NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

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 **Merck Sharp & Dohme (MSD)**

2. **Clarification questions and company responses**

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

4. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews (KSR)**

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from **Merck Sharp & Dohme (MSD)**
   a. Company response
   b. Appendix

7. **Technical engagement response & expert statement from experts:**
   a. Dr Mark Harries – clinical expert, nominated by Melanoma Focus
   b. Dr Pippa Corrie – clinical expert, nominated by Merck Sharp & Dohme
   c. Michael Yelton – patient expert, nominated by Melanoma Focus

8. **Evidence Review Group critique of company response to technical engagement** prepared by **Kleijnen Systematic Reviews (KSR)**

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

Single technology appraisal

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence

[ID3908]

Document B

Company evidence submission

February 2022

File name	Version	Contains confidential information	Date
ID3908 Pembro Stage 2 Melanoma Document-B [REDACTED].docx	1.0	Yes	14th February 2022

Contents

Tables and figures

Tables

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List of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
AE	Adverse events
AEOSI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ApaT	All-patients-as-treated
BCG	Bacillus Calmette-Guérin
BID	Twice daily
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CNS	Central nervous system
CSR	Clinical study report
CT	Computerised tomography
DM	Distant metastases
DMFS	Distant metastasis-free survival
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EHR	Electronic health record
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HTA	Health technology assessment
IA1	Primary interim analysis
IA2	Second interim analysis
IARC	International Agency for Research on Cancer
ICER	Incremental cost-effectiveness ratio
IO	Immune-oncology
ITC	Indirect treatment comparison
ITM	In transit metastases

ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
KPS	Karnofsky performance status
LPS	Lansky Play-Performance Scale
LRR	Locoregional recurrence
LS	Least squares
LYG	Life years gained
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRI	Magnetic resonance imaging
MSE	Mean squared error
N	Number of patients
NHS	National Health Service
NICE	National Institute for Heath and Care Excellence
NMA	Network meta-analysis
NR	Not reached
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient access scheme
PD-1	Programmed (cell) death protein 1
PD-L 1/2	Programmed (cell) death ligand 1/2
PET	Positron emission tomography
PET	Positron-emission tomography
PFS	Progression-free survival
PRFS	Progression/recurrence-free survival
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QLQ	Quality-of-Life Questionnaire
QxW	Every x weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RF	Recurrence-free
RFS	Recurrence-free survival
ROB	Risk-of-bias
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review

SmPC	Summary of product characteristics
SMR	Society for Melanoma Research
SSO	Society of Surgical Oncology
TA	Technology appraisal
TNM	Tumour, nodes, metastases
TSD	Technical Support Document
TTST	Time to subsequent therapy
UK	United Kingdom
US	United States
USON	US Oncology Network
USON	US Oncology Network
UV	Ultraviolet
VAS	Visual analogue scale
WTP	Willingness to pay

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

B.1.1 *Decision problem*

Pembrolizumab is anticipated to receive an updated marketing authorisation [redacted].[1] This submission focuses on the extension to the technology's current marketing authorisation: patients with stage 2B or 2C melanoma and who have undergone complete resection. The National Institute for Health and Care Excellence (NICE) have previously appraised and recommended pembrolizumab for the adjuvant treatment of resected stage 3 melanoma (TA776).[2]

The decision problem addressed within this submission is consistent with the National Institute for Health and Care Excellence (NICE) final scope for this appraisal. This is presented in Table 1 along with any differences between the decision problem in this submission and the NICE final scope.

Table 1: The decision problem

	Final scope issued by NICE[3]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection (at high risk of recurrence).	People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection.	By definition, patients with 2B and 2C melanoma are at high risk of recurrence.
Intervention	Pembrolizumab	Pembrolizumab	N/A
Comparator(s)	Routine surveillance	Routine surveillance	N/A
Outcomes	• Overall survival (OS) • Recurrence-free survival (RFS) • Distant metastasis-free survival (DMFS) • Adverse effects of treatment • Health-related quality of life (HRQoL)	• RFS • Adverse effects of treatment • HRQoL	As the analyses of OS and DMFS are event driven (final analyses expected to take place when [redacted] events and [redacted] events have occurred, respectively), these data are not yet available from KEYNOTE-716.

As no further changes from the final scope issued by NICE are proposed, the table has been condensed as per NICE guidance.
Abbreviations: DMFS: distant metastasis-free survival; HRQoL: health-related quality of life; NICE: National Institute for Health and Care Excellence; OS: overall survival; RFS: recurrence-free survival.
Source: NICE Final Scope.[3]

B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, expected marketing authorisation, costs and administration requirements associated with pembrolizumab for the treatment of patients with stage 2B and 2C melanoma is presented in Table 2. The summary of product characteristic (SmPC) for pembrolizumab is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a humanised monoclonal antibody which binds to the anti-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. In binding to the PD-1 receptor, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T-cells in the tumour microenvironment and antitumour inactivity.[4, 5]
Marketing authorisation/CE mark status	An application for variations to the terms of marketing authorisation for pembrolizumab was submitted to the European Medicines Agency (EMA) on [redacted]. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected for this indication in [redacted]. The marketing authorisation for pembrolizumab in this indication is expected to be granted by the European Commission in [redacted], and subsequently adopted by the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pembrolizumab is anticipated to be indicated for use [redacted].[1] The Summary of Product Characteristics (SmPC) for pembrolizumab in this indication is provided in Appendix C. Pembrolizumab is already approved by the EMA as a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults and as a monotherapy for the adjuvant treatment of adults with stage 3 melanoma and lymph node involvement who have undergone complete resection. In addition, pembrolizumab, as monotherapy or in combination with other agents, is licenced for specific indications in:[5] • Non-small cell lung cancer • Classical Hodgkin lymphoma • Urothelial carcinoma • Head and neck squamous cell carcinoma • Renal cell carcinoma • Colorectal cancer • Oesophageal cancer • Triple-negative breast cancer

