redacted]

		Comparison of baseline characteristics and RFS results indicates that KEYNOTE-053/SWOG-S1404 and KEYNOTE-054 enrolled similar patient populations and observed similar RFS outcomes. On this basis, it is plausible that the KEYNOTE-053/SWOG-S1404 OS data is a highly appropriate validation source for pembrolizumab in KEYNOTE-054, and therefore the OS results available from KEYNOTE-053/SWOG-S1404 provide a robust indication of the OS results that could be expected with adjuvant pembrolizumab in KEYNOTE-054. Further, KEYNOTE-053/SWOG-S1404 provides OS data for adjuvant pembrolizumab up to 60 months, with mature data up to 3.5 years and is therefore the only source to provide OS data beyond 18 months in the absence of OS data from KEYNOTE-054. The results of this trial are therefore highly relevant for decision-making. The ERG has noted that KEYNOTE-053/SWOG-S1404 reports a significant RFS benefit for pembrolizumab but a non-significant benefit for OS. However, this interpretation of the OS evidence from KEYNOTE-053/SWOG-S1404 does not account for the following considerations: • The protocol pre-specified that final analysis of RFS and OS should take place when the targeted number of survival events (n=374) had occurred, or at 3.5 years after the last patient was randomised, whichever occurred soonest. At 3.5 years, only 199/374 (53%) of targeted OS events had occurred [1], therefore the OS endpoint analysis was still immature and was underpowered to detect a statistically significant difference. • KEYNOTE-053/SWOG-S1404 compared adjuvant pembrolizumab versus an active comparator (ipilimumab or high dose interferon), rather than versus placebo as in KEYNOTE-054 (and in this appraisal). • In the CheckMate-238 trial, OS analysis at 4 years showed nivolumab reduced the risk of death by 13% versus ipilimumab, although this was not statistically significant when analysed at 73% of the survival events needed for an adequately powered analysis [2]. In KEYNOTE-053/SWOG-S1404, pembrolizumab reduced the risk of death by 16%. However, this also did not meet the pre-specified level of significance when analysed at 53% of the targeted survival events.

		While the OS results for KEYNOTE-053/SWOG-S1404 (which are indicative of a trend in OS benefit) remain immature, the study remains highly relevant for the purposes of this appraisal. The only other source of OS data for pembrolizumab is the SACT cohort. While OS data from SACT provide some evidence for the OS, differences in patient characteristics (see response to Issue 2) mean these do not resolve the uncertainty around the OS projections. Further, SACT cannot address the relative OS treatment effect of pembrolizumab versus routine surveillance. **KEYNOTE-053/SWOG-S1404 ITC** To estimate the relative effect of adjuvant pembrolizumab in KEYNOTE-054 versus routine surveillance, alongside this response MSD has conducted an indirect treatment comparison (ITC) using data from KEYNOTE-053/SWOG-S1404 and the EORTC-18071 trial of adjuvant ipilimumab versus placebo. To maximise comparability between the trials, data from KEYNOTE-053/SWOG-S1404 were obtained for stage III patients only, and further restricted to the subgroup of patients who were pre-specified to receive ipilimumab as the control treatment. The ITC showed that adjuvant pembrolizumab [redacted]. **PRFS2 analysis from KEYNOTE-054** Further, MSD have also presented data from the PRFS2 analysis in KEYNOTE-054, which show that [redacted] Finally, the value of adjuvant therapies and the benefit to patients of remaining relapse-free for an extended period should be reiterated: patients are effectively free

		from any residual disease and can experience a normal quality of life. Pembrolizumab has demonstrated a durable, statistically significant benefit in RFS over an extended median follow-up of 45.5 months. Pembrolizumab also demonstrated a statistically significant improvement in DMFS, meaning patients are less likely to develop distant metastases which are associated with poor survival outcomes and more complex and costly healthcare management. Therefore, as a consequence of delaying disease recurrence, patients treated with adjuvant pembrolizumab have the opportunity to experience a high quality of life for longer than patients under routine surveillance, and it is highly plausible that an improvement in OS could also be observed as supported by RCT evidence with other adjuvant therapies [2, 3].
Key issue 2: Company cost utility model does not generate reliable OS results for patients receiving pembrolizumab	**YES**	**<u>Validation sources</u>** The ERG substantiate this claim based on comparison of the modelled pembrolizumab OS projections with the OS data for pembrolizumab observed in the SACT cohort. However, there are important differences in the patient characteristics between the KEYNOTE-054 and SACT cohorts which limit the relevance of the SACT data for validating the OS estimates: • **BRAF status**: Fewer patients had positive BRAF mutation status in SACT compared with KEYNOTE-054 (19% vs 47.5%, respectively). BRAF mutation positive patients may receive additional targeted treatment options for metastatic disease [4] and therefore are likely to have better survival outcomes • **Age**: Patients in SACT were older than in KEYNOTE-054 (64 years vs 54 years, respectively) • **Fitness**: Patients in SACT were less fit than in KEYNOTE-054 (ECOG PS 0: 69% vs 94.4%, respectively) Given these differences in prognostic factors, it is logical to expect lower OS in SACT compared with KEYNOTE-054, and to conclude that the SACT data do not provide a good indication of the OS expected with pembrolizumab in KEYNOTE-054. It is also therefore expected that the model's OS projections for pembrolizumab are higher than those seen in SACT.

		In contrast, the baseline characteristics of patients in KEYNOTE-053/SWOG-S1404 are highly comparable to the patients in KEYNOTE-054, and the observed RFS curve for pembrolizumab in KEYNOTE-053/SWOG-S1404 is very closely aligned with the RFS observed in KEYNOTE-054 (Figure 1). MSD have provided OS data for the stage III ipilimumab-control subgroup from this trial, further increasing the comparability. As such, OS data from KEYNOTE-053/SWOG-S1404 are likely to provide a good indication of the OS that can be expected with pembrolizumab in KEYNOTE-054, and this trial is therefore an important source to validate the model's OS estimates for pembrolizumab. As such, this trial should be given full consideration as a validation source. Comparison of the observed OS from KEYNOTE-053/SWOG-S1404 with the predicted OS for pembrolizumab in the model in fact reveals a very close alignment in the first 3.5 years (the point to which mature OS data are available), offering confidence that the model projections, in the short term at least, are robust. After 3.5 years the data are not fully mature, but it is plausible that the model does underpredict long term OS versus the KEYNOTE-053/SWOG-S1404 data (Figure 2); this should be considered conservative.

		Figure 2: Comparison of predicted OS for pembrolizumab versus external validation sources  Abbreviations: OS, overall survival. Note also that the OS projections presented in the submission are estimated from a combination of parametric functions used to model RF→LR, RF→DM (Generalised gamma and Gompertz, respectively) and the PFS/OS from the DM health state. Whilst OS is a model output, its long-term projections over time have been validated by UK clinical experts who deemed them to be reasonable (see A15.2 – Validation page 66 of CS). **<u>Exploratory scenarios</u>** As stated in the Company submission and as noted by the ERG, the OS estimates in the model are a function of all other health state transitions and therefore the OS projections cannot easily be modified in isolation to explore the impact of OS on the cost-effectiveness results.

In line with the guidance in NICE DSU TSD 14 [5], the same combination of parametric functions is used in both treatment arms of the model (RF→LR, Generalised gamma; RF→DM, Gompertz).

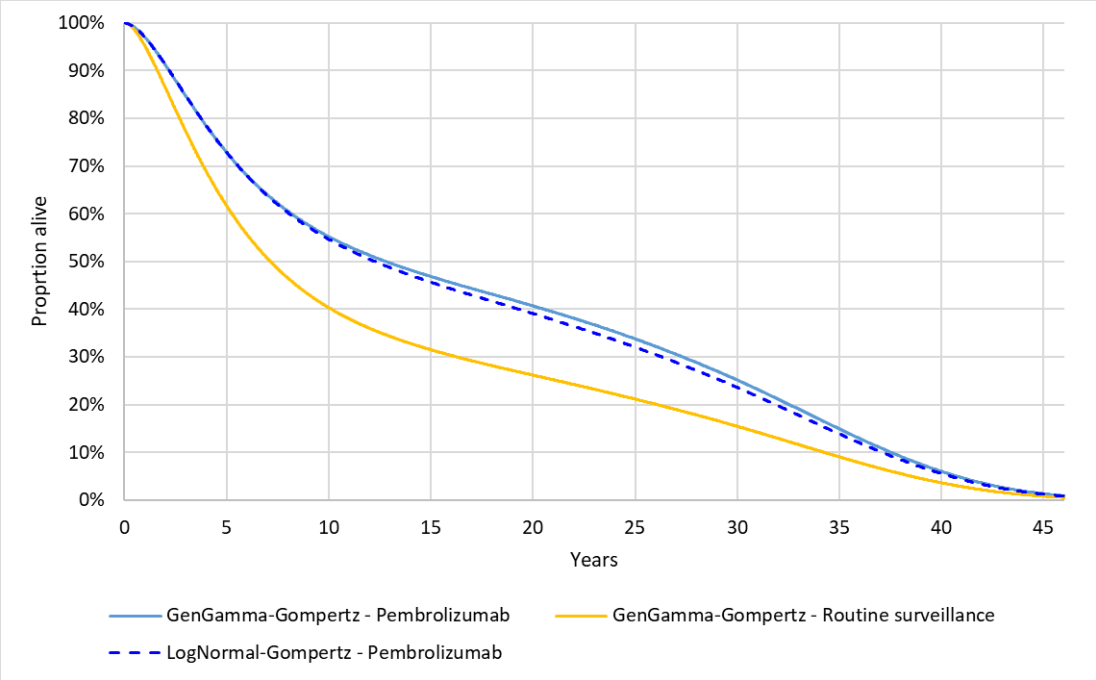
However, MSD recognise that given the absence of OS data from KEYNOTE-054 there remains some uncertainty as to the OS benefit with pembrolizumab. Therefore we conducted a scenario analysis in which a more pessimistic (but still clinically plausible based on clinical expert opinion) combination of parametric functions was applied in the **pembrolizumab arm only** (Table 2; Figure 3). To achieve this within the current model structure, it was necessary to fit a different combination of curves to each arm (in contrary to NICE Decision Support Unit [DSU] Technical Support Document [TSD] 14 guidance), leading to a greater plateau in the routine surveillance arm compared with pembrolizumab which is likely to be unrealistic.

Table 2: Scenario A, conservative pembrolizumab – varying combination of parametric functions

Scenario	Pembrolizumab		Routine surveillance		ICER (£/QALY)
	RF→LR	RF→DM	RF→LR	RF→DM	
Base case	Gen Gamma	Gompertz	Gen Gamma	Gompertz	9,357
Scenario A	Lognormal	Gompertz	Gen Gamma	Gompertz	12,231

Abbreviations: DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LR, locoregional; QALY, quality-adjusted life year; RF, recurrence-free.

Figure 3: Scenario A, conservative pembrolizumab: Long term OS projections with alternative parametric function combinations



Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario.

Note that this scenario also affects the extrapolations for RFS and DMFS; however, it demonstrates that reducing long-term RFS, DMFS and OS for pembrolizumab only slightly increases the ICER.

Key issue 3: Company cost utility model does not generate reliable OS results for patients receiving routine surveillance	**YES**	**Validation sources** MSD has presented a comprehensive discussion of several external sources that can be used to validate the OS projections for routine surveillance. All external sources and datasets have some limitations, however the COMBI-AD and EORTC-18071 trials, and the composite curve previously developed by the same ERG, all have merit and should be taken into consideration. As stated in the company submission, all OS projections for both arms have been validated by UK clinical experts and were deemed to be clinically reasonable. In addition, the hazard ratio (HR) generated by the ITC of KEYNOTE-053/SWOG-S1404 and EORTC-18071 ([redacted]) can be applied to the Kaplan-Meier OS data for pembrolizumab from KEYNOTE-053/SWOG-S1404 to estimate the Kaplan-Meier OS for routine surveillance. This estimated OS curve based on the ITC results is closely aligned with the OS curve predicted by the model for routine surveillance (Figure 4).

		Figure 4: Predicted OS curve for routine surveillance versus estimated OS from ITC of EORTC-18071 and KEYNOTE-053/SWOG-S1404  Abbreviations: ITC, indirect treatment comparison; OS, overall survival. The ERG considers that the Gershenwald/AJCC data are the most appropriate to validate the routine surveillance OS projections. However, MSD have raised several important concerns with this dataset that limits its suitability and must be taken into account: • Gershenwald/AJCC data are from the point of diagnosis of stage III melanoma, rather than treatment initiation – in practice there is a delay between diagnosis, resection, and treatment initiation which will lower the OS seen in KEYNOTE-054 • KEYNOTE-054 excluded stage IIIA patients with <1mm metastases in the lymph nodes, who have much better OS than those with ≥1mm metastases whereas Gershenwald/AJCC is highly likely to include this patient group. As

		patient-level data from the Gershenwald/AJCC dataset are not available, it is not possible to make appropriate adjustments • Gershenwald/AJCC data relate to melanoma-specific survival, whereas the model considers overall survival • Gershenwald/AJCC survival reflects data only for patients for who all relevant covariates are known, which may distort the data towards better survival • The OS presented in Gershenwald/AJCC is substantially higher than in all other sources with available OS data for routine surveillance (i.e. COMBI-AD, EORTC-18071, ERG composite curve; Figure 5) • **In addition, OS data from Gershenwald/AJCC also exceeds the OS curves observed with active adjuvant treatment in CheckMate238 and SACT (Figure 6).** This indicates that the dataset is unlikely to represent the same population being considered in this appraisal. **Consequently, it is clinically implausible to consider SACT the most appropriate source to validate pembrolizumab OS while simultaneously using Gershenwald/AJCC to validate routine surveillance OS.**

		Figure 5: Predicted OS curve for routine surveillance versus external sources (including ITC of EORTC-18071 and KEYNOTE-053/SWOG-S1404)  Abbreviations: ERG, evidence review group; MSS, melanoma-specific survival; ITC, indirect treatment comparison; OS, overall survival.

		Figure 6: Predicted OS curves for pembrolizumab versus external sources (including comparison with Gershenwald/AJCC for routine surveillance)  Abbreviations: MSS, melanoma-specific survival; OS, overall survival. As discussed in the response to Issue 2 above, KEYNOTE-053/SWOG-S1404 is a highly relevant source of OS data for adjuvant pembrolizumab and should be the key source used to validate the OS projections for pembrolizumab. MSD have presented some important concerns associated with the Gershenwald/AJCC data which limits the relevance of this dataset as the validation source for routine surveillance and indicates that the OS curve for routine surveillance will be below that reported in the Gershenwald/AJCC publication. There are several other sources, including the KEYNOTE-053/SWOG-S1404 ITC, which are useful for validating the routine surveillance projections.

		However, based on the OS data from KEYNOTE-053/SWOG-S1404, the ITC results, and external sources available for routine surveillance, a durable OS benefit with adjuvant pembrolizumab should be expected regardless of the source used for routine surveillance validation (Figure 5). **<u>Long term OS projections</u>** The ERG have highlighted that the proportion of OS events that need to have occurred to enable analysis of OS in KEYNOTE-054 ([redacted]%) is not forecast to occur until [redacted] (i.e. [redacted] after the initial trial completion date), however the model projects that [redacted] of patients will have died after [redacted]. However, it is important to note the following points: • Firstly, the [redacted] of patients predicted by the model to have died after [redacted] refers to the routine surveillance arm only; as per the KEYNOTE-054 protocol, OS analysis will be conducted once [redacted]% of the *total trial population* events have occurred. The model predicts that [redacted]% of the total population will have died by [redacted], due to a survival benefit for the pembrolizumab arm. • Secondly, MSD acknowledge that, based on the external sources discussed in the submission and presented in Figure 5, long term OS may be underestimated in the model. However, this is true for both treatment arms and based on the external sources a long-term survival benefit with adjuvant pembrolizumab should still be expected. The ITC presented by MSD alongside this response [redacted]. As noted by the ERG, this underprediction results from relatively low survival estimates generated from the DM health state, demonstrated by comparing the average survival in the DM health state with pembrolizumab in the current model compared with the model used in TA366 ([redacted] years vs [redacted] years, respectively). This is an artefact of the memory-less nature of Markov modelling in which transition probabilities at each cycle must only depend upon a patient's current health state and calendar time. As noted by Briggs, Claxton, & Sculpher (2011) [6], the exponential

distribution is commonly used to represent transition probabilities starting from intermediate health states in a Markov cohort model, as the hazard rate does not depend on time since entry into the health state. To use alternative distributions it would be necessary to track time in health state which would require thousands of tunnel states and significantly increase the computational burden of the model. This would not be well justified for this model, particularly given the close alignment between predicted OS using the exponential function and observed OS for pembrolizumab in advanced/metastatic melanoma in the KEYNOTE-006 trial. The exponential function may result in pessimistic long-term projections as it is defined by a single parameter and is therefore less flexible than other functions**.**

However, it is important to reiterate that this limitation applies to both treatment arms (therefore has a limited impact on the overall cost-effectiveness estimates), and to acknowledge that it is an inherent limitation of the model structure that OS curves (which are a model output) cannot be directly adjusted. Extensive scenarios exploring the distribution of different subsequent therapies were presented in the company submission, including in combination with different parametric functions (reproduced in Table 3), to further explore the impact of costs and transitions from this health state.

Table 3: Summary of key scenarios presented in the Company submission

#	Description	ICER
1	Alternative curves: RF→LR Gompertz; RF→DM Gompertz	10,404
	Alternative curves: RF→LR Lognormal; RF→DM Gompertz	8,718
2†	Alternative market shares for treatments of advanced melanoma, Ipsos (unadjusted) – routine surveillance arm	Dominant
3†	Alternative market shares for treatments of advanced melanoma, KOL scenario 1	4,891

		4†	Alternative best-fitting curves (RF→LR Gompertz; RF→DM Gompertz) AND Alternative market shares for treatments of advanced melanoma (Scenario 1 + 2)	537
			Alternative best-fitting curves (RF→LR Lognormal; RF→DM Gompertz) AND Alternative market shares for treatments of advanced melanoma (Scenario 1 + 2)	Dominant

† See Company Submission for full description of scenarios.

Exploratory scenarios

To explore the impact of this potential underprediction of long-term OS on the ICER, we have conducted a series of scenario analyses where parameters affecting long term OS were varied (Scenarios B–E).

Firstly, we conducted scenario analyses in which different combinations of parametric functions for RF→LR and RF→DM were applied to each arm to improve OS for the routine surveillance arm relative to adjuvant pembrolizumab. However as discussed in Issue 2 above, this is not a recommended approach to survival modelling, and this also alters the RFS and DMFS estimates for routine surveillance which confounds the interpretation of the ICER (Table 4).

- Scenario B: A more optimistic combination of parametric functions for RF→LR and RF→DM was applied in the **routine surveillance arm only**. This increases the long-term OS for routine surveillance (Figure 7).
- Scenario C (Combined scenarios A [see Issue 2] + B above; highly pessimistic against adjuvant pembrolizumab considering the nature of modeling assumptions): A more *optimistic* combination of parametric functions for RF→LR and RF→DM was applied in the routine surveillance arm, and a more *conservative* combination of functions was applied in the pembrolizumab arm, further reducing the long term OS benefit with pembrolizumab (Figure 8).

These analyses demonstrate that improving long-term RFS, DMFS and OS for routine surveillance relative to pembrolizumab increases the ICER, but the ICER for adjuvant pembrolizumab remains below the £30,000/QALY threshold. Note that these

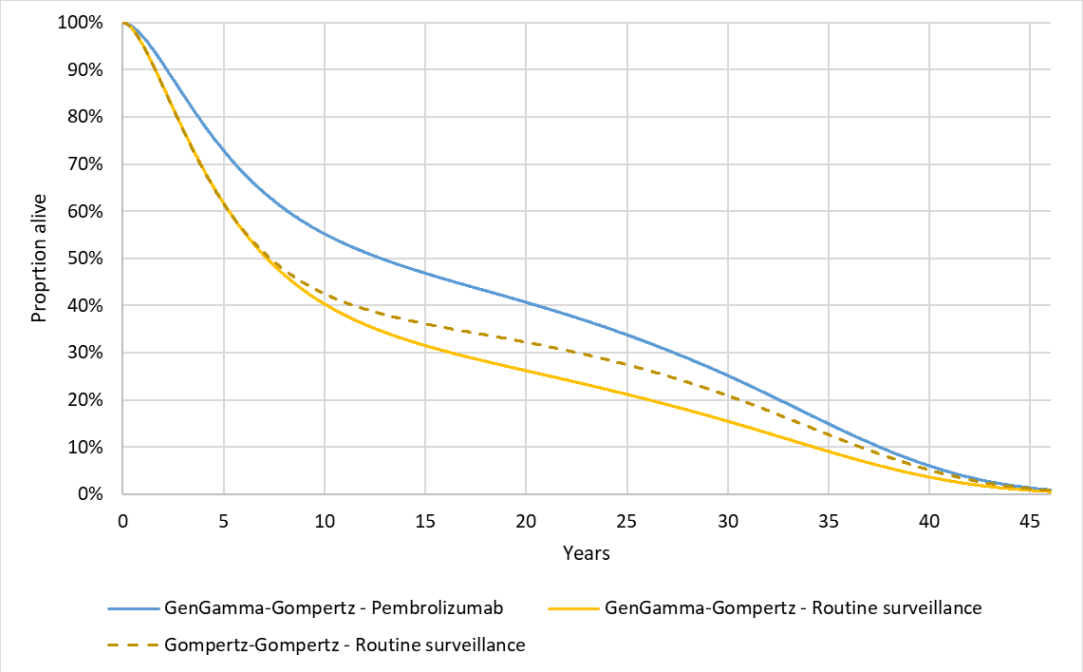
scenarios utilise different parametric functions contrary to NICE DSU guidance, and result in a greater plateau in the routine surveillance arm compared with pembrolizumab which is likely to be unrealistic and clinically implausible.

Table 4: Scenario analysis B–C – varying combination of parametric functions by treatment arm

Scenario	Pembrolizumab		Routine surveillance		ICER (£/QALY)
	RF→LR	RF→DM	RF→LR	RF→DM	
Base case	Gen Gamma	Gompertz	Gen Gamma	Gompertz	9,357
B	Gen Gamma	Gompertz	Gompertz	Gompertz	21,126
C	Log Normal	Gompertz	Gompertz	Gompertz	26,493

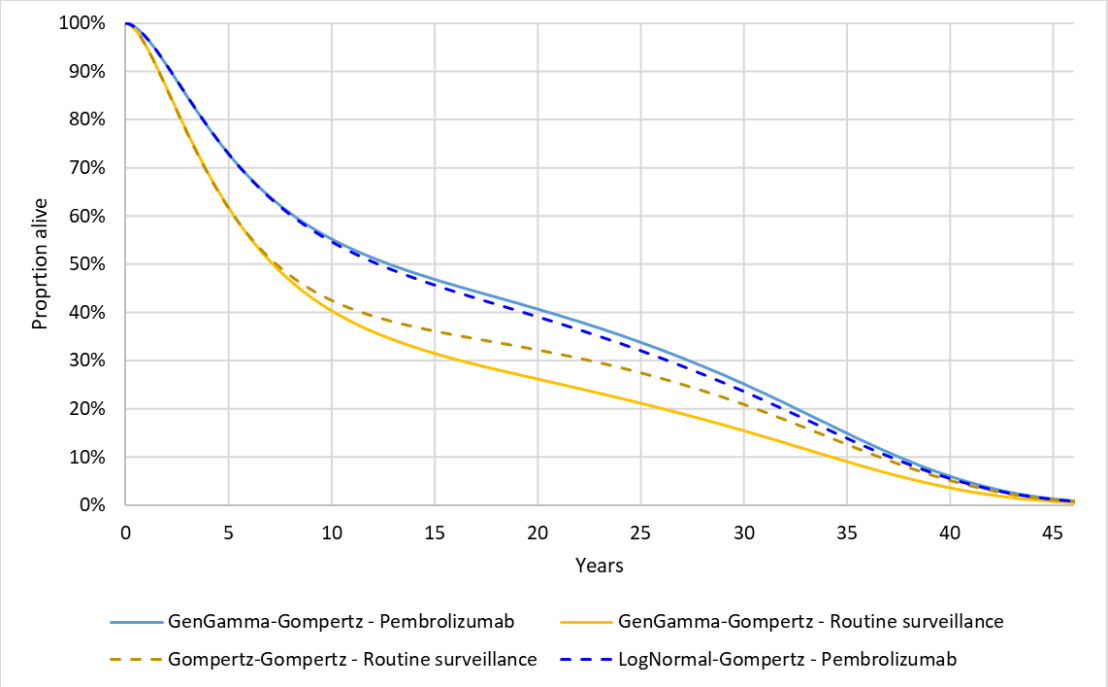
Abbreviations: DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LR, locoregional; QALY, quality-adjusted life year; RF, recurrence-free.

Figure 7: Scenario B, optimistic routine surveillance: Long term OS projections with alternative parametric function combinations



Notes: Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario.

Figure 8: Scenario C, combined effect: Long term OS projections with alternative parametric function combinations



Notes: Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario.

Secondly, we conducted further exploratory analyses that varied the exponential rate used to model OS from the DM health state and thus uplift the OS projections only without affecting the RFS and DMFS estimates. Considering the structure of the model, **this is the most robust and informative approach to explore the impact of increasing survival from the DM health state and thus addressing the underprediction of long-term OS**:

		• Scenario D: We performed a threshold analysis to identify the exponential rate parameter for OS in the DM health state required to result in an average survival of [redacted] years with pembrolizumab in the DM health state, in line with the findings in TA366 – this value is [redacted]. The OS projections observed when this exponential rate is entered into the model are shown in Figure 9. • Scenario E: We also performed a threshold analysis to identify the exponential rate parameter for OS in the DM health state required for the proportion of deaths necessary for OS analysis in KEYNOTE-054 ([redacted]%) to be reached at [redacted], as per current forecasting – this value is [redacted]. The OS projections observed when this exponential rate is entered into the model are shown in • • • Figure 10. • The cost-effectiveness results from these additional scenarios are shown in • •

		• Table 5. In both scenarios, OS curves were higher (and life years increased) in both treatment arms as the exponential rate decreased. However the absolute and proportional improvements in survival were larger in the routine surveillance arm compared with the pembrolizumab arm (absolute improvement in LYs vs base case – Scenario D: pembrolizumab, [redacted] LYs; routine surveillance, [redacted] LYs; Scenario E: pembrolizumab, [redacted] LYs; routine surveillance, [redacted] LYs) and therefore the benefit of adjuvant pembrolizumab on OS was reduced as the exponential rate decreased. In addition, the total costs increased in both arms as survival increased, due to longer time spent on subsequent therapies, but the *incremental cost* for pembrolizumab vs routine surveillance was reduced. • Consequently, as survival increased and the OS treatment benefit of pembrolizumab decreased, in both scenarios the ICER decreased compared with the base case analysis (Scenario D: £9,060/QALY; Scenario E: £8,613/QALY). This demonstrates that adjuvant pembrolizumab remains cost-effective, even as the OS benefit versus routine surveillance decreases. • As seen from Figure 9 and

		• [redacted] • [redacted] • Figure 10, these adjustments effectively indicate that the model now predicts a higher OS in both treatment arms compared with the observed trial data and relevant external sources, the OS benefit with adjuvant pembrolizumab is reduced, and pembrolizumab remains cost-effective. **Figure 9: Scenario D – Predicted OS with exponential rate uplift based on average survival in DM state from TA366 (exponential rate: [redacted]), versus external sources** [redacted]

		Figure 10: Scenario E – Predicted OS with exponential rate uplift based on projected timeframe for OS analysis of KEYNOTE-054 (exponential rate: [redacted]), versus external sources [redacted]

Table 5: Scenario analyses D–E – Cost-effectiveness results in exponential rate uplift scenarios

	Scenario D: Exp rate uplifted so average survival in DM state aligned with KN006 ([redacted] years [[redacted] in base case]; exp [redacted])		**Scenario E: Exp rate uplifted so % dead at 10 years aligned with KN054 projections ([redacted]%; exp [redacted])**	
Outcome	**Pembrolizumab**	**Routine surveillance**	**Pembrolizumab**	**Routine surveillance**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	7.70	[redacted]	8.31
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]	-	[redacted]	-
Incremental QALYs	[redacted]	-	[redacted]	-
Incremental LYs	[redacted]	-	[redacted]	-
ICER (£/QALY)	**9,060**	**-**	**8,613**	