	• Endometrial carcinoma Contraindications include hypersensitivity to the active substance or to any of the excipients (L-histidine; L-histidine hydrochloride monohydrate; Sucrose; Polysorbate 80 (E433); Water for injections).
Method of administration and dosage	Pembrolizumab is administered via intravenous infusion, initiated and supervised by specialist physicians experienced in the treatment of cancer. The anticipated posology of pembrolizumab, for this indication, is as follows: The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W), administered as an intravenous infusion over 30 minutes. Pembrolizumab should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.
Additional tests or investigations	No additional tests or investigations are required before initiating pembrolizumab treatment in this indication.
List price and average cost of a course of treatment	List price: £2,630 per 100mg vial Relative dose intensity (RDI) in KEYNOTE-716: [redacted]% **200 mg Q3W** • Cost per administration (list price): £5,260 • Average cost per administration, adjusted for RDI (list price): [redacted] **400 mg Q6W** • Cost per administration (list price): £10,520 • Average cost per administration, adjusted for RDI (list price): [redacted]
Patient access scheme (if applicable)	A patient access scheme (PAS) is in place which makes pembrolizumab available to the NHS for a discount of [redacted]%. [redacted]

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency; PD-1/2: programmed (cell) death protein; PD-L1/2: programmed death ligand 1/2; QxW: every x weeks; RDI, relative dose intensity; SmPC: Summary of Product Characteristics.

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

Disease overview

- Melanoma is a malignant tumour that develops from melanocytes found in the basal layer of the epidermis.[6] It is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases.[7]
- Clinical stage 2B and 2C melanoma accounts for approximately half of patients with stage 2 disease,[8] and at this stage, indicates no sign of regional metastasis.[9]
- Patients with stage 2B and 2C melanoma are at high risk of disease recurrence after complete surgical resection and have demonstrated similar recurrence rates to patients with stage 3A and 3B melanoma (5-year recurrence rates: 32% and 46% for stage 2B and 2C; 44% and 45% for stage 3A and 3B).[8-13]

Clinical management and unmet need

- Patients with stage 2B and 2C melanoma are recommended to be treated with surgery (tumour removal and wide local excision) with curative intent, followed by routine surveillance for early detection of recurrence.[14, 15]
- There are currently no treatment options beyond resection to prevent recurrence for patients with stage 2 melanoma in the UK.
- In contrast, patients with stage 3 melanoma, who have similar recurrence risk to patients with stage 2B and 2C disease,[8-13] have the option of adjuvant systemic therapy following surgical resection of the tumour to target residual micro-metastatic disease and prevent recurrence.[2, 16, 17]
- Adjuvant pembrolizumab after complete resection has been shown to significantly improve RFS and DMFS in patients with resected stage 3 melanoma,[18] and the clinical benefits of adjuvant therapy are likely to also be applicable for patients with high-risk stage 2 melanoma. Given the high risk of recurrence or death for patients with 2B and 2C melanoma, there is an unmet need for effective adjuvant treatment options that reduce the risk of disease recurrence.

Positioning of adjuvant pembrolizumab

- Adjuvant pembrolizumab is anticipated to be used in clinical practice in England as adjuvant therapy for adult patients with stage 2B and 2C melanoma and is expected to be used following surgical resection alongside the currently recommended routine surveillance.
- Introduction of pembrolizumab as an adjuvant therapy for patients with stage 2 melanoma would represent a step-change in the management of early-stage melanoma, shifting the treatment pathway towards proactively preventing recurrence. This approach is in line with the NHS long-term plan which sets out commitments for action that the NHS will take to improve prevention of disease.[19]

B.1.3.1 Disease overview

Pathogenesis

Melanoma is a malignant tumour that develops from melanocytes found in the basal layer of the epidermis.[6] Melanoma is attributed a clinical stage, according to the characteristics of the tumour and the associated spread, which is defined by Tumour, Nodes, Metastases (TNM) classification. Individual T, N and M stages describe the size/extent of the primary tumour (including depth measured by Breslow's tumour thickness and presence of ulceration

[breakdown of skin on top of melanoma]), number of cancerous lymph nodes and whether the cancer has metastasised, respectively.[20] The combination of T, N and M stages corresponds with a clinical stage group, according to the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[9]

Stage 2 melanoma is defined as having no evidence of regional metastases, although there is a possibility of non-nodal microscopic metastases.[21] Stage 2 can be further divided into Stage 2A–C, according to primary tumour thickness and ulceration, as described in Table 3. Stage 2B and 2C melanoma are node-negative, however they are characterised by deep primary tumours with or without ulceration.[13]

Table 3: Melanoma staging systems – stage 2 as per AJCC 8th edition

Clinical stage group	AJCC Tumour, Nodes, Metastases (TNM) classification system			
	Primary tumour category (T)	Primary tumour description	Lymph node category (N)†	Metastases category (M)‡
2A	pT2b	> 1.0–2.0 mm thickness with ulceration	N0	M0
	pT3a	> 2.0–4.0 mm thickness without ulceration	N0	M0
2B	pT3b	> 2.0–4.0 mm thickness with ulceration	N0	M0
	pT4a	> 4.0 mm thickness without ulceration	N0	M0
2C	pT4b	> 4.0 mm thickness with ulceration	N0	M0

This submission focuses on stage 2B and 2C.
†N0 denotes there is no metastasis in regional lymph nodes; ‡M0 denotes there is no distant metastasis.
Abbreviations: AJCC: American Joint Committee on Cancer.
Source: Gershenwald et al (2017). AJCC Cancer Staging Manual, 8th Edition.[9]

Epidemiology

Melanoma is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases with more than a quarter of new cases in England in 2019 (27.5%) being diagnosed in people aged 54 and under.[7, 22] During 2019, 15,261 new cases of melanoma were diagnosed in England.[22] Of the stageable cases (13,008), 2,488 (19.1%) were stage 2.[23] Approximately half of patients with stage 2 melanoma will have stage 2B or 2C disease.[8] Incidence rates for melanoma are projected to rise by 7% in the UK between 2014 and 2035, to 32 cases per 100,000 people by 2035.[7]