Abbreviations: DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

All of the analyses above address the uncertainty around long term projections for both pembrolizumab and routine surveillance and clearly demonstrate that the intervention remains a cost-effective use of NHS resources. **Scenarios D and E are the most informative to demonstrate the impact that increasing long term survival (i.e. reducing underprediction versus external sources) and reducing**

		the OS benefit of adjuvant pembrolizumab have on the cost-effectiveness results.
Key issue 4: The company assumption that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon is not supported by evidence	**NO**	MSD would like to take the opportunity to address the interpretation of this Issue, reiterate the assumptions used within the cost-effectiveness model for adjuvant pembrolizumab, and to provide additional clarifications regarding the duration of treatment benefit for pembrolizumab in KEYNOTE-054. **<u>Conservative modelling assumptions</u>** Firstly, the model employs the conservative assumption that there is **no ongoing benefit of pembrolizumab after recurrence**, and therefore that the reduced risk of recurrence with pembrolizumab versus routine surveillance is only maintained while patients remain recurrence-free: • PFS and OS in the DM state are informed based only on the distribution of subsequent treatments, not the adjuvant treatment arm, and the transition probabilities from DM to death therefore actually favour routine surveillance. • Although transitions from the LR to DM health state are informed by KEYNOTE-054 data, due to the crossover design of KEYNOTE-054 ([redacted] patients on placebo received adjuvant pembrolizumab after LR recurrence; refer to Table 42 of the Company Submission) transition probabilities from LR→DM and LR→Death also favour the routine surveillance arm of the

		model. This means that the treatment benefit of pembrolizumab (i.e. reduced risk of recurrence) is only maintained for the RF→LR and RF→DM transitions. **It is therefore not accurate to state that 'the effect of pembrolizumab on RFS and DMFS is maintained for the whole model horizon' as this is not the case after recurrence.** It is more accurate to state that **the reduced risk of recurrence with pembrolizumab versus routine surveillance is maintained while patients remain in the RF health state (i.e. for the *RF→LR and RF→DM transitions)*.** The fact that transitions from LR→DM and DM→Death favour routine surveillance is a highly conservative assumption that biases in favour of routine surveillance. As noted above, the conservatism of this assumption results from the lack of adjustment for crossover for patients who received adjuvant pembrolizumab after placebo following LR relapse. **<u>Extended follow-up shows sustained RFS and DMFS benefit</u>** Secondly, longer follow-up data from KEYNOTE-054 have been included within the submission. The RFS results from the later follow up (median follow up 45.5 months) are consistent with the results in the original submission; pembrolizumab demonstrates statistically significant, sustained improvement in RFS over time. The same is observed for DMFS, with a clear separation of the KM curves observed over time despite the high level of cross over from the routine surveillance arm observed in the trial ([redacted] patients with LR recurrence). However, MSD acknowledge the increased censoring in the data from month 40.5 onwards which is the minimum follow up time of the last patient randomised within the study. The ERG noted in their report and in response to the factual accuracy check that, based on the Kaplan-Meier data from KEYNOTE-054, it appears that the risk of first recurrence or distant metastasis was lower from months zero to month 36 for adjuvant pembrolizumab compared with routine surveillance, but that the risk in both arms was approximately equal from 24 months onwards for both RFS and DMFS. Most recurrences for stage III resected melanoma occur in the first 2 years post-surgical resection. After this point the rate of recurrence, regardless of adjuvant treatment, reduces significantly with very few recurrences occurring after 5 years of

		RFS [7, 8]. Consequently, very few recurrences in either treatment arm are expected after the recurrence rate plateaus in KEYNOTE-054. As such, the plateau observed in the RFS KM curves in KEYNOTE-054 may not be indicative of loss of treatment benefit with pembrolizumab. The rate of recurrence in both arms is naturally very low beyond this point and therefore the benefit cannot be observed in the data due to the sample size. Specifically, a much larger sample size would be needed to detect this at longer follow-up. However, it is clinically reasonable to consider that the benefit of pembrolizumab still persists with longer follow up after complete resection, as confirmed by UK clinical experts consulted by MSD [9]. In terms of the cost-effectiveness model, this means that although the relative treatment effect of pembrolizumab (i.e. reduced risk of recurrence) is maintained while patients remain in the RF health state, recurrence rates are substantially lower after the first 2 years such that the absolute difference in patients transitioning to the LR and DM health states after this point is small and therefore the impact on the ICER of an equal risk of recurrence in both arms after a specific time point would therefore be relatively low. **No evidence of non-proportional hazards** Further, following the evidence provided by MSD at clarification questions and the findings reported by Eggermont et al, 2018 [10], the ERG were satisfied that there is no evidence that the RFS hazards in KEYNOTE-054 are not proportional. The RFS HRs over time provided by MSD also demonstrate that the observed HR is largely stable after the first 6 months through to end of follow-up, indicating that the treatment benefit endures. **PRFS2 analysis from KEYNOTE-054** In addition, MSD conducted PRFS2 analysis based on the IA2 data cut, however the ERG did not discuss this evidence within its report. In KEYNOTE-054, PRFS2 was defined as time from randomisation to earliest of: • 1st disease progression after initial unresectable recurrence • 2nd recurrence after resectable 1st recurrence • Death

		Pembrolizumab provided [redacted] [redacted].

Supportive literature

The clinical evidence from KEYNOTE-054 is consistent with other clinical trials and it indicates that there is a durable separation of curves for RFS and DMFS. This has also been consistently observed in other adjuvant melanoma trials including CheckMate238, EORTC-18071 (CA184-029) and the COMBI-AD [2, 3, 11]. Therefore, for the time period for which clinical trial data exists for the use of adjuvant IO therapies, there is no evidence that the treatment effect for RFS or DMFS does not endure beyond adjuvant treatment cessation.

Additional evidence from metastatic melanoma are supportive of a persistent treatment effect. Due to their unique mode of action, immunotherapies have been associated with prolonged survival over time in a subset of patients with metastatic disease across a number of tumours including melanoma. For metastatic melanoma in particular, this “immune-therapeutic effect”, has been characterised across a number of publications by *Schadendorf et al 2016, Robert et al 2019 and Larkin et al 2019* amongst others, all of which demonstrate a prolonged and durable survival benefit [12-15]. Therefore the evidence base from the metastatic melanoma setting is also supportive of an enduring treatment benefit.

		The totality of the clinical evidence in the adjuvant setting from KEYNOTE-054 (RFS, DMFS and PRFS2) alongside evidence from the metastatic melanoma suggests a durable treatment benefit of IO agents. Finally, it is important to reiterate again that modelling assumptions used within this submission are conservative and would be expected to bias against pembrolizumab in terms of cost-effectiveness.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1:	NA	NA	NA
Additional issue 2:	NA	NA	NA

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA

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NICE National Institute for Health and Care Excellence

Technical engagement response

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

Appendix: Additional evidence

Additional KEYNOTE-053/SWOG-S1404 analysis: Stage III, ipilimumab control subgroup

Patients in KEYNOTE-053/SWOG-S1404 were pre-assigned to investigator's choice of high dose interferon (HDI) or ipilimumab and then randomized to receive pembrolizumab or control treatment. The protocol also allowed stage IV patients to be included. To maximise relevance to the decision problem and comparability with the EORTC-18071 trial (see 'KEYNOTE-053/SWOG-S1404 ITC'), only stage III patients pre-assigned to ipilimumab are considered in the data analysis presented here.

Baseline characteristics

Table 1: KEYNOTE-053/SWOG-S1404 baseline patient characteristics vs KEYNOTE-054 – stage III pre-specified ipilimumab control subgroup

Characteristic, n (%)	KEYNOTE-053/SWOG-S1404	
	Ipilimumab	Pembrolizumab
	(N=[redacted])	(N=[redacted])
Age		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]
<50 years	[redacted]	[redacted]
50 to <65 years	[redacted]	[redacted]
=>65 years	[redacted]	[redacted]
Stage (AJCCv7)		
Stage IIIA(N2a)	[redacted]	[redacted]
Stage IIIB	[redacted]	[redacted]
Stage IIIC	[redacted]	[redacted]
PD-L1 Status		
Indeterminate	[redacted]	[redacted]
PD-L1+	[redacted]	[redacted]
PD-L1-	[redacted]	[redacted]
ECOG PS		
PS0	[redacted]	[redacted]
PS1	[redacted]	[redacted]

Characteristic, n (%)	KEYNOTE-053/SWOG-S1404	
	Ipilimumab	Pembrolizumab
BRAF Status		
BRAF+	[redacted]	[redacted]
BRAF-	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Sex		
F	[redacted]	[redacted]
M	[redacted]	[redacted]
Ulceration		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Number of positive lymph nodes		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2 or 3	[redacted]	[redacted]
4 or more	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Type of lymph node involvement		
Macroscopic	[redacted]	[redacted]
Microscopic	[redacted]	[redacted]
Not reported	[redacted]	[redacted]

Recurrence-free survival

Table 2: KEYNOTE-053/SWOG-S1404 RFS analysis, stage III pre-specified ipilimumab control subgroup

Treatment	N	Number of Events (%)	HR‡ (95% CI)	p-Value§
Ipilimumab	[redacted]	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]

Recurrence-free survival is defined as time from randomization to disease recurrence, or death, whichever occurs first.

‡ Based on Cox regression model with treatment as a covariate stratified by Stage (IIIA(N2a), IIIB, IIIC), PD-L1 status (positive, negative, indeterminant) and planned control regimen (high-dose interferon when choice, ipilimumab when choice, high-dose interferon when only choice).

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

(Database Cutoff Date: 19MAR2021).

Table 3: KEYNOTE-053/SWOG-S1404 RFS rate over time, stage III pre-specified ipilimumab control subgroup

	Ipilimumab (N=[redacted])	Pembrolizumab (N=[redacted])

RFS Rate at 6 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 12 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 18 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 24 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 30 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 36 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 42 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 48 Months in % (95% CI)	[redacted]	[redacted]
RFS Rate at 54 Months in % (95% CI)	[redacted]	[redacted]
Recurrence-free survival is defined as time from randomization to disease recurrence, or death, whichever occurs first.		

(Database Cutoff Date: 19MAR2021).

Figure 1: KEYNOTE-053/SWOG-S1404 RFS Kaplan-Meier estimates, stage III pre-specified ipilimumab control subgroup

[redacted]

'FDA-approved regimen' consisted of ipilimumab or high-dose interferon, based on investigator's choice. In this figure, the data have been restricted to patients who were pre-specified, prior to randomisation, to receive ipilimumab as the control regimen.

Overall survival

Table 4: KEYNOTE-053/SWOG-S1404 OS analysis, stage III pre-specified ipilimumab control subgroup

Treatment	N	Number of Events (%)	HR‡ (95% CI)	p-Value§
Ipilimumab Pembrolizumab	[redacted] [redacted]	[redacted] [redacted]	- [redacted]	- [redacted]
Overall survival is defined as time from randomization to death. § One-sided p-value based on log-rank test.				

(Database Cutoff Date: 19MAR2021).

Table 5: KEYNOTE-053/SWOG-S1404 OS rate over time, stage III pre-specified ipilimumab control subgroup

	Ipilimumab (N=[redacted])	Pembrolizumab (N=[redacted])
OS Rate at 6 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 12 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 18 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 24 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 30 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 36 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 42 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 48 Months in % (95% CI)	[redacted]	[redacted]
OS Rate at 54 Months in % (95% CI)	[redacted]	[redacted]
Overall survival is defined as time from randomization to death.		

(Database Cutoff Date: 19MAR2021).

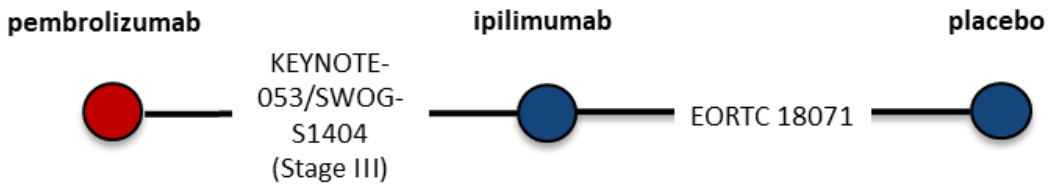
Figure 2: KEYNOTE-053/SWOG-S1404 OS Kaplan-Meier estimates, stage III pre-specified ipilimumab control subgroup

'FDA-approved regimen' consisted of ipilimumab or high-dose interferon, based on investigator's choice; this analysis has been restricted to patients who received ipilimumab in the comparator arm and their pre-specified counterparts in the pembrolizumab arm.

KEYNOTE-053/SWOG-S1404 ITC

MSD conducted an indirect treatment comparison (ITC) to obtain a relative treatment effect estimate for adjuvant pembrolizumab versus placebo, using data from KEYNOTE-053/SWOG-S1404 and EORTC-18071. This analysis is intended to provide an indication of the relative effect of pembrolizumab versus placebo on OS in the absence of OS data from KEYNOTE-054. The network is illustrated in Figure 3.

Figure 3: Network structure



KEYNOTE-053/SWOG-S1404 and EORTC-18071 were similar in terms of study design and inclusion criteria including minimum age for enrolment, maximum ECOG performance status score, disease-free status, and prior therapy. The treatment and dosing schedule for ipilimumab was identical between the two studies. There are however a few differences to note:

- KEYNOTE-053/SWOG-S1404 allowed inclusion of Stage III-IV patients, while EORTC-18071 enrolment was strictly Stage III patients.
- EORTC 18071 enrolled more patients with stage IIIA disease (21%) compared to KEYNOTE-053 ([redacted]) as categorized by AJCC v7.
- EORTC-18071 enrolled only cutaneous melanoma while KEYNOTE-053/SWOG-S1404 also allowed enrolment of mucosal or unknown primary origin melanoma.
    - Primary non-cutaneous melanomas are generally more aggressive than cutaneous.
- EORTC-18071 publications did not report ECOG performance status separately by 0 or 1, or LDH level, PD-L1 status, or BRAF status
- Patients in KEYNOTE-053/SWOG-S1404 were pre-assigned to investigator's choice of high dose interferon (HDI) or ipilimumab and then randomized to receive pembrolizumab or control treatment.

Data from KEYNOTE-053/SWOG-S1404 were obtained for stage III patients only, and further restricted to the subgroup of patients who were pre-specified to receive ipilimumab as the control treatment. This approach was taken to ensure the populations being compared in the ITC were as similar as possible. RFS and OS outcomes were similarly defined, however RFS was investigator-assessed in KEYNOTE-053/SWOG-S1404 and assessed by a blinded independent review committee in EORTC-18071 (Table 6).

Table 6: Definition of reported outcomes

Outcome	KEYNOTE-053/SWOG-S1404	EORTC-18071
Recurrence-free survival / **Relapse-free survival**	Time from date of randomization to date of first documentation of relapse or death due to any cause. Endpoint was investigator assessed.	Time from randomization until the date of first recurrence (local, regional, or distant metastases) or death from any cause. Date of recurrence as assessed by a blinded independent review committee.
Overall survival	Time from date of randomization to date of death due to any cause.	Time from randomization until death from any cause.
Distant metastasis-free survival	Not reported.	Time from randomization until the date of the first distant metastasis or death from any cause. Disease status as assessed by a blinded independent review committee.

An assessment of baseline risk between the two studies showed that patients in the ipilimumab treatment group of KEYNOTE-053/SWOG-S1404 and EORTC-18071 are observed to experience similar RFS. OS for patients in the ipilimumab treatment group of KEYNOTE-053/SWOG-S1404 was greater than observed patients treated with ipilimumab in EORTC 18071 from month 24 onwards, most likely due to developments in the treatment of metastatic disease in recent years.

Bayesian network meta-analysis (NMA) was performed using a model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial. The NMA was conducted with an assumption of proportional hazards which may not reflect changes in the HRs over time. Because only one study informed each connection in the network, a fixed-effects NMA model was used which may underestimate the width of the credible intervals in the presence of between-study heterogeneity. The trials informing the ITC were similar in study design, baseline patient characteristics, and outcome definitions suggesting the ITC was not biased by an imbalance in potential relative treatment effect modifiers.

The results of the ITC are presented in Table 7 and Table 8 for RFS and OS, respectively. Pembrolizumab [redacted]

Table 7: Results of fixed-effects ITC: RFS

Trial	Comparator	Reference	HR (95% CI)	log(HR)	SE	Sample size
EORTC 18071	placebo	ipilimumab	1.32 (1.12, 1.56)	0.27	0.08	476 | 475

Trial	Comparator	Reference	HR (95% CI)	log(HR)	SE	Sample size
KEYNOTE-053/SWOG-S1404	pembrolizumab	ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
ITC†	**pembrolizumab**	**placebo**	[redacted]	**-**	-	-

Abbreviations: CI, confidence interval; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; RFS, recurrence-free survival; SE, standard error.
† DIC: [redacted]; deviance: [redacted]

Table 8: Results of fixed-effects ITC: OS

Trial	Comparator	Reference	HR (95% CI)	log(HR)	SE	Sample size
EORTC 18071	placebo	ipilimumab	1.39 (1.14, 1.72)	0.33	0.11	476 | 475
KEYNOTE-053/SWOG-S1404	pembrolizumab	ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
ITC†	**pembrolizumab**	**placebo**	[redacted]	-	-	-

Abbreviations: CI, confidence interval; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; SE, standard error.
† DIC: [redacted]; deviance: [redacted]

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Clinical expert statement & technical engagement response form

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [IDF3776]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing 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. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **14 October 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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PART 1 – Treating a patient with resected melanoma with high risk of recurrence and current treatment options	
About you	
1. Your name	**Paul Lorigan**
2. Name of organisation	**University of Manchester and Christie NHS Foundation Trust**
3. Job title or position	**Professor of Medical Oncology/Honorary Consultant**
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 resected melanoma with high risk of recurrence? ☒ a specialist in the clinical evidence base for resected melanoma with high risk of recurrence 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)	☒ 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
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for resected melanoma with high risk of recurrence	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of adjuvant therapy is to reduce the risk of recurrence and death from melanoma. Historically, overall survival (OS) was the only accepted endpoint. However for a number of reasons, relapse free survival (RFS) and distant metastasis free survival (DMFS) have become major endpoints in melanoma and most other solid tumours. These include 1) Patients value time without cancer 2) DMFS is a surrogate for OS and also reflects the need for further treatment 3) due to advances in the treatment of melanoma, OS outcomes may not be available for many years after the trial has completed.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	In the adjuvant setting, risk reduction is usually presented as a hazard ratio. This then needs to be converted in to an absolute benefit. A hazard ratio/risk reduction of > 25% reduction in risk of recurrence is usually considered clinically useful for RFS, but the toxicity profile of the intervention also needs to be considered. Smaller values are acceptable for OS

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in resected melanoma with high risk of recurrence?	Yes. Stage3 melanoma is a very heterogeneous disease but many patients have a high risk of developing metastatic disease. For those who that go on to develop metastatic disease, the median expected OS is < 5 years, the majority will still die of their disease. The currently approved adjuvant technologies (pembrolizumab, nivolumab and dabrafenib + trametinib) are major advances in this area, reducing the risk of recurrence by 35-50%. Further advances are needed to 1) identify more effective treatments 2) highlight those who need treatment and those who do not need treatment and are cured by surgery 3) minimise toxicity. Studies are ongoing in all of these areas.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Adjuvant treatment with pembrolizumab, nivolumab or dabrafenib + trmaetinib is considered a standard of care for resected stage 3 and Stage 4 melanoma.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	European Society for Medical Oncology (ESMO), European Association of Dermato Oncology (EADO) and National Comprehensive Cancer Network (NCCN) guidelines all support the use of adjuvant therapy
• 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.)	Pathways of care are well defined in the UK with patients discussed by specialist MDTs and treatment managed along agreed protocols with regular review and assessment mandated by NHS England

• What impact would the technology have on the current pathway of care?	The current technology is already standard of care. It has had major impact on resource use, capacity etc, but this has been largely addressed over the last 3 years.
12. 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?	There is no difference.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology is provided in specialist centres. Approval for treatment is required form NHS England, using the Bluteq forms.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There is little or no extra investment needed at this stage, thought the technology does add a significant burden to stretched resources.
13. Do you expect the technology to provide clinically meaningful	

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	The technology is currently standard of care.
• Do you expect the technology to increase health-related quality of life more than current care?	The technology is currently standard of care
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are certain groups of patients where co-morbidities mean that the technology is not safe to administer e.g. severe autoimmune disease, organ transplant recipients, significant co-morbidities where patients would not tolerate potential toxicities
The use of the technology	
15. 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	There are no new changes. The recent move from 3-weekly to 6-weekly treatment made a significant difference in terms of pressure on services.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing is required and no additional rules need to be applied. Guidelines on monitoring, imaging etc are already in place and adhered to.
17. 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?	The direct costs of treating patients with metastatic disease is substantially higher on a per patient basis than the cost of treating patients in the adjuvant setting (drug costs, treatment duration, investigations, toxicity management etc).
18. 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	It is already standard of care. Further work is now needed to better identify who needs treatment and who does not.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. For years adjuvant studies had little impact on RFS. This technology has shown a clinically meaningful reduction in the risk of recurrence.
• Does the use of the technology address any particular unmet need of the patient population?	Patients value time without relapse, even if the overall outcome is the same. Time spent cancer free is associated with better quality of life.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Quality of life studies Keynote 054 showed no detrimental impact of the tehe technology on QoL (Bottomley et al. Lancet Oncol. 2021 May;22(5):655-664. doi: 10.1016/S1470-2045(21)00081-4. PMID: 33857414). Side effects are an issue and one we need to take very seriously. Stage 3 disease is very heterogenous and the absolute benefit to patients depends on the stage of disease. Furthermore, while the pivotal trial recruited only higher risk Stage 3 disease, the drug was approved in all Stage 3 patients. In addition, there has been a change in staging system (now AJCC version 8) with better outcome for earlier stage disease. This means that patients with lower risk Stage 3 disease have modest absolute benefit but a potential risk of major toxicity. 10-15% of patients stop treatment due to toxicity, often with severe toxicity e.g. colitis. A small number (4-5%) develop life limiting and irreversible endocrine toxicity (diabetes, hypophysitis, adrenalitis) (Higham et al. Eur J Cancer. 2020 Jun;132:207-210. doi: 10.1016/j.ejca.2020.03.016. PMID: 32388064

Sources of evidence	
20. 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?	Distant metastasis free survival is an accurate surrogate for overall survival and reflects clinical benefit. The close correlation of RFS and DMFS in this study suggests it will have an impact on OS.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, please see above.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
21. Are you aware of any relevant evidence that might not be found	The recently presented preliminary results of the Keynote 716 study of pembrolizumab in resected Stage 2 melanoma patients revealed an almost identical outcome i.e. HR for RFS 0.65. (Luke et al. ESMO Sept 2021). The

by a systematic review of the trial evidence?	study had an identical design to Keynote 054 but enrolled patients with resected stage 2b and 2c disease. This supports the finding of Keynote 054 in Stage 3 disease.
22. How do data on real-world experience compare with the trial data?	As highlighted by the ERG, it is difficult to directly compare trial outcomes and real world data. The pivotal trial excluded some high risk patients (intransit mets and satellite metastases) and all lower risk Stage 3 patients (sentinel node tumour deposit <1mm). It also had strict eligibility on PS. Approximately half the patient had a BRAF mutation, which impacts on further treatment options and OS. There was a difference in RFS in BRAF mutated (HR 0.51) and BRAF WT (HR 0.66). The SACT data do not contain any data on stage distribution. Patients were mostly BRAF wildtype, had a worse PS and were older.
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.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Absence of any KEYNOTE- 054 OS K-M data	This is not unexpected. There are 3 other pivotal trials in this scenario and none has yet presented definitive OS data. (CheckMate 238, Combi AD and CheckMate 915). However the following data are available. • EORTC 18071 ipilimumab vs placebo showed a clear survival benefit for ipilimumab over placebo • Checkmate 238 ipilimumab vs nivolumab: early survival data shows no clear survival benefit for nivolumab but need to remember this was against ipilimumab, which shows a survival benefit vs placebo • Combi AD dabrafenib + trametinib vs placebo: preliminary survival data show a survival benefit for adjuvant D+T • Checkmate 915: nivolumab vs modified combo ipilimumab+ nivo showed no difference in RFS, again need to note that this was a comparison of 2 active treatments.

Company cost utility model does not generate reliable OS results for patients receiving pembrolizumab	The RFS and DMFS findings of the Keynote 054 study are very similar to other pivotal studies (Checkmate 238, Combi AD, CheckMate 915) showing that the results from Keynote 054 are not an outlier.
Company cost utility model does not generate reliable OS results for patients receiving routine surveillance	There is a lot of debate about the whether the OS curves for AJCC V.8 are representative of this patient population or are overly optimistic. The data for AJCC V.8 come from 10 large academic centres, they are not population based registry data. There are 3 major publications that report worse outcomes for Stage 3 patients than those reported by AJCC V.8. (Garbe et al. J Clin Oncol. 2020 Aug 1;38(22):2543-2551. doi: 10.1200/JCO.19.03034. PMID: 32530760. Isaksson et al. Annals of Surg Oncol 2019; 26: 2839-45. Kanaki et al. Eur J Cancer. 2019 Sep; 119:18-29. doi: 10.1016/j.ejca.2019.06.011. PMID: 31401470). The study by Isaksson et al. reports data from a population based registry. The others are clinical trial and/or hospital registry based data. To my eye, the survival curves presented for untreated patients Figure 2 in this NICE submission are not those published for AJCC V.8. Figure 2 predicts a 10 year overall survival of 40%, whereas it is 69% in the Gershenwald publication. Perhaps I have misunderstood this.
The company assumption that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon is not supported by evidence	For the Keynote 054 trial, the median FU for PFS was 42 months and median FU for DMFS was 3.5 years. At these time points, there was no suggestion that the curves were coming together for either parameter. Therefore the advantage accrued in the early part of the trial is maintained, suggesting either 1) ongoing immune surveillance due to activation of the immune system or 2) a proportion of patients have been cured with eradication of micro metastatic disease. In the Combi AD study of targeted therapy, the RFS came closer together once the treatment was stopped, suggesting some benefit was lost when drug was stopped, but did not come together completely, suggesting that a proportion of patients may have been cured.

[insert issue as described in ERG report	
[insert issue as described in ERG report	
Are there any important issues that have been missed in ERG report?	Data from the Keynote 716 study of adjuvant pembrolizumab in resected Stage 2 disease showed a similar impact on RFS as Keynote 054 (Luke et al. ESMO 2021).

PART 3 -Key messages

24. In up to 5 sentences, please summarise the key messages of your statement:

- The data from the Keynote 054 study is consistent with 5 other large pivotal studies (CheckMate 238, Combi AD, Keynote 716, CheckMate 915 and EORTC 18071).
- Adjuvant pembrolizumab has a major impact on RFS and DMFS and is a standard of care.
- DMFS is considered a reliable surrogate for OS.
- The AJCC V.8 may overestimate survival for patients on observation.
- There are no new safety signals or other concerns. QoL is not adversely impacted.

Thank you for your time.

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

.....

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [IDF3776]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing 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. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **14 October 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with resected melanoma with high risk of recurrence and current treatment options	
About you	
1. Your name	**Sophie Papa**
2. Name of organisation	**King's College London and Guy's and St Thomas' NHS Foundation Trust**
3. Job title or position	**Clinical Reader in Immune Oncology 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? ☒ a specialist in the treatment of people with resected melanoma with high risk of recurrence? ☐ a specialist in the clinical evidence base for resected melanoma with high risk of recurrence 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)	☒ 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
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for resected melanoma with high risk of recurrence	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to prevent recurrence of disease.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	The primary clinically significant treatment response is the absence of recurrence of melanoma. The secondary clinically significant response is the absence of distant metastatic disease

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in resected melanoma with high risk of recurrence?	Yes. High risk resected melanoma has a high risk of relapse. On relapse patients need further treatment with a mixture of surgery and SACT. SACT can include years of immune therapy and the sue of long term targeted therapy where molecular testing favours that treatment. This is associated with life limiting consequences, cost and complications.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	We currently manage stage III melanoma with primary resection. This is followed with Wide local excision and sentinel lymph node resection where appropriate and acceptable to the patient. This results in complete staging. Stage III melanoma patients are then considered for adjuvant therapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Melanoma Focus. NICE Guidance
• 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 well defined. The most likely area of variability is in the use of completion lymph node dissection. Surgical trials have made this largely redundant but it is occasionally still performed.

• What impact would the technology have on the current pathway of care?	We are currently using pembrolizumab as SOC for stage III resected melanoma. This technology is a component of the management of stage III disease. Its ongoing availability is required for world class melanoma care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	It does not differ
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist melanoma oncology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The technology has been in place for 2 years. This has led, in combination with Dabrafenib and Trametinib and Nivolumab, to a significant increase in workload for melanoma oncology teams. Teams have adapted to increase capacity to manage the demand.
13. Do you expect the technology to provide clinically meaningful	Again, we are currently using pembrolizumab as SOC for BRAF wt melanoma stage III adjuvant treatment. Compared to no access to immune therapy then yes, this treatment with adjuvant pembrolizumab will provide meaningful clinical benefit to our patients.