A comprehensive review undertaken by the International Agency for Research on Cancer (IARC) identified that the main risk factors associated with the development of melanoma include a familial history of melanoma, fair skin type and hair colour, high density of moles, previous history of melanoma, and additional environmental factors such as intense or chronic exposure to ultraviolet light.[24-27]

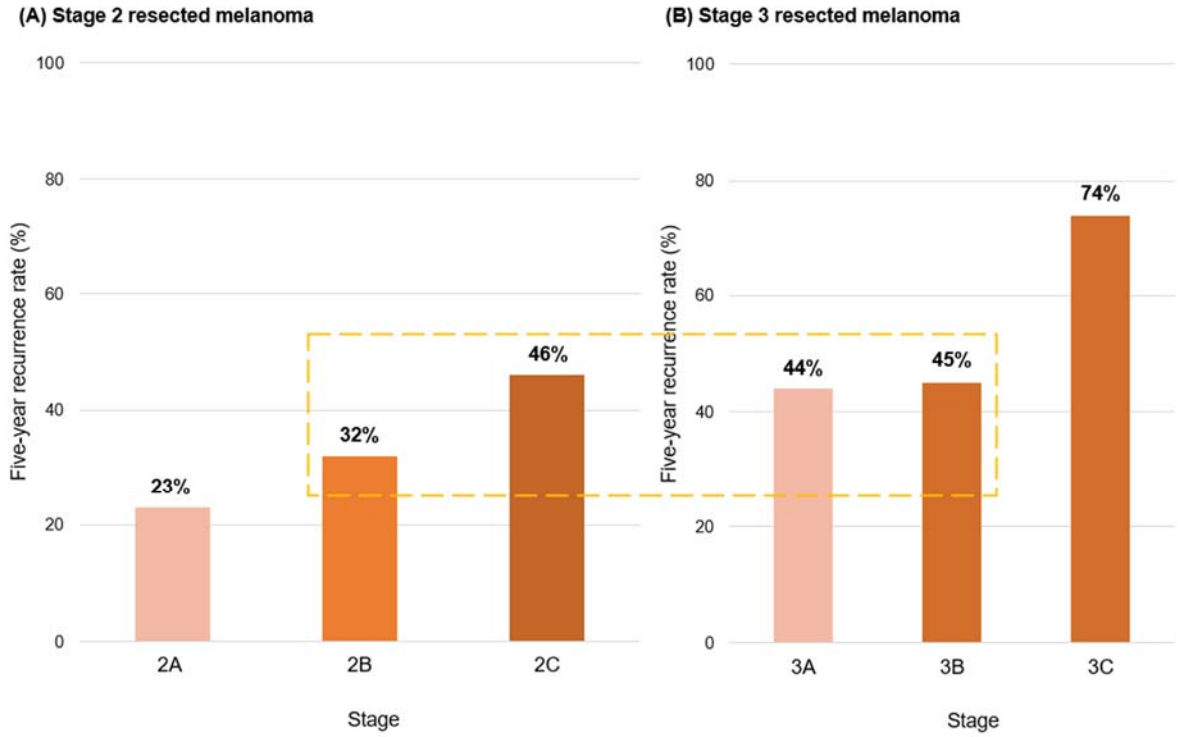
The depth of the primary tumour is the leading prognostic factor in stage 2 melanoma where the probability of survival declines as depth (measured in millimetres) increases.[28] In addition, the presence of ulceration proportionately lowers patient survival rates compared with those with nonulcerated tumours of the equivalent T category.[9, 28]

Melanoma is one of the most aggressive types of skin cancer, contributing to over 90% of all cutaneous tumour deaths globally.[29] In the UK, melanoma skin cancer is the 19th most common cause of cancer death, accounting for 1% of all cancer deaths.[30] In 2019, 1,922 people died from melanoma in England.[31] Despite recent advances in the metastatic setting, prognosis for advanced melanoma remains poor. It is therefore paramount to reduce the risk of recurrent disease with early effective treatment.

Melanoma recurrence and survival outcomes

Patients with stage 2B and 2C cutaneous melanoma are at high risk of disease recurrence after complete surgical resection, with previous studies demonstrating comparable recurrence rates to those of patients with stage 3A and 3B melanoma.[8-13] Five-year recurrence rates are shown in Figure 1; of the patients with stage 2B and 2C melanoma who progress, 50% do so within the first two years after resection of the primary tumour.[10, 13]

Figure 1: Five-year recurrence rates according to stage of melanoma



Data for stage 2 resected melanoma (A) are based on a retrospective review of 738 adult patients from 1993–2013. Patients included in this study were treated in North America.[13]
Data for stage 3 resected melanoma (B) are based on a retrospective chart review of 251 patients from 2011–2016. Patients included in this study were treated in North America, South America and Europe.[10]
Source: Lee (2017);[13] Mohr (2019).[10]

These data are supported by a recent, large real-world study which found 44.1% of patients with stage 2B and 2C disease experienced recurrence or death after a median follow-up of 38.8 months.[32]

Following surgery, stage 2B and 2C melanomas often recur with distant metastases, the rate of which is comparable between stage 2C and stage 3 melanoma (52% and 53% of relapses are recurrence with distant metastases, respectively).[10, 13, 32] The prognosis for metastatic disease is poor; less than 30% of patients with distant metastases survive for more than 5 years. The median duration of distant metastasis-free survival (DMFS), observed in real-world data, from complete surgical resection has been estimated at 113.0 months for stage 2B disease and 49.9 months for stage 2C disease.[32]

Recurrence following surgical resection is associated with substantial patient morbidity and mortality.[8] Similar to recurrence-free survival (RFS), overall survival (OS) rates are also comparable between stage 2B, stage 2C and stage 3 melanoma. Five-year OS rates have been calculated at 83.6% for stage 2B, 71.0% for stage 2C, 81.0% for stage 3A and 85.6% for stage 3B melanoma,[12] meaning that 16.4%, 29.0%, 19.0% and 14.4% of patients with

stage 2B, 2C, 3A and 3B melanoma, respectively, will die within five years from diagnosis. Further studies confirm that OS outcomes for stage 2B and 2C melanoma are similar or worse than the outcomes of patients with stage 3 disease.[33, 34]