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes (more than no adjuvant treatment availability)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes as correlates to the absence of recurrence of disease.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Clinical trial data does not offer information on use in ECOG-PS 2 patients. This means that we have uncertainty about benefit in this group. Treatment may be more or less effective in these patients. Similarly, we have no data on the use in patient with auto-immune diseases and as such use in these patients is uncertain from a risk perspective.
The use of the technology	
15. 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	Using adjuvant immune therapy requires infrastructure to enable sufficient clinical time, chair time and provision of management of side effects. This is all in place nationally as we have been using Pembrolizumab for stage III melanoma for 2 years. Whilst on treatment for the year there are more hospital appointments, blood tests adn scans then there would be is patients were on standard follow up.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Consideration is given to stage IIIA melanoma <1mm nodal deposit where there is a shortage of data from clinical trials on the role of adjuvant therapy. Licenses cover the use and this should be discussed with patients on an individual basis. Stopping due to toxicity is based on ASCO and ESMO guidelines on the management of checkpoint inhibitor toxicity.
17. 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
18. 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. The improvement in RFS for pembrolizumab in stage III disease is ground breaking. Especially when compared to marginal benefits for approved agents in similar diseases (breast cancer etc). The relapse rate for stage 3 melanoma is high and the morbidity and mortality associated with relapse is significant burden. This is particularly so for the younger peak in melanoma incidence in the working age population.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. Prior to this technology development this population only had watchful waiting/surveillance.
• Does the use of the technology address any particular unmet need of the patient population?	Currently patients with stage 3 disease are treated with surgical resection and surveillance. This population has a high risk of relapse with local, regional and distant metastatic disease. Relapse is associated with the need for further treatment (surgical, SACT) and significant impact of overall survival. Reducing relapse in this population is a key unmet need. Further to this, we have had access to this technology for two years now and built up clinical experience with safe and effective delivery to address the unmet need in the community.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Checkpoint inhibitors (CPIs) are associated with immune related adverse events (irAEs). This side effects involve inflammation or auto-immunity. Common irAEs occur (fatigue, itching) in a significant minority of patients. The next tier of irAEs include skin rashes, thyroid damage, bowel inflammation and liver inflammation. These occur in <10% patients treated. Finally, anything can happen with any organ potentially affected. Rarer side effects are rare, but can occasionally be very severe (cardiac myositis, neurological complications). Since the initial licensing of CPI therapy 10 years ago the community has developed management approaches to minimise the impact of these irAEs on patient quality of life. Occasionally severe irAEs may occur with associated morbidity.
Sources of evidence	

20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes (except see section 22 about populations)
• If not, how could the results be extrapolated to the UK setting?	Consideration could be given to the data on OS for stage 4 BRAF mutant melanoma. We now know that this population have a superior survival compared BRAF wt disease and this could be factored into the considerations.
• What, in your view, are the most important outcomes, and were they measured in the trials?	RFS is the key outcome. This was measured. OS will be key (and it is being measured) but as the survival outcomes have improved so much for melanoma over recent years we have wait for this result, and interpret it in the light of evolving therapeutic options in the advanced setting.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	RFS is not being used as a surrogate measure, but its relationship to OS in the data is described. This is based on robust data from other clinical situations. I am satisfied that we can be as sure as possible at this point that the remarkable RFS differences we are seeing in these data are going to translate into OS benefit for our patients.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. We understand CPI toxicity well now with over 10 years of licensed use of CPI drugs in melanoma (advanced as well as stage 3 more latterly).
21. Are you aware of any relevant evidence that might not be found	No

by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	There is always a shift between the populations recruited to clinical trials and the reality of clinical practice. This is reflected in the Keynote data and the SACT data. The lower percentage of BRAF mutant patients and the higher age is reflective of current practice. Most teams will favour BRAF+MEK targeted treatment for stage III disease if there is a BRAF mutation.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to my knowledge
23b. Consider whether these issues are different from issues with current care and why.	N/A

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Absence of any KEYNOTE-054 OS K-M data	This is reflecting the improvement in outcomes we have seen in melanoma (reflected in the significant up swing in workload in our clinical practices) in recent years. We are just going to have to be patient for these data and act appropriately on the RFS data we have.
Company cost utility model does not generate reliable OS results for patients receiving pembrolizumab	This section of the ERG I found interesting and challenging. We are in a changing world for OS for melanoma. The AJCC data is based on real world information which favours its utility. It is key to me though that the two data sets overlap each other for the first few years. It is in the longer term projections that we have separation. This is where the uncertainty is greatest in either data set.
Company cost utility model does not generate reliable OS	Ditto to the above.

results for patients receiving routine surveillance	
The company assumption that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon is not supported by evidence	This is a circular comment. We do not have long term data to support RFS and DMFS beyond a few years. So there is no evidence beyond a few years. This is an assumption.
[insert issue as described in ERG report	
[insert issue as described in ERG report	
Are there any important issues that have been missed in ERG report?	I do not think so.
PART 3 -Key messages	
24. In up to 5 sentences, please summarise the key messages of your statement:	

- Adjuvant Pembrolizumab for stage III resected melanoma is effective in significantly improving RFS.
- RFS is a very meaningful endpoint in and of itself for this patient population at this point
- Avoidance of relapse is a key objective for stage III resected melanoma patients.
-
-

Thank you for your time.

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

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Technology appraisal committee A - Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID3776]

POINTS TO NOTE: information relevant to NICE technology appraisal taking place on Tuesday 2nd November 2021 (Diane Cannon, Melanoma UK)

- Melanoma UK is grateful to NICE for the approval of all the treatments that have come along since the days when the only treatment available for melanoma was dacarbazine and radiotherapy.
- Whilst the advancement in treatment options continues to improve, there's still approximately 50% of patients who will still have no treatment option open to them other than watch and wait.
- 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?
- This and future technology is vital for our patients as it gives them hope and an opportunity to live longer.
- The continued success of this treatment could improve a patient's life and although there is a commercial decision to be made, please 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.
- Melanoma UK is keen to represent the patient voice today and would like to share some of the feedback we have received from our patient community – see below.

<u>In a few sentences try to explain what it is like to live with melanoma:</u>

- *"It is an absolute roller coaster! When things are going well you can pretend to be normal and live closer to a normal life, when they aren't your world falls out the bottom!"*
- *"Living with melanoma is a roller coaster ride - from finding strengths I didnt know I had, to experiencing anxiety around scan results and fear of recurrence / further spread. Knowing that my life could very well be cut short due to melanoma is hard to deal with sometimes."*
- *"Unpredictable from scan to scan."*

<u>What has being treated with adjuvant Pembrolizumab meant to you?</u>

- *It is an amazing opportunity to be able to be treated with Pembrolizumab and I am still here to tell you!*
- *Im stage 3C, so high risk for recurrence. I consider myself very fortunate to have had adjuvant Pembrolizumab available to me, to improve my chances of remaining metastases free.*

- *I'm a stage 3 patient currently on adjuvant Pembro treatment (12 months). I have been so grateful to have this treatment to improve the chances of my cancer not coming back. Since diagnosis I have been acutely aware that just a few years ago this would not have been an option for me, I would have just had to watch and wait. Adjuvant treatment gives hope for a return to some normality and is such a recent improvement to the overall treatment options in melanoma.*
- *The adjuvant treatment for stage 3 melanoma patients significantly improves your chances that melanoma won't come back. For so long there was nothing available for stage 3 patients and Pembrolizumab is saving my life.*
- *It means I can spend quality time with my family – I never thought I would have that opportunity so please do not take that away.*
- *It has given me hope for life.*
- *Hope, for me as a single parent, and for the future of everyone dealing with melanoma.*
- *Means I feel like I'm actually being treated rather than left to die.*
- *It has given me a better chance of having a longer life and mentally I am far better for having adjuvant pembrolizumab than just leaving things to chance.*
- *It's given me the best chance of ensuring the cancer doesn't return and knowing that thought gives me and my family something to cling on to.*
- *It has given me hope that it can keep the melanoma at bay to see my boys grow up.*
- *From a physical point of view, having and choosing the option of adjuvant therapy allowed me to VASTLY improve my chances of being here to watch my 2 young children grow up.*
- *Adjuvant Pembro treatment gives me as a stage 3 patient hope for the future.*
- *Without this treatment I wouldn't be here today.*
- *It has given me a future.*

What do you think of the current treatments available for melanoma patients on the NHS?

- *"Treatments available on the NHS for Melanoma have significantly improved but are still very limited - there are several effective and innovative treatments available in other countries that yield great results, but we dont have access to them here."*
- *"I think there should be more options available to patients who are unable to tolerate a treatment. My side effects have been few but even with them, I will tolerate them as they are saving my life."*

If you had to choose one/few words to describe what being on adjuvant Pembrolizumab has meant to you, what would it be?

- *Game changer*
- *HOPE*
- *Lifeline*
- *Life Saver*
- *Life*
- *It's life changing*

Additional comments linked to adjuvant Pembrolizumab that our patients would like the NICE committee to read

- *This is a great treatment and should be made available to all patients who would benefit from it.*
- *The thought that this treatment may not be an option fills me with dread and it would devastate those with this awful disease, myself included. Please don't take away the hope we are clinging on to.*
- *A diagnosis with melanoma is something you cannot understand until it happens to you. A whirlwind of treatment and hospital care begins, the terror you feel is overwhelming, then you are told it's stage 3 and you need to meet with an oncologist, the terror increases. Then the oncologist explains there is a treatment option that will improve the odds in your favour, who wouldn't grab that chance with both hands. Please don't take this option away.*
- *From a financial perspective, adjuvant treatment to prevent stage 3 cancer returning has to be a cheaper option than treatment of stage 4 and all the costs that incurs.*
- *As far as I'm concerned 'Watch and wait' is not a medical option. It's the medical community saying go away and learn to live with the daily pressure of examining your own skin, whilst trying not to be paranoid and live a reasonably 'normal' life. Until you live in that situation I don't think you can comprehend that fear. Every twinge, headache, lump and bump could be cancer. Has it spread? Should I call my doctor? Before I had adjuvant Pembro I was preparing to die. Now I am just living my life.*
- *I understand that all drugs have to make financial sense, but surely for the 25% of people you are saving, and who would then not have to go through multiple more treatments, higher toxicity risk and the hugely underestimated psychological impact, it's worth it. I understand this is only the fiscal impact, but hey if we were looking at what was best for the patient there would be no discussion. Other treatment options, targeted therapies, radiotherapy, gamma knife, chemo and further surgery, along with all the blood tests, scans, supportive medicine to keep side effects at bay, hospital appts and more than likely hospitalisation at times how is this cheaper in the long term?*

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 13 October 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

ERG KEY POINTS

The company response to technical engagement includes a considerable amount of information. The ERG, however, considers that this information does not help resolve the key issue, i.e., that KEYNOTE-054 trial OS data cannot be fully discussed by the NICE Appraisal Committee.

The company predicts that KEYNOTE-054 trial OS data will not be analysed until [redacted]. However, the company model results suggest the number of deaths needed to analyse KEYNOTE-054 trial data should be reached by the end of [redacted]; this means that although the structure of the company model may be appropriate, the outputs from the model are not realistic.

The important issue when assessing the cost effectiveness of pembrolizumab versus routine surveillance is the relative effectiveness (as demonstrated by OS) of the two drugs. This is because OS is the key driver of costs and QALYs. In the company model, OS is an output and can only be altered by adjusting any one of several parameters, including RFS and DMFS, for one or more of the model treatment arms. However, adjustments to these parameters can lead to values that are either not in line with the KEYNOTE-054 trial results, and/or are clinically implausible, and/or are not evidenced. In summary, without access to KEYNOTE-054 trial OS data, neither the company nor the ERG can generate OS estimates, even within the period that trial data are available, that can be demonstrated to be reliable.

The ERG:

- considers that the company model pembrolizumab arm OS projections may be clinically plausible based on results from the KEYNOTE-053 trial; however, KEYNOTE-053 trial pembrolizumab arm RFS results are superior to KEYNOTE-054 trial RFS results and, if there is a direct link between RFS and OS, then this suggests that KEYNOTE-053 trial pembrolizumab OS results would be superior to KEYNOTE-054 trial OS results
- agrees with the company that model base case routine surveillance OS results are likely to be underestimates compared to KEYNOTE-054 trial OS data
- considers that company OS ITC results should not be used to inform decision making as no adjustments were made to account for the differences in subsequent treatments received by patients enrolled in the included trials.

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Absence of any KEYNOTE-054 OS K-M data	**YES** **(New analyses on evidence already submitted at the ERG clarification question stage)**	As explained in the company submission, the overall survival (OS) endpoint analysis for KEYNOTE-054 is event driven. Patients are living longer than predicted, therefore deaths are accruing more slowly than anticipated. As such, the pre-specified number of death events required for analysis of OS has not been reached and is currently expected to occur in [redacted] based on the latest forecasting. MSD flagged to NICE in 2019 that OS data from KEYNOTE-054 would not be available for the Cancer Drugs Fund (CDF) Review and were advised to proceed and submit based on the latest distant metastases-free survival (DMFS) evidence only (final analysis), without OS data from KEYNOTE-054. It should also be noted that the OS data from KEYNOTE-054 are likely to be confounded by the crossover nature of the trial design. In the routine surveillance arm, [redacted] patients who had a LR recurrence crossed over to receive pembrolizumab, which is expected to improve survival in the routine surveillance arm. **<u>KEYNOTE-053/SWOG-S1404 data are highly relevant to decision-making</u>** MSD acknowledges that the absence of OS data from KEYNOTE-054 does present uncertainty. However, the availability of OS data for adjuvant pembrolizumab from the KEYNOTE-053/SWOG-S1404 Phase III randomised controlled trial (RCT) [1] helps to reduce this uncertainty. Despite small differences in staging (KEYNOTE-053/SWOG-S1404 enrolled some stage IV patients), the baseline characteristics are highly comparable between the two trials. Results from this trial [redacted]

[redacted] In the absence of data from KEYNOTE-054, the results from KEYNOTE-053/SWOG-S1404 should be considered highly relevant to this appraisal regardless of current publication status.

To supplement the KEYNOTE-053/SWOG-S1404 trial data presented at ASCO [1], MSD have provided additional evidence with this response that offers further detail on the recurrence-free survival (RFS) and OS results observed in KEYNOTE-053/SWOG-S1404 for the **stage III subgroup of patients who were pre-specified to have ipilimumab as control** ("Additional KEYNOTE-053/SWOG-S1404 analysis"), to assist with comparison of the KEYNOTE-054 trial results and reduce uncertainty. These data are based on the March 2021 data cut (3.5 years after the last patient was randomised) and comparison with the KEYNOTE-054 trial shows that:

- The baseline characteristics of the KEYNOTE-054 and KEYNOTE-053/SWOG-S1404 trial populations are highly comparable (Table 1), with the only deviation between the populations observed in BRAF mutation status. The high proportion of patients with 'Unknown' BRAF status in KEYNOTE-053/SWOG-S1404 reflects that BRAF mutation testing was not required by the study protocol. However, note that adjuvant pembrolizumab provides treatment benefit regardless of BRAF status.

Table 1: KEYNOTE-053/SWOG-S1404 baseline patient characteristics vs KEYNOTE-054 – stage III pre-specified ipilimumab control subgroup

Characteristic, n (%)	KEYNOTE-053/SWOG-S1404		KEYNOTE-054
	Ipilimumab	Pembrolizumab	
	(N=[redacted])	(N=[redacted])	(N=1,019)
Age			
Mean	[redacted]	[redacted]	53.7
Median	[redacted]	[redacted]	54.0
Min, Max	[redacted]	[redacted]	(19, 88)
Standard Deviation	[redacted]	[redacted]	13.9

		<50 years	[redacted]	[redacted]	379 (37.2)
		50 to <65 years	[redacted]	[redacted]	389 (38.2)
		=>65 years	[redacted]	[redacted]	251 (24.6)
		Stage (AJCCv7)			
		Stage IIIA(N2a)	[redacted]	[redacted]	160 (15.7)
		Stage IIIB	[redacted]	[redacted]	467 (45.8)
		Stage IIIC	[redacted]	[redacted]	392 (38.4)
		PD-L1 Status			
		Indeterminate	[redacted]	[redacted]	50 (4.9)
		PD-L1+	[redacted]	[redacted]	853 (83.7)
		PD-L1-	[redacted]	[redacted]	116 (11.4)
		ECOG PS			
		PS0	[redacted]	[redacted]	960 (94.2)
		PS1	[redacted]	[redacted]	59 (5.8)
		BRAF Status			
		BRAF+	[redacted]	[redacted]	506 (49.7)
		BRAF-	[redacted]	[redacted]	449 (44.1)
		Unknown	[redacted]	[redacted]	64 (6.3)
		Sex			

F	[redacted]	[redacted]	391 (38.4)
M	[redacted]	[redacted]	628 (61.6)
Ulceration			
Yes	[redacted]	[redacted]	405 (39.7)
No	[redacted]	[redacted]	481 (47.2)
Unknown	[redacted]	[redacted]	133 (13.1)
Number of positive lymph nodes			
0	[redacted]	[redacted]	0
1	[redacted]	[redacted]	464 (45.5)
2 or 3	[redacted]	[redacted]	340 (33.4)
4 or more	[redacted]	[redacted]	215 (21.1)
Not Reported	[redacted]	[redacted]	0
Type of lymph node involvement			
Macroscopic	[redacted]	[redacted]	674 (66.1)
Microscopic	[redacted]	[redacted]	345 (33.9)
Not reported	[redacted]	[redacted]	0

- The observed RFS curve for pembrolizumab in KEYNOTE-053/SWOG-S1404 is very closely aligned with the RFS observed in KEYNOTE-054 (Figure 1).

Figure 1: Comparison of observed RFS with pembrolizumab from KEYNOTE-054 and KEYNOTE-053/SWOG-S1404, stage III pre-specified ipilimumab control subgroup

		[redacted] Comparison of baseline characteristics and RFS results indicates that KEYNOTE-053/SWOG-S1404 and KEYNOTE-054 enrolled similar patient populations and observed similar RFS outcomes. On this basis, it is plausible that the KEYNOTE-053/SWOG-S1404 OS data is a highly appropriate validation source for pembrolizumab in KEYNOTE-054, and therefore the OS results available from KEYNOTE-053/SWOG-S1404 provide a robust indication of the OS results that could be expected with adjuvant pembrolizumab in KEYNOTE-054. Further, KEYNOTE-053/SWOG-S1404 provides OS data for adjuvant pembrolizumab up to 60 months, with mature data up to 3.5 years and is therefore the only source to provide OS data beyond 18 months in the absence of OS data from KEYNOTE-054. The results of this trial are therefore highly relevant for decision-making. The ERG has noted that KEYNOTE-053/SWOG-S1404 reports a significant RFS benefit for pembrolizumab but a non-significant benefit for OS. However, this interpretation of the OS evidence from KEYNOTE-053/SWOG-S1404 does not account for the following considerations:

		• The protocol pre-specified that final analysis of RFS and OS should take place when the targeted number of survival events (n=374) had occurred, or at 3.5 years after the last patient was randomised, whichever occurred soonest. At 3.5 years, only 199/374 (53%) of targeted OS events had occurred [1], therefore the OS endpoint analysis was still immature and was underpowered to detect a statistically significant difference. • KEYNOTE-053/SWOG-S1404 compared adjuvant pembrolizumab versus an active comparator (ipilimumab or high dose interferon), rather than versus placebo as in KEYNOTE-054 (and in this appraisal). • In the CheckMate-238 trial, OS analysis at 4 years showed nivolumab reduced the risk of death by 13% versus ipilimumab, although this was not statistically significant when analysed at 73% of the survival events needed for an adequately powered analysis [2]. In KEYNOTE-053/SWOG-S1404, pembrolizumab reduced the risk of death by 16%. However, this also did not meet the pre-specified level of significance when analysed at 53% of the targeted survival events. While the OS results for KEYNOTE-053/SWOG-S1404 (which are indicative of a trend in OS benefit) remain immature, the study remains highly relevant for the purposes of this appraisal. The only other source of OS data for pembrolizumab is the SACT cohort. While OS data from SACT provide some evidence for the OS, differences in patient characteristics (see response to Issue 2) mean these do not resolve the uncertainty around the OS projections. Further, SACT cannot address the relative OS treatment effect of pembrolizumab versus routine surveillance. **<u>KEYNOTE-053/SWOG-S1404 ITC</u>** To estimate the relative effect of adjuvant pembrolizumab in KEYNOTE-054 versus routine surveillance, alongside this response MSD has conducted an indirect treatment comparison (ITC) using data from KEYNOTE-053/SWOG-S1404 and the EORTC-18071 trial of adjuvant ipilimumab versus placebo. To maximise comparability between the trials, data from KEYNOTE-053/SWOG-S1404 were

		obtained for stage III patients only, and further restricted to the subgroup of patients who were pre-specified to receive ipilimumab as the control treatment. The ITC showed that adjuvant pembrolizumab [redacted]. **PRFS2 analysis from KEYNOTE-054** Further, MSD have also presented data from the PRFS2 analysis in KEYNOTE-054, which show that [redacted] Finally, the value of adjuvant therapies and the benefit to patients of remaining relapse-free for an extended period should be reiterated: patients are effectively free from any residual disease and can experience a normal quality of life. Pembrolizumab has demonstrated a durable, statistically significant benefit in RFS over an extended median follow-up of 45.5 months. Pembrolizumab also demonstrated a statistically significant improvement in DMFS, meaning patients are less likely to develop distant metastases which are associated with poor survival outcomes and more complex and costly healthcare management. Therefore, as a consequence of delaying disease recurrence, patients treated with adjuvant pembrolizumab have the opportunity to experience a high quality of life for longer than patients under routine surveillance,

		and it is highly plausible that an improvement in OS could also be observed as supported by RCT evidence with other adjuvant therapies [2, 3].
ERG comment		The ERG highlights: • If treatment with pembrolizumab after a LR increases OS for patients previously receiving routine surveillance then, as this effect only relates to [redacted]% of patients in this arm, the overall effect of crossover on an analysis of KEYNOTE-054 trial OS data would be small. • It is inconsistent for the company (company response to technical engagement Appendix) to imply that KEYNOTE-053 OS results suggest that there is a difference in OS between pembrolizumab and ipilimumab ([redacted]% and [redacted]% respectively; a difference of [redacted] %) whilst also considering that the bigger difference in RFS seen between the pembrolizumab arms of the KEYNOTE-053 and KEYNOTE-054 trials (XXXX% and [redacted]% respectively, a difference of [redacted]%) to be 'very closely aligned'. • The company appears to be arguing that, as there is an active control arm (i.e., ipilimumab) in the KEYNOTE-053 trial, whilst RFS is improved with pembrolizumab in the trial no OS improvement with pembrolizumab should be expected. The ERG considers that if RFS is a predictor of OS then this should be independent of any treatment that is or is not given. Results from the KEYNOTE-053 trial support the ERG's view that RFS may not always be linked to OS and that where no OS evidence is available it should not be assumed that improvements in RFS automatically mean that there will be improvements in OS. • Any economic benefit derived from treatment with pembrolizumab that results in a longer average length of time spent in the RFS state compared with routine surveillance is captured in the company model in the form of lower healthcare costs and higher utility values in the RFS state. • The company ITC does not provide OS HR estimates for the comparison of pembrolizumab versus routine surveillance that can be used to inform decision making. The EORTC-18071 trial recruited patients between 2008 and 2011; however, FDA/EMA approval of the use of nivolumab or pembrolizumab

		in the metastatic setting did not occur before 2014, and approval of dabrafenib in the metastatic setting did not occur until 2013. The effect of these treatments on the OS of patients with metastatic disease will therefore not have been seen in the EORTC-18071 trial. In contrast, in the KEYNOTE-053 trial, these treatments were available to patients in the metastatic setting during the trial period. This difference in subsequent therapies between the trials means that OS ITC results will not be robust without adjusting for the effect of different subsequent treatments.
Key issue 2: Company cost utility model does not generate reliable OS results for patients receiving pembrolizumab	**YES**	**Validation sources** The ERG substantiate this claim based on comparison of the modelled pembrolizumab OS projections with the OS data for pembrolizumab observed in the SACT cohort. However, there are important differences in the patient characteristics between the KEYNOTE-054 and SACT cohorts which limit the relevance of the SACT data for validating the OS estimates: • **BRAF status**: Fewer patients had positive BRAF mutation status in SACT compared with KEYNOTE-054 (19% vs 47.5%, respectively). BRAF mutation positive patients may receive additional targeted treatment options for metastatic disease [4] and therefore are likely to have better survival outcomes • **Age**: Patients in SACT were older than in KEYNOTE-054 (64 years vs 54 years, respectively) • **Fitness**: Patients in SACT were less fit than in KEYNOTE-054 (ECOG PS 0: 69% vs 94.4%, respectively) Given these differences in prognostic factors, it is logical to expect lower OS in SACT compared with KEYNOTE-054, and to conclude that the SACT data do not provide a good indication of the OS expected with pembrolizumab in KEYNOTE-054. It is also therefore expected that the model's OS projections for pembrolizumab are higher than those seen in SACT. In contrast, the baseline characteristics of patients in KEYNOTE-053/SWOG-S1404 are highly comparable to the patients in KEYNOTE-054, and the observed RFS curve

		for pembrolizumab in KEYNOTE-053/SWOG-S1404 is very closely aligned with the RFS observed in KEYNOTE-054 (Figure 1). MSD have provided OS data for the stage III ipilimumab-control subgroup from this trial, further increasing the comparability. As such, OS data from KEYNOTE-053/SWOG-S1404 are likely to provide a good indication of the OS that can be expected with pembrolizumab in KEYNOTE-054, and this trial is therefore an important source to validate the model's OS estimates for pembrolizumab. As such, this trial should be given full consideration as a validation source. Comparison of the observed OS from KEYNOTE-053/SWOG-S1404 with the predicted OS for pembrolizumab in the model in fact reveals a very close alignment in the first 3.5 years (the point to which mature OS data are available), offering confidence that the model projections, in the short term at least, are robust. After 3.5 years the data are not fully mature, but it is plausible that the model does underpredict long term OS versus the KEYNOTE-053/SWOG-S1404 data (Figure 2); this should be considered conservative. **Figure 2: Comparison of predicted OS for pembrolizumab versus external validation sources** 

Abbreviations: OS, overall survival.

Note also that the OS projections presented in the submission are estimated from a combination of parametric functions used to model RF→LR, RF→DM (Generalised gamma and Gompertz, respectively) and the PFS/OS from the DM health state. Whilst OS is a model output, its long-term projections over time have been validated by UK clinical experts who deemed them to be reasonable (see A15.2 – Validation page 66 of CS).

Exploratory scenarios

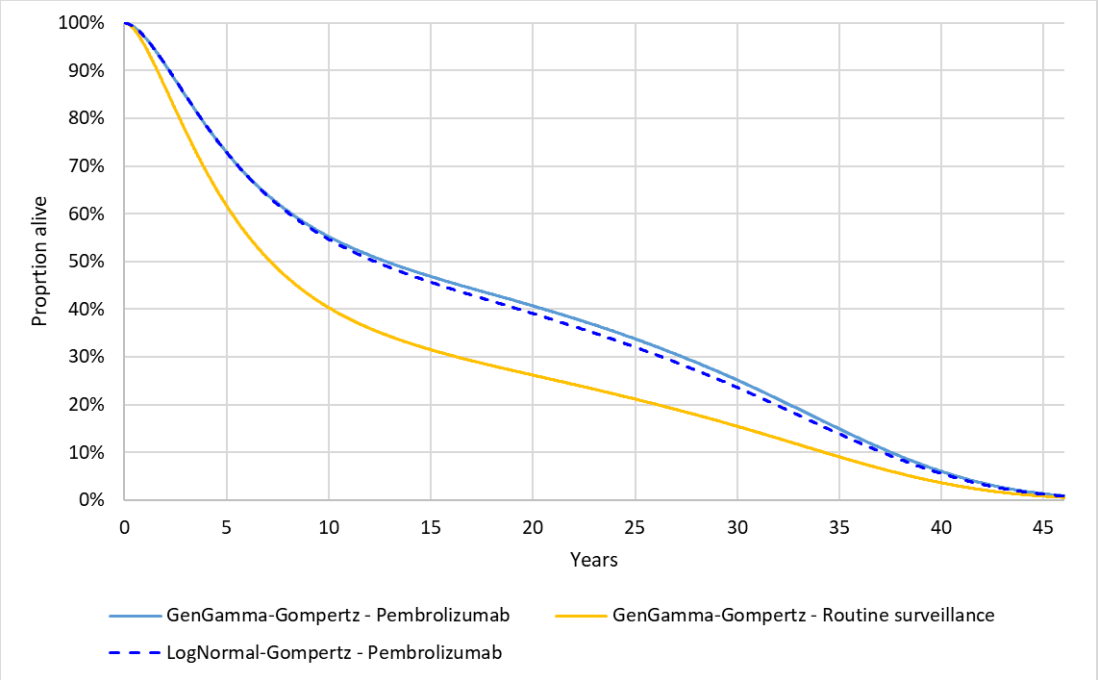
As stated in the Company submission and as noted by the ERG, the OS estimates in the model are a function of all other health state transitions and therefore the OS projections cannot easily be modified in isolation to explore the impact of OS on the cost-effectiveness results.