Disease burden

The high risk of recurrence in stage 2B and 2C melanoma causes a substantial quality-of-life burden for patients, with disease recurrence requiring aggressive treatment to halt further progression.[35] Moreover, melanoma has a substantial psychological burden.[36] Post-surgery, patients grapple with the ongoing threat of recurrence and requirements of avoidance of sunburns, extended unprotected solar or artificial UV exposure, and lifelong regular self-examinations of the skin and peripheral lymph nodes.[36] Former patients have described an enduring fear of developing a new melanoma; follow-up examinations may (re)activate these fears.[36] Fear of disease recurrence has been found to be a negative predictor of distress or low quality-of-life.[36] Compared with the general population, former melanoma patients are at increased risk of depression.[36] For some patients, the option of adjuvant therapy in resected stage 2 melanoma with high risk of recurrence may reduce the mental distress associated with fear of recurrence.[37]

The economic burden of stage 2B and 2C melanoma is high, with costs associated with both initial surgical treatment and routine surveillance, and expensive systemic treatment following recurrence.[35] In the year following recurrence, the mean total healthcare cost in stages 2B and 2C is comparable to stage 3A.[11] The economic burden of melanoma generally increases with disease severity. Thus, there is an unmet need for improved treatment options in earlier stages of melanoma, which would reduce both the downstream costs and human burden associated with recurrence and progression.

B.1.3.2 Clinical pathway of care

Current clinical pathway of care in England

Clinical guidelines for assessment, management and follow-up of stage 2 melanoma are summarised in Table 4. Patients with stage 2 melanoma are currently treated with surgery (tumour removal and wide local excision) with curative intent, followed by routine surveillance for early detection of recurrence.

Table 4: Clinical guidelines for stage 2 melanoma management and follow-up

Organisation	Recommendations for assessment and management of stage 2 melanoma	Recommendations for follow-up of stage 2 melanoma
NICE NG14, 2015[14,†]	**Risk assessment:** Consider sentinel lymph node biopsy as a staging rather than a therapeutic procedure for people with stage 1B–2C melanoma with a Breslow thickness[‡] of more than 1 mm **Surgical:** Offer excision with a clinical margin of at least 2 cm to people with stage 2 melanoma	• For people who have had stages 2A–2C melanoma, consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years o Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up to people who have had stages 2A–2B melanoma or stage 2C melanoma with a negative sentinel lymph node biopsy • For people who have had stage 2C melanoma with no sentinel lymph node biopsy, or stage 3 melanoma, consider follow up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years o Consider surveillance imaging as part of follow up for people who have had stage 2C melanoma with no sentinel lymph node biopsy or stage 3 melanoma and who would become eligible for systemic therapy as a result of early detection of metastatic disease if: (a) there is a clinical trial of the value of regular imaging or (b) the specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging 6 monthly for 3 years is identified
The European Society for Medical Oncology (ESMO), 2019[15]	**Risk assessment:** Sentinel lymph node biopsy is recommended for all patients with pT1b or higher **Surgical:** Wide local excision of primary tumours with safety margins of 0.5 cm for in situ melanomas, 1 cm for tumours with a tumour thickness up to 2 mm and 2 cm for thicker tumours is recommended	• Melanoma patients should be instructed in the avoidance of sunburns, extended unprotected solar or artificial UV exposure, and in lifelong regular self-examinations of the skin and peripheral lymph nodes • During melanoma follow-up, patients are clinically monitored in order to detect a relapse and to recognise additional skin tumours, especially secondary melanomas, as early as possible • There is no consensus on optimal schedule, follow-up or the utility of imaging and blood tests for patients with resected melanoma; recommendations vary from follow-up visits every 3 months, during the first 3 years and every 6–12 months thereafter, to no

Organisation	Recommendations for assessment and management of stage 2 melanoma	Recommendations for follow-up of stage 2 melanoma
		organised follow-up at all. National guidelines should be consulted, and approaches tailored according to individual risk • Consider surveillance imaging (ultrasound, CT or whole-body PET/PET-CT scans) in high-risk patients, e.g. those with thick primary tumours

†The NICE guidance precedes the 8th edition of the AJCC Cancer Staging Manual, however there were no changes to stage 2 melanoma T-stage classifications in the 8th edition.
‡Measure from the surface of the epidermal granular layer to the point of maximum tumour thickness at a right angle to adjacent epidermis.
Abbreviations: AJCC: American Joint Committee on Cancer; CT: computerised tomography; ESMO: European Society for Medical Oncology; NICE: National Institute for Health and Care Excellence; PET: positron emission tomography; UV: ultraviolet.

Unmet treatment need

There are currently no treatment options beyond resection to prevent recurrence for patients with stage 2 melanoma in England. Adjuvant treatment could be used to further reduce the risk of recurrence at earlier disease stages, rather than waiting for loco-regional or distant recurrence to occur first.

In contrast, patients with stage 3 melanoma have the option of adjuvant systemic therapy following surgical resection of the tumour (with or without lymphadenectomy), which aims to remove any residual microscopic disease and reduce the risk of recurrence and progression to metastatic disease.[2] In clinical practice in England, around 90% of patients with stage 3 melanoma receive adjuvant therapy following surgical resection with NICE recommending the use of pembrolizumab (TA766), nivolumab (TA684) and dabrafenib with trametinib (TA544 [*BRAF* V600 mutation-positive patients]).[2, 16-18, 38]

Adjuvant pembrolizumab after complete resection has been shown to significantly improve RFS and DMFS in patients with resected stage 3 melanoma.[18] These clinical trial findings have also been confirmed in the real-world setting, demonstrating that adjuvant pembrolizumab has contributed to improvements in outcomes for melanoma patients.[39] As patients with 2B and 2C melanoma have analogous recurrence and survival risks to patients with stage 3 melanoma,[10, 13] the clinical benefits of adjuvant therapy are also applicable for patients with high-risk stage 2 melanoma. Given the high risk of recurrence or death for patients with 2B and 2C melanoma, there is an unmet need for effective adjuvant treatment options that reduce the risk of disease recurrence. While subsequent improvements in overall survival resulting from reduced recurrence are also desirable, for patients with

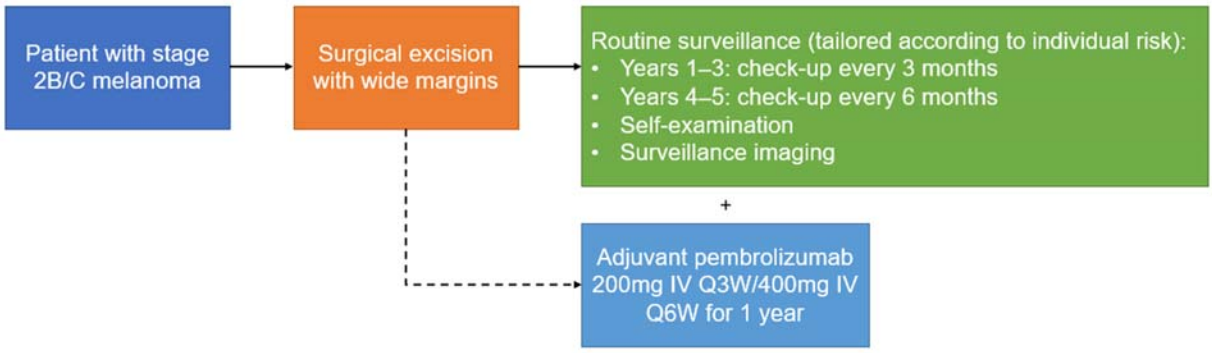
melanoma the length of time without disease recurrence is highly valued regardless of the potential associated improvement in survival.[2] Patients have stated “the stress of living with melanoma can be seen physically, mentally, and emotionally” along with uncertainty about the future in terms of the cancer returning. [2] Clinical experts have also explained if a patient is disease free for an extended time period this has a substantial benefit for their quality of life.[2] Consequently, the value of adjuvant treatment is in both its potential to improve long-term survival outcomes and also in allowing patients to experience extended periods of life that are disease-free.

Despite recent advances in the metastatic setting, prognosis for advanced melanoma remains poor. The introduction of pembrolizumab as an adjuvant therapy for patients with stage 2 melanoma would be a step-change in the management of early-stage melanoma, shifting treatment pathways towards earlier preventative treatment, proactively allowing more patients to benefit from a reduced risk of recurrence. This approach is in line with the NHS long-term plan which sets out commitments for action that the NHS will take to improve prevention of disease.[19] Clinical experts have also validated this, supporting the use of immunotherapy in the adjuvant setting as a means of reducing the risk of disease recurrence and reducing costs and complexities associated with the management of metastatic melanoma.[40]

Positioning of pembrolizumab relative to the current treatment pathway

Pembrolizumab is anticipated to be used in clinical practice in England as adjuvant therapy for patients with stage 2B and 2C melanoma following surgical resection alongside the currently recommended routine surveillance. Therefore, in the absence of any recommended adjuvant therapies, the comparator considered for this appraisal is routine surveillance only. Figure 2 shows the proposed positioning of pembrolizumab relative to the current treatment pathway (i.e. routine surveillance).

Figure 2: Proposed positioning of pembrolizumab relative to the current treatment pathway



Abbreviations: QxW: every x weeks; IV: intravenous.
Source: NICE NG14, 2015.[14]
Adjuvant pembrolizumab dosing in line with draft SmPC.[1]

The expected positioning of pembrolizumab in clinical practice is consistent with the phase 3 KEYNOTE-716 trial, the pivotal clinical trial for the use of the pembrolizumab in this indication. KEYNOTE-716 demonstrates that the use of adjuvant pembrolizumab significantly reduces the risk of recurrence compared with placebo in stage 2B and 2C melanoma. Consequently, pembrolizumab provides an effective option for the adjuvant treatment of stage 2B/2C melanoma with the potential to address the unmet need experienced by these patients.

Pembrolizumab is the most widely used immuno-oncology therapy for adjuvant treatment for stage 3, in part due to the availability and flexibility of the Q6W dosing option of pembrolizumab which benefits both patients and clinicians.[18, 38, 41] Furthermore, introduction of earlier preventative therapy to reduce the risk of metastatic disease and disease recurrence may result in reduced capacity constraints with later line therapies.

B.1.4 *Equality considerations*

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

The double-blind, randomised, placebo-controlled phase III trial, KEYNOTE-716, investigates the use of adjuvant pembrolizumab for reducing recurrence risk in patients with surgically resected stage 2B and 2C melanoma.

- Patients (n=976) were randomised 1:1 to receive adjuvant pembrolizumab (adult dose: 200 mg intravenously [IV]; paediatric dose: 2 mg/kg IV; n=487) every three weeks (Q3W), or saline placebo IV Q3W for 17 cycles (~1 year; n=489). Treatment commenced less than 12 weeks after complete surgical resection.[42]
- Results are presented from the interim analysis 2 (IA2; data cut-off 21st June 2021).[42]
- KEYNOTE-716 is well aligned with the decision problem specified in the NICE scope and the trial results are directly relevant to treatment in NHS clinical practice.

KEYNOTE-716 met its primary endpoint, demonstrating a statistically significant improvement in RFS in patients treated with adjuvant pembrolizumab compared with placebo.

- Adjuvant pembrolizumab demonstrated a 39% decreased risk of disease recurrence or death (IA2 hazard ratio [HR]=0.61; 95% CI: 0.45, 0.82; nominal p=[redacted]) in the intention-to-treat (ITT) population.[42]
- RFS results in prespecified demographic and clinical subgroups were generally consistent with the primary analysis.
- HRQoL was measured by EORTC QLQ-C30 and EQ-5D-5L. At Week 48, the difference in LS means of the EQ-5D-5L VAS of [redacted] showed [redacted].

Safety outcomes were consistent with the established, manageable safety profile of adjuvant pembrolizumab monotherapy.

- The proportion of patients experiencing any AE was comparable between the adjuvant pembrolizumab group (95.4% [461/483]) and placebo group (91.4% [444/486]).[42]
- Adverse events of special interest (AEOSIs) were predefined and corresponded to immune-mediated events and infusion-related reactions associated with adjuvant pembrolizumab. The rate of AEOSIs was higher in the pembrolizumab group compared with the placebo group ([redacted] versus [redacted]).[42]
- Type and severity of AEOSIs were consistent with the established adjuvant pembrolizumab safety profile. The most frequently reported were Grade 1 or 2, and were manageable with corticosteroids and/or hormone replacement therapy, and/or treatment interruption/discontinuation.[42]

Adjuvant pembrolizumab for stage 2B and 2C melanoma represents an important step-change in the management of early-stage melanoma, enabling more patients to remain recurrence-free.

- The preventative treatment option of pembrolizumab may provide patients with invaluable hope of sustained health, rather than awaiting recurrence, and worsening of their condition, before being treated.

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence from RCTs, non-randomised clinical trials and observation trials on the efficacy and safety of adjuvant therapies in adult and paediatric (≥12 years) patients with surgically resected stage 2B and 2C melanoma.

The SLR was conducted in September 2021 and, in total, identified seven publications reporting on seven unique studies. One included study, a phase III RCT, KEYNOTE-716, reported on pembrolizumab as the intervention. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The primary source of clinical evidence for the use of pembrolizumab is the KEYNOTE-716 trial, a double-blind, randomised, placebo-controlled, multi-centre, phase III trial to determine the efficacy and safety of pembrolizumab for reducing disease recurrence in patients (≥12 years) with surgically resected stage 2B and 2C cutaneous melanoma. The publication identified in the SLR which reported on the KEYNOTE-716 trial was an abstract presented at the European Society for Medical Oncology (ESMO) conference 2021;[43] further methodology details and trial results are presented from the clinical study report (CSR) and a second presentation at the Society for Melanoma Research (SMR) conference 2021.[44] A summary of the clinical effectiveness evidence from KEYNOTE-716 is presented in Table 5.

Table 5: Clinical effectiveness evidence for pembrolizumab

Study	**KEYNOTE-716 (NCT03553836)**		
Study design	Phase III, multi-centre, randomised, double-blind, placebo-controlled study		
Population	Patients aged ≥12 years with recently surgically resected and histologically/pathologically confirmed new diagnosis of Stage 2B or 2C cutaneous melanoma		
Intervention(s)	Pembrolizumab (N=487) administered intravenously over 17 cycles at 2 mg/kg (max. 200 mg) Q3W for paediatric participants (≥12 and <18 years old); 200 mg Q3W for adults (≥18 years of age)		
Comparator(s)	Placebo (N=489) administered intravenously over 17 cycles		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	KEYNOTE-716 is the pivotal phase III trial for pembrolizumab as adjuvant therapy for stage 2B and 2C melanoma. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in this submission.		

Reported outcomes specified in the decision problem	• **RFS** (primary endpoint) • **AEs** • **HRQoL** (assessed by EORTC QLQ-C30 and **EQ-5D-5L**) DMFS and OS are also being collected in KEYNOTE-716, however these are event-driven outcomes and the number of events required to enable analysis have not yet been reached. Currently, at IA2, reported events have reached [redacted] DMFS events and [redacted] OS events, representing only [redacted] and [redacted] of the final number of events needed for analysis, respectively.[45]
All other reported outcomes	No additional clinical outcomes were measured in the trial

Bold text indicates the outcome is used in the cost-effectiveness model.
Abbreviations: AEs: adverse events; DMFS: distant metastasis-free survival; EQ-5D-5L: EuroQoL-5 dimension questionnaire-5 levels; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL: health-related quality of life; IV: intravenous; N: number of patients; OS: overall survival; QxW: every x weeks; RFS: recurrence-free survival.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.3 *KEYNOTE-716: Summary of methodology*

B.2.3.1 Summary of trial methodology

KEYNOTE-716 is a phase III, randomised, double-blind, multi-centre study of pembrolizumab monotherapy versus placebo for the adjuvant treatment of patients with resected high-risk stage 2 melanoma.

The treatment phase of the study consists of two parts. In Part 1, patients were randomised 1:1 to receive adjuvant therapy with pembrolizumab (adult dose: 200 mg intravenously [IV]; paediatric dose: 2 mg/kg IV) Q3W, or saline placebo IV Q3W for 17 cycles (~1 year). Treatment commenced less than 12 weeks after complete surgical resection. Patients were stratified in Part 1 as follows: one stratum for paediatric patients (≥12 years of age and <18 years of age) and three strata for adult patients (≥18 years of age) based on T-stage tumour thickness and ulceration (T3b, T4a, T4b).

Patients were monitored for disease recurrence by imaging including full chest/abdomen/pelvis computed tomography (CT) and/or magnetic resonance imaging (MRI), neck CT and/or MRI for head and neck primaries, and other CT and/or MRI (as clinically needed) every six months during treatment and at the end of treatment. Disease recurrence was confirmed by investigator radiographically and/or by exam/biopsy and, when clinically appropriate, confirmed by the site via pathology. Patients are also monitored for disease recurrence post-treatment (every six months from Years 2–4 from randomisation

and then once in Year 5 from randomisation or until disease recurrence). Patients who have disease recurrence are then unblinded.

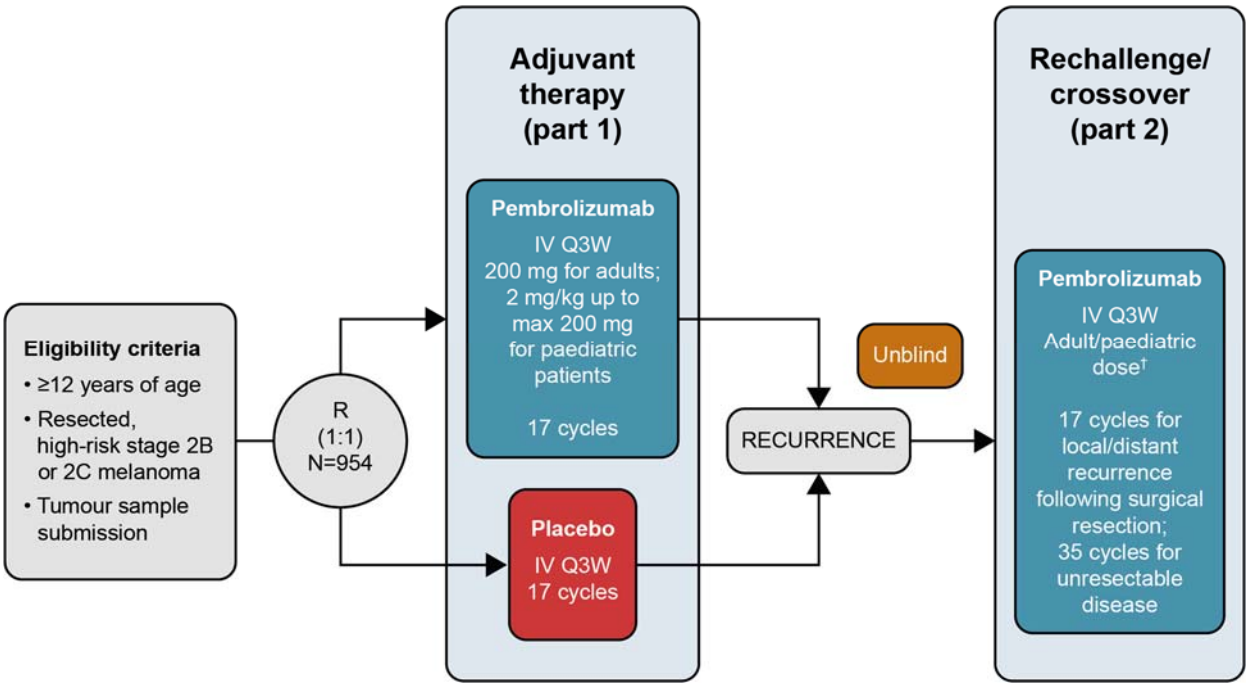
Part 2 is the unblinded crossover/rechallenge phase of the study in which eligible patients with disease recurrence, from either the pembrolizumab arm or placebo arm, can receive adjuvant treatment with pembrolizumab. Pembrolizumab is administered Q3W for 17 cycles after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis). Patients receive up to 35 cycles of pembrolizumab Q3W for unresectable disease recurrence (regional metastatic lymph nodes, in-transit, satellite, microsatellite metastases and unresectable distant recurrence).

After the end of treatment in Parts 1 and 2, each patient will be followed for the occurrence of safety events. Patients who discontinue for reasons other than confirmed metastatic disease recurrence will be followed for disease status until metastatic disease recurrence is confirmed. Patients who initiate a non-study cancer treatment will have post-treatment DMFS follow-up until metastatic disease recurrence is documented. All patients will be followed by telephone for overall survival until death or the end of the study.

The efficacy and safety results presented in this submission are from Part 1 only.

A summary of the trial design and methodology for KEYNOTE-716 (NCT03553836) is presented in Figure 3 and Table 6.

Figure 3: KEYNOTE-716 study design



†Adult dose, 200 mg Q3W; paediatric dose, 2 mg/kg Q3W (to a maximum of 200 mg Q3W).
Abbreviations: IV: intravenous; N: number of patients; QxW: every x weeks.
Source: Luke et al. 2020.[46]

Table 6: Summary of methodology for KEYNOTE-716

Trial name	KEYNOTE-716 (NCT03553836)
Location	160 centres in 16 countries: Australia, Belgium, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Poland, South Africa, Spain, Switzerland, United Kingdom (4 sites; [redacted] patients) and United States
Trial design	Phase III, multi-centre, randomised, double-blind, placebo-controlled study
Duration of study	KEYNOTE-716 is ongoing. Each patient will participate in the study for approximately 15 years from the time the patient (or their legally acceptable representative) provides documented informed consent through the final contact. The trial start date was 12th September 2018, and the estimated study completion date is 21st October 2033. Key milestones for RFS analysis were as follows: • RFS Interim analysis 1 (IA1) data cut-off date: 4th December 2020 • RFS Interim analysis 2 (IA2) data cut-off date: 21st June 2021
Method of randomisation	Treatment allocation/randomisation occurred centrally using an interactive response technology system. Patients were assigned randomly in a 1:1 ratio to pembrolizumab study treatment or saline placebo study treatment in Part 1
Method of blinding	In Part 1 of this study a double-blinding technique was used. Pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site personnel. The patient and the investigator involved in the study treatment administration or clinical evaluation of the patients were unaware of the group assignments

Trial drugs and method of administration	Pembrolizumab: • Dose formulation: Solution for infusion • Unit dose strength: 4 mL vial of 25 mg/mL pembrolizumab • Dosage levels: 2 mg/kg (max 200 mg) Q3W for paediatric patients (≥12 and <18 years old); 200 mg Q3W for adults (≥18 years of age) • Route of administration: IV infusion via infusion pump • Regimen/treatment period: up to 17 cycles in Part 1 (then an optional 17 or 35 cycles in Part 2 [if resectable or unresectable, respectively]) Saline placebo: • Dose formulation: Solution for infusion • Route of administration: IV infusion via infusion pump • Regimen/treatment period: 17 cycles (Part 1)
Permitted and disallowed concomitant medication	The following are specific restrictions or prohibitions for concomitant therapy or vaccination during the course of the study: • Antineoplastic systemic chemotherapy, immunotherapy or biological therapy not specified in the protocol • Investigational agents other than pembrolizumab • Radiation therapy • Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed. • Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI that is suspected to have an immunologic aetiology. Inhaled or topical steroids are allowed, and systemic steroids at doses ≤5mg/m2/day (maximum allowed 10 mg/day) prednisone or equivalent for paediatric participants (≥12 years old and <18 years old) and ≤10 mg/day prednisone or equivalent are allowed for adults
Primary outcomes (including scoring methods and timings of assessments)	RFS, measured as time from randomisation to (1) any recurrence (local or regional, or distant) as assessed by the investigator, or (2) death due to any cause (both cancer and noncancer causes of death)
Secondary outcomes (including scoring methods and timings of assessments)	**Secondary efficacy endpoints:** • DMFS: The time from randomisation to appearance of a distant metastasis as assessed by the investigator • OS: The time from randomisation to death due to any cause **Safety endpoints:** • AEs • Discontinuation of study treatment due to AEs **Exploratory efficacy endpoints:** • HRQoL:

	o CFB in EORTC QLQ-C30 Global Health Status/QoL o CFB in EQ-5D-5L score • TTST: The time from randomisation to the date of first subsequent therapy (e.g. surgery, radiation therapy, antineoplastic therapy) or death (any cause) • PRFS2: The time from randomisation to the earliest of the following: date of 1st disease progression beyond the initial unresectable disease recurrence; date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence; date of death • Identification of molecular biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or mechanism of action
Pre-specified subgroup analyses	N/A

Abbreviations: AEs: adverse events; BCG: Bacille Calmette-Guérin; CFB: change from baseline; DMFS: distant metastasis-free survival; ECI: event of clinical interest; EQ-5D-5L: EuroQoL-5 Dimension Questionnaire-5 Levels; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL: health-related quality of life; IV: intravenous; N: number of patients; OS: overall survival; PRFS2: progression/recurrence-free survival 2; QoL: quality of life; QxW: every x weeks; RFS: recurrence-free survival; TTST: time to subsequent therapy.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

Eligibility criteria

The key eligibility criteria for KEYNOTE-716 are presented in Table 7. The full eligibility criteria can be found in Appendix L.1.

Table 7: Key eligibility criteria for KEYNOTE-716 (Part 1)

Inclusion criteria	Exclusion criteria
• ≥12 years of age • Histologically/pathologically confirmed, newly diagnosed Stage IIB or IIC cutaneous melanoma (tumour stage of T3b, T4a, or T4b) with pathologically confirmed negative sentinel lymph node biopsy • Not previously treated for melanoma beyond complete surgical resection • No more than 12 weeks between final surgical resection and randomisation, with complete surgical wound healing • No evidence of metastatic disease on imaging as determined investigator assessment; suspicious lesions amenable to biopsy confirmed negative for malignancy • Performance status of 0 or 1 on the ECOG Performance Scale at the time of enrolment, LPS score ≥50 (for patients ≤16 years old), or a KPS score ≥50 (for patients >16 and <18 years old)	• Has a known additional malignancy that is progressing or has required active antineoplastic therapy (including hormonal) within the past 5 years • Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment • Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor • Has received prior systemic anticancer therapy for melanoma including investigational agents • Has received a live vaccine within 30 days prior to the first dose of study drug

Abbreviations: ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky performance status; LPS: Lansky performance status; PD-1: programmed (cell) death protein 1; PD-L1/2: programmed (cell) death ligand 1/2.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.3.2 Baseline characteristics

A total of 976 patients were randomised to receive pembrolizumab (N=487) or placebo (N=489). Overall, baseline characteristics were well-balanced between the two treatment arms. The mean age (SD) was [redacted] ([redacted]) years in the pembrolizumab group and [redacted] ([redacted]) years in the placebo group. The median age (range) was 60.0 (16, 84) years in the pembrolizumab group and 61.0 (17, 87) years in the placebo group. Both groups contained more males than females. The majority of patients were White, which is expected as fair skin type is a risk factor for melanoma.[7] Across both groups, 64.0% of patients had stage 2B melanoma and 34.8% of patients had stage 2C melanoma.

Clinical experts confirmed that the baseline characteristics of patients in the KEYNOTE-716 are representative of the population in England.[40] Furthermore, data published by Public Health England reports that 58% of patients diagnosed with stage 2B or 2C melanoma in 2016 and 2017 were male, whilst 42% were female. Of patients diagnosed in this period, 94% were white, 57% had stage 2B melanoma and 43% had stage 2C.[47] The baseline characteristics of patients in the KEYNOTE-716 trial reflect these data, and as such, can be considered generalisable to the population in England.

A summary of the baseline characteristics of patients enrolled in the KEYNOTE-716 trial is presented in Table 8.

Table 8: Baseline characteristics of patients in the ITT population of KEYNOTE-716

Characteristic	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Sex, n (%)			
Male	300 (61.6)	289 (59.1)	589 (60.3)
Female	187 (38.4)	200 (40.9)	387 (39.7)
Age (Years), n (%)			
12–17	1 (0.2)	1 (0.2)	2 (0.2)
18–64	302 (62.0)	294 (60.1)	596 (61.1)
≥65	184 (37.8)	194 (39.7)	378 (38.7)
Mean	[redacted]	[redacted]	[redacted]
Median	60.0	61.0	61.0
Race, n (%)			
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]

Characteristic	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Black or African American White	[redacted]	[redacted]	[redacted]
White	435 (89.3)	439 (89.8)	874 (89.5)
Missing	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
US	95 (19.5)	80 (16.4)	175 (17.9)
Non-US	392 (80.5)	409 (83.6)	801 (82.1)
ECOG, n (%)[†]			
0	454 (93.2)	452 (92.4)	906 (92.8)
1	32 (6.6)	35 (7.2)	67 (6.9)
2	0	1 (0.2)	1 (0.1)
N/A	[redacted]	[redacted]	[redacted]
KPS Status, n (%)[‡]			
100 – Normal. No complaints. No evidence of disease	[redacted]	[redacted]	[redacted