In line with the guidance in NICE DSU TSD 14 [5], the same combination of parametric functions is used in both treatment arms of the model (RF→LR, Generalised gamma; RF→DM, Gompertz).

However, MSD recognise that given the absence of OS data from KEYNOTE-054 there remains some uncertainty as to the OS benefit with pembrolizumab. Therefore we conducted a scenario analysis in which a more pessimistic (but still clinically plausible based on clinical expert opinion) combination of parametric functions was applied in the **pembrolizumab arm only** (Table 2; Figure 3). To achieve this within the current model structure, it was necessary to fit a different combination of curves to each arm (in contrary to NICE Decision Support Unit [DSU] Technical Support Document [TSD] 14 guidance), leading to a greater plateau in the routine surveillance arm compared with pembrolizumab which is likely to be unrealistic.

Table 2: Scenario A, conservative pembrolizumab – varying combination of parametric functions

Scenario	Pembrolizumab		Routine surveillance		ICER (£/QALY)
	RF→LR	RF→DM	RF→LR	RF→DM	
Base case	Gen Gamma	Gompertz	Gen Gamma	Gompertz	9,357

		Scenario A | Lognormal | Gompertz | Gen Gamma | Gompertz | 12,231 Abbreviations: DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LR, locoregional; QALY, quality-adjusted life year; RF, recurrence-free. **Figure 3: Scenario A, conservative pembrolizumab: Long term OS projections with alternative parametric function combinations**  Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario. Note that this scenario also affects the extrapolations for RFS and DMFS; however, it demonstrates that reducing long-term RFS, DMFS and OS for pembrolizumab only slightly increases the ICER.
ERG comment		The ERG highlights that:

		• The SACT data provide OS evidence for NHS patients treated with pembrolizumab in the adjuvant setting. The company correctly notes that comparisons of real-world data to trial outcomes are not necessarily robust. However, the company has largely validated company model routine surveillance arm OS estimates using registry study data and clinical opinion (i.e., what has been observed or expected in the real world). It is inconsistent to use trial data to validate model OS projections for one arm and to use real-world evidence to validate model OS projections for the other model arm. • As stated in the ERG response to Key Issue 1, at 3.5 years, KEYNOTE-053 trial pembrolizumab arm RFS is potentially superior to KEYNOTE-054 trial pembrolizumab arm RFS. If a predictive link between RFS and OS exists, then it is not unreasonable to assume that long-term OS for patients treated with pembrolizumab in the KEYNOTE-054 trial will be worse than the OS of patients treated with pembrolizumab in the KEYNOTE-053 trial. • The ERG does not consider that Scenario A is conservative. It appears to be based on the arbitrary selection of an alternative RF-LR curve for the patients in the model pembrolizumab arm and choosing this curve makes little difference to OS for these patients.

Key issue 3: Company cost utility model does not generate reliable OS results for patients receiving routine surveillance	**YES**	**Validation sources** MSD has presented a comprehensive discussion of several external sources that can be used to validate the OS projections for routine surveillance. All external sources and datasets have some limitations, however the COMBI-AD and EORTC-18071 trials, and the composite curve previously developed by the same ERG, all have merit and should be taken into consideration. As stated in the company submission, all OS projections for both arms have been validated by UK clinical experts and were deemed to be clinically reasonable. In addition, the hazard ratio (HR) generated by the ITC of KEYNOTE-053/SWOG-S1404 and EORTC-18071 ([redacted]) can be applied to the Kaplan-Meier OS data for pembrolizumab from KEYNOTE-053/SWOG-S1404 to estimate the Kaplan-Meier OS for routine surveillance. This estimated OS curve based on the ITC results is closely aligned with the OS curve predicted by the model for routine surveillance (Figure 4).

		Figure 4: Predicted OS curve for routine surveillance versus estimated OS from ITC of EORTC-18071 and KEYNOTE-053/SWOG-S1404  Abbreviations: ITC, indirect treatment comparison; OS, overall survival. The ERG considers that the Gershenwald/AJCC data are the most appropriate to validate the routine surveillance OS projections. However, MSD have raised several important concerns with this dataset that limits its suitability and must be taken into account: • Gershenwald/AJCC data are from the point of diagnosis of stage III melanoma, rather than treatment initiation – in practice there is a delay between diagnosis, resection, and treatment initiation which will lower the OS seen in KEYNOTE-054 • KEYNOTE-054 excluded stage IIIA patients with <1mm metastases in the lymph nodes, who have much better OS than those with ≥1mm metastases whereas Gershenwald/AJCC is highly likely to include this patient group. As

		patient-level data from the Gershenwald/AJCC dataset are not available, it is not possible to make appropriate adjustments • Gershenwald/AJCC data relate to melanoma-specific survival, whereas the model considers overall survival • Gershenwald/AJCC survival reflects data only for patients for who all relevant covariates are known, which may distort the data towards better survival • The OS presented in Gershenwald/AJCC is substantially higher than in all other sources with available OS data for routine surveillance (i.e. COMBI-AD, EORTC-18071, ERG composite curve; Figure 5) • **In addition, OS data from Gershenwald/AJCC also exceeds the OS curves observed with active adjuvant treatment in CheckMate238 and SACT (Figure 6).** This indicates that the dataset is unlikely to represent the same population being considered in this appraisal. **Consequently, it is clinically implausible to consider SACT the most appropriate source to validate pembrolizumab OS while simultaneously using Gershenwald/AJCC to validate routine surveillance OS.**

Figure 5: Predicted OS curve for routine surveillance versus external sources (including ITC of EORTC-18071 and KEYNOTE-053/SWOG-S1404)

Abbreviations: ERG, evidence review group; MSS, melanoma-specific survival; ITC, indirect treatment comparison; OS, overall survival.

Figure 6: Predicted OS curves for pembrolizumab versus external sources (including comparison with Gershenwald/AJCC for routine surveillance)

		 Abbreviations: MSS, melanoma-specific survival; OS, overall survival. As discussed in the response to Issue 2 above, KEYNOTE-053/SWOG-S1404 is a highly relevant source of OS data for adjuvant pembrolizumab and should be the key source used to validate the OS projections for pembrolizumab. MSD have presented some important concerns associated with the Gershenwald/AJCC data which limits the relevance of this dataset as the validation source for routine surveillance and indicates that the OS curve for routine surveillance will be below that reported in the Gershenwald/AJCC publication. There are several other sources, including the KEYNOTE-053/SWOG-S1404 ITC, which are useful for validating the routine surveillance projections. **However, based on the OS data from KEYNOTE-053/SWOG-S1404, the ITC results, and external sources available for routine surveillance, a durable OS benefit with adjuvant pembrolizumab should be expected regardless of the source used for routine surveillance validation (Figure 5).**

		Long term OS projections The ERG have highlighted that the proportion of OS events that need to have occurred to enable analysis of OS in KEYNOTE-054 ([redacted]%) is not forecast to occur until [redacted] (i.e. [redacted] after the initial trial completion date), however the model projects that [redacted] of patients will have died after [redacted]. However, it is important to note the following points: • Firstly, the [redacted] of patients predicted by the model to have died after [redacted] refers to the routine surveillance arm only; as per the KEYNOTE-054 protocol, OS analysis will be conducted once [redacted]% of the *total trial population* events have occurred. The model predicts that [redacted]% of the total population will have died by [redacted], due to a survival benefit for the pembrolizumab arm. • Secondly, MSD acknowledge that, based on the external sources discussed in the submission and presented in Figure 5, long term OS may be underestimated in the model. However, this is true for both treatment arms and based on the external sources a long-term survival benefit with adjuvant pembrolizumab should still be expected. The ITC presented by MSD alongside this response [redacted] As noted by the ERG, this underprediction results from relatively low survival estimates generated from the DM health state, demonstrated by comparing the average survival in the DM health state with pembrolizumab in the current model compared with the model used in TA366 ([redacted] years vs [redacted] years, respectively). This is an artefact of the memory-less nature of Markov modelling in which transition probabilities at each cycle must only depend upon a patient's current health state and calendar time. As noted by Briggs, Claxton, & Sculpher (2011) [6], the exponential distribution is commonly used to represent transition probabilities starting from intermediate health states in a Markov cohort model, as the hazard rate does not depend on time since entry into the health state. To use alternative distributions it

would be necessary to track time in health state which would require thousands of tunnel states and significantly increase the computational burden of the model. This would not be well justified for this model, particularly given the close alignment between predicted OS using the exponential function and observed OS for pembrolizumab in advanced/metastatic melanoma in the KEYNOTE-006 trial. The exponential function may result in pessimistic long-term projections as it is defined by a single parameter and is therefore less flexible than other functions**.**

However, it is important to reiterate that this limitation applies to both treatment arms (therefore has a limited impact on the overall cost-effectiveness estimates), and to acknowledge that it is an inherent limitation of the model structure that OS curves (which are a model output) cannot be directly adjusted. Extensive scenarios exploring the distribution of different subsequent therapies were presented in the company submission, including in combination with different parametric functions (reproduced in Table 3), to further explore the impact of costs and transitions from this health state.

Table 3: Summary of key scenarios presented in the Company submission

#	Description	ICER
1	Alternative curves: RF→LR Gompertz; RF→DM Gompertz	10,404
	Alternative curves: RF→LR Lognormal; RF→DM Gompertz	8,718
2†	Alternative market shares for treatments of advanced melanoma, Ipsos (unadjusted) – routine surveillance arm	Dominant
3†	Alternative market shares for treatments of advanced melanoma, KOL scenario 1	4,891
4†	Alternative best-fitting curves (RF→LR Gompertz; RF→DM Gompertz) AND Alternative market shares for treatments of advanced melanoma (Scenario 1 + 2)	537

		Alternative best-fitting curves (RF→LR Lognormal; RF→DM Gompertz) AND Alternative market shares for treatments of advanced melanoma (Scenario 1 + 2)	Dominant

† See Company Submission for full description of scenarios.

Exploratory scenarios

To explore the impact of this potential underprediction of long-term OS on the ICER, we have conducted a series of scenario analyses where parameters affecting long term OS were varied (Scenarios B–E).

Firstly, we conducted scenario analyses in which different combinations of parametric functions for RF→LR and RF→DM were applied to each arm to improve OS for the routine surveillance arm relative to adjuvant pembrolizumab. However as discussed in Issue 2 above, this is not a recommended approach to survival modelling, and this also alters the RFS and DMFS estimates for routine surveillance which confounds the interpretation of the ICER (Table 4).

- Scenario B: A more optimistic combination of parametric functions for RF→LR and RF→DM was applied in the **routine surveillance arm only**. This increases the long-term OS for routine surveillance (Figure 7).
- Scenario C (Combined scenarios A [see Issue 2] + B above; highly pessimistic against adjuvant pembrolizumab considering the nature of modeling assumptions): A more *optimistic* combination of parametric functions for RF→LR and RF→DM was applied in the routine surveillance arm, and a more *conservative* combination of functions was applied in the pembrolizumab arm, further reducing the long term OS benefit with pembrolizumab (Figure 8).

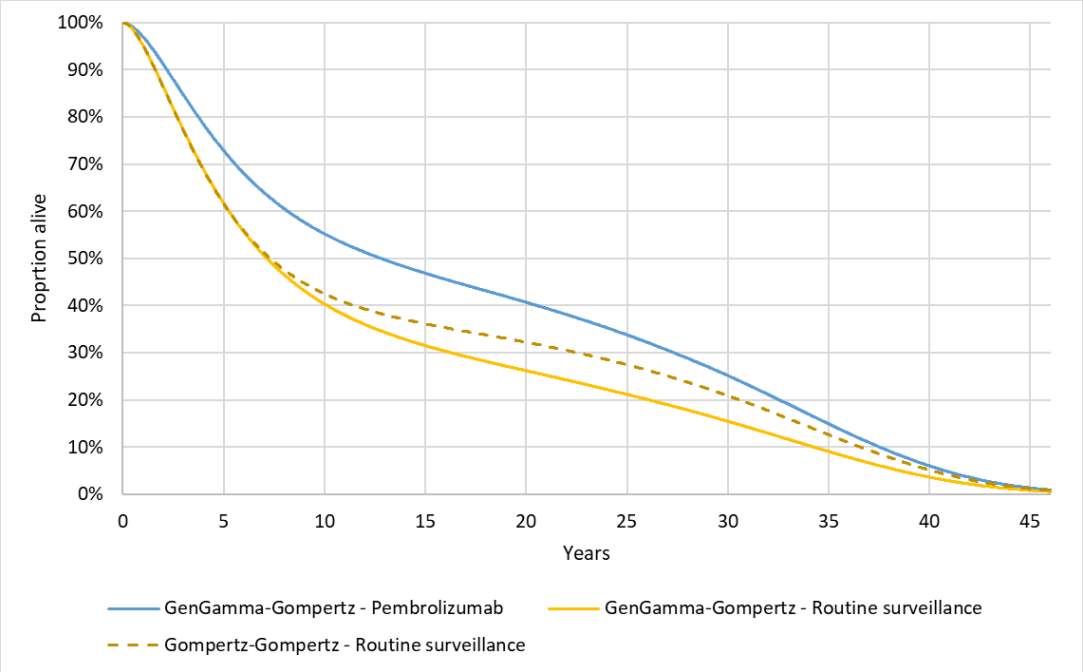
These analyses demonstrate that improving long-term RFS, DMFS and OS for routine surveillance relative to pembrolizumab increases the ICER, but the ICER for adjuvant pembrolizumab remains below the £30,000/QALY threshold. Note that these scenarios utilise different parametric functions contrary to NICE DSU guidance, and result in a greater plateau in the routine surveillance arm compared with pembrolizumab which is likely to be unrealistic and clinically implausible.

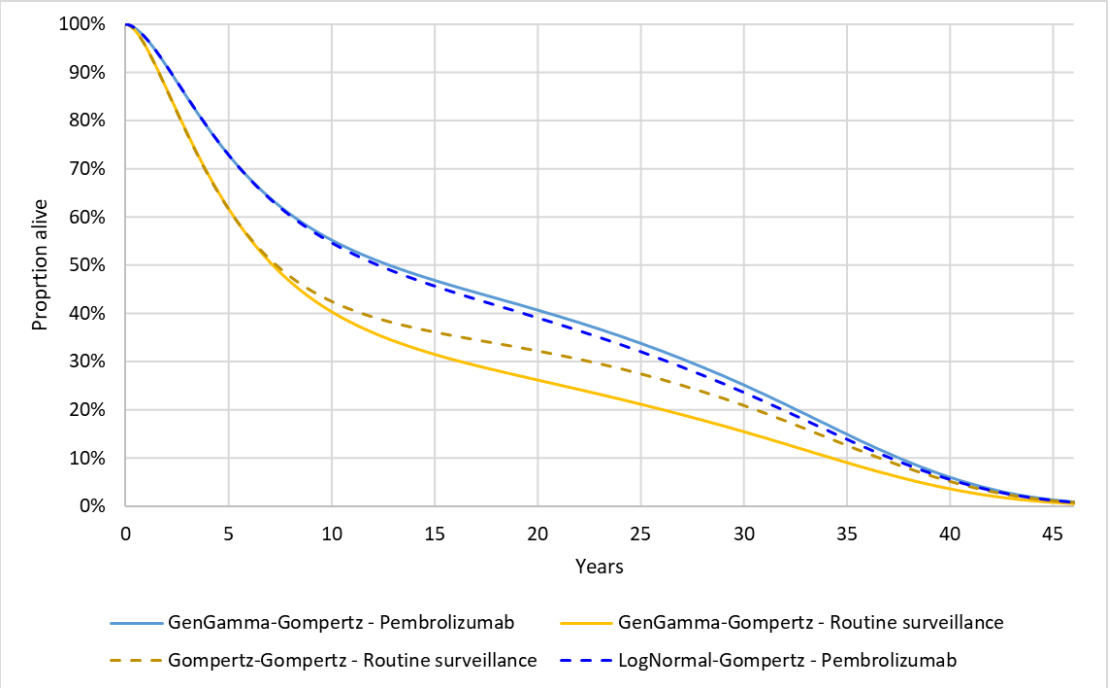
Table 4: Scenario analysis B–C – varying combination of parametric functions by treatment arm

Scenario	Pembrolizumab		Routine surveillance		ICER (£/QALY)
	RF→LR	RF→DM	RF→LR	RF→DM	
Base case	Gen Gamma	Gompertz	Gen Gamma	Gompertz	9,357
B	Gen Gamma	Gompertz	Gompertz	Gompertz	21,126
C	Log Normal	Gompertz	Gompertz	Gompertz	26,493

Abbreviations: DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LR, locoregional; QALY, quality-adjusted life year; RF, recurrence-free.

Figure 7: Scenario B, optimistic routine surveillance: Long term OS projections with alternative parametric function combinations



		Notes: Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario. **Figure 8: Scenario C, combined effect: Long term OS projections with alternative parametric function combinations** 

		Notes: Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario. Secondly, we conducted further exploratory analyses that varied the exponential rate used to model OS from the DM health state and thus uplift the OS projections only without affecting the RFS and DMFS estimates. Considering the structure of the model, **this is the most robust and informative approach to explore the impact of increasing survival from the DM health state and thus addressing the underprediction of long-term OS**: • Scenario D: We performed a threshold analysis to identify the exponential rate parameter for OS in the DM health state required to result in an average survival of [redacted] years with pembrolizumab in the DM health state, in line with the findings in TA366 – this value is [redacted]. The OS projections observed when this exponential rate is entered into the model are shown in Figure 9. • Scenario E: We also performed a threshold analysis to identify the exponential rate parameter for OS in the DM health state required for the proportion of deaths necessary for OS analysis in KEYNOTE-054 ([redacted]%) to be reached at [redacted], as per current forecasting – this value is [redacted]. The OS projections observed when this exponential rate is entered into the model are shown in Figure 10. • The cost-effectiveness results from these additional scenarios are shown in Table 5. In both scenarios, OS curves were higher (and life years increased) in both treatment arms as the exponential rate decreased. However the absolute and proportional improvements in survival were larger in the routine surveillance arm compared with the pembrolizumab arm (absolute improvement in LYs vs base case – Scenario D: pembrolizumab, [redacted] LYs; routine surveillance, [redacted] LYs; Scenario E: pembrolizumab, [redacted] LYs; routine surveillance, [redacted] LYs) and therefore the benefit of adjuvant pembrolizumab on OS was reduced as the exponential rate decreased. In addition, the total costs increased in both arms as survival increased, due to

		longer time spent on subsequent therapies, but the *incremental cost* for pembrolizumab vs routine surveillance was reduced. • Consequently, as survival increased and the OS treatment benefit of pembrolizumab decreased, in both scenarios the ICER decreased compared with the base case analysis (Scenario D: £9,060/QALY; Scenario E: £8,613/QALY). This demonstrates that adjuvant pembrolizumab remains cost-effective, even as the OS benefit versus routine surveillance decreases. • As seen from Figure 9 and Figure 10, these adjustments effectively indicate that the model now predicts a higher OS in both treatment arms compared with the observed trial data and relevant external sources, the OS benefit with adjuvant pembrolizumab is reduced, and pembrolizumab remains cost-effective.

Figure 9: Scenario D – Predicted OS with exponential rate uplift based on average survival in DM state from TA366 (exponential rate: [redacted]), versus external sources

Figure 10: Scenario E – Predicted OS with exponential rate uplift based on projected timeframe for OS analysis of KEYNOTE-054 (exponential rate: [redacted]), versus external sources

[redacted]

Table 5: Scenario analyses D–E – Cost-effectiveness results in exponential rate uplift scenarios

	Scenario D: Exp rate uplifted so average survival in DM state aligned with KN006 ([redacted] years [redacted] in base case]; exp [redacted])		**Scenario E: Exp rate uplifted so % dead at 10 years aligned with KN054 projections ([redacted]%; exp [redacted])**	
Outcome	**Pembrolizumab**	**Routine surveillance**	**Pembrolizumab**	**Routine surveillance**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	7.70	[redacted]	8.31
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]

Incremental costs	[redacted]	-	[redacted]	-
Incremental QALYs	[redacted]	-	[redacted]	-
Incremental LYs	[redacted]	-	[redacted]	-
ICER (£/QALY)	**9,060**	**-**	**8,613**	

Abbreviations: DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

All of the analyses above address the uncertainty around long term projections for both pembrolizumab and routine surveillance and clearly demonstrate that the intervention remains a cost-effective use of NHS resources. **Scenarios D and E are the most informative to demonstrate the impact that increasing long term survival (i.e. reducing underprediction versus external sources) and reducing the OS benefit of adjuvant pembrolizumab have on the cost-effectiveness results.**

ERG comment		The ERG highlights that: • The ERG's estimate of 5 years is accurate (the ERG stated that [redacted]% of deaths had occurred in the model at the end of 5 years, i.e., at 6 years). • As explained in response to Key Issue 1, the ERG considers that company ITC OS results should not be used to inform decision making as the subsequent treatments available to patients in the included trials are very different across the trials. • The ERG notes that the scenarios produced by the company all still assume a substantial survival benefit for pembrolizumab versus routine surveillance which has yet to be evidenced. These new company analyses are speculative and are not evidence based.
Key issue 4: The company assumption that the effect of pembrolizumab on RFS and DMFS endures for the whole model time horizon is not supported by evidence	**NO**	MSD would like to take the opportunity to address the interpretation of this Issue, reiterate the assumptions used within the cost-effectiveness model for adjuvant pembrolizumab, and to provide additional clarifications regarding the duration of treatment benefit for pembrolizumab in KEYNOTE-054. **<u>Conservative modelling assumptions</u>** Firstly, the model employs the conservative assumption that there is **no ongoing benefit of pembrolizumab after recurrence**, and therefore that the reduced risk of recurrence with pembrolizumab versus routine surveillance is only maintained while patients remain recurrence-free: • PFS and OS in the DM state are informed based only on the distribution of subsequent treatments, not the adjuvant treatment arm, and the transition probabilities from DM to death therefore actually favour routine surveillance. • Although transitions from the LR to DM health state are informed by KEYNOTE-054 data, due to the crossover design of KEYNOTE-054 ([redacted] patients on placebo received adjuvant pembrolizumab after LR recurrence; refer to Table 42 of the Company Submission) transition probabilities from LR→DM and LR→Death also favour the routine surveillance

		arm of the model. This means that the treatment benefit of pembrolizumab (i.e. reduced risk of recurrence) is only maintained for the RF→LR and RF→DM transitions. **It is therefore not accurate to state that 'the effect of pembrolizumab on RFS and DMFS is maintained for the whole model horizon' as this is not the case after recurrence.** It is more accurate to state that **the reduced risk of recurrence with pembrolizumab versus routine surveillance is maintained while patients remain in the RF health state (i.e. for the *RF→LR and RF→DM transitions)*.** The fact that transitions from LR→DM and DM→Death favour routine surveillance is a highly conservative assumption that biases in favour of routine surveillance. As noted above, the conservatism of this assumption results from the lack of adjustment for crossover for patients who received adjuvant pembrolizumab after placebo following LR relapse. **<u>Extended follow-up shows sustained RFS and DMFS benefit</u>** Secondly, longer follow-up data from KEYNOTE-054 have been included within the submission. The RFS results from the later follow up (median follow up 45.5 months) are consistent with the results in the original submission; pembrolizumab demonstrates statistically significant, sustained improvement in RFS over time. The same is observed for DMFS, with a clear separation of the KM curves observed over time despite the high level of cross over from the routine surveillance arm observed in the trial ([redacted] patients with LR recurrence). However, MSD acknowledge the increased censoring in the data from month 40.5 onwards which is the minimum follow up time of the last patient randomised within the study. The ERG noted in their report and in response to the factual accuracy check that, based on the Kaplan-Meier data from KEYNOTE-054, it appears that the risk of first recurrence or distant metastasis was lower from months zero to month 36 for adjuvant pembrolizumab compared with routine surveillance, but that the risk in both arms was approximately equal from 24 months onwards for both RFS and DMFS. Most recurrences for stage III resected melanoma occur in the first 2 years post-surgical resection. After this point the rate of recurrence, regardless of adjuvant treatment, reduces significantly with very few recurrences occurring after 5 years of

		RFS [7, 8]. Consequently, very few recurrences in either treatment arm are expected after the recurrence rate plateaus in KEYNOTE-054. As such, the plateau observed in the RFS KM curves in KEYNOTE-054 may not be indicative of loss of treatment benefit with pembrolizumab. The rate of recurrence in both arms is naturally very low beyond this point and therefore the benefit cannot be observed in the data due to the sample size. Specifically, a much larger sample size would be needed to detect this at longer follow-up. However, it is clinically reasonable to consider that the benefit of pembrolizumab still persists with longer follow up after complete resection, as confirmed by UK clinical experts consulted by MSD [9]. In terms of the cost-effectiveness model, this means that although the relative treatment effect of pembrolizumab (i.e. reduced risk of recurrence) is maintained while patients remain in the RF health state, recurrence rates are substantially lower after the first 2 years such that the absolute difference in patients transitioning to the LR and DM health states after this point is small and therefore the impact on the ICER of an equal risk of recurrence in both arms after a specific time point would therefore be relatively low. **No evidence of non-proportional hazards** Further, following the evidence provided by MSD at clarification questions and the findings reported by Eggermont et al, 2018 [10], the ERG were satisfied that there is no evidence that the RFS hazards in KEYNOTE-054 are not proportional. The RFS HRs over time provided by MSD also demonstrate that the observed HR is largely stable after the first 6 months through to end of follow-up, indicating that the treatment benefit endures. **PRFS2 analysis from KEYNOTE-054** In addition, MSD conducted PRFS2 analysis based on the IA2 data cut, however the ERG did not discuss this evidence within its report. In KEYNOTE-054, PRFS2 was defined as time from randomisation to earliest of: • 1st disease progression after initial unresectable recurrence • 2nd recurrence after resectable 1st recurrence • Death

		Pembrolizumab provided [redacted] **Supportive literature** The clinical evidence from KEYNOTE-054 is consistent with other clinical trials and it indicates that there is a durable separation of curves for RFS and DMFS. This has also been consistently observed in other adjuvant melanoma trials including CheckMate238, EORTC-18071 (CA184-029) and the COMBI-AD [2, 3, 11]. Therefore, for the time period for which clinical trial data exists for the use of adjuvant IO therapies, there is no evidence that the treatment effect for RFS or DMFS does not endure beyond adjuvant treatment cessation. Additional evidence from metastatic melanoma are supportive of a persistent treatment effect. Due to their unique mode of action, immunotherapies have been associated with prolonged survival over time in a subset of patients with metastatic disease across a number of tumours including melanoma. For metastatic melanoma in particular, this "immune-therapeutic effect", has been characterised across a number of publications by *Schadendorf et al 2016, Robert et al 2019 and Larkin et al 2019* amongst others, all of which demonstrate a prolonged and durable survival

		benefit [12-15]. Therefore the evidence base from the metastatic melanoma setting is also supportive of an enduring treatment benefit. The totality of the clinical evidence in the adjuvant setting from KEYNOTE-054 (RFS, DMFS and PRFS2) alongside evidence from the metastatic melanoma suggests a durable treatment benefit of IO agents. Finally, it is important to reiterate again that modelling assumptions used within this submission are conservative and would be expected to bias against pembrolizumab in terms of cost-effectiveness.
ERG comment		The ERG highlights that the KEYNOTE-054 trial primary end point is RFS and that the benefit of treatment with pembrolizumab compared with routine surveillance, in terms of a lower risk of first recurrence, appears to have disappeared by the end of 3 years (ERG CDF Review Report, Section 4.4).

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1:	NA	NA	NA
Additional issue 2:	NA	NA	NA

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA

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ID3776 Pembrolizumab melanoma (CDF Review of TA553)

Additional information provided by the ERG

ERG Note

In the company model, the difference in life years between the pembrolizumab and routine surveillance arms is [redacted] years, favouring treatment with pembrolizumab. If life expectancy is only influenced by the time spent in the DMFS state, then this means that the life expectancy of patients who remain in the DMFS has to be approximately [redacted] years longer than the life expectancy of patients who experience a distant metastasis.

Liverpool Reviews and Implementation Group

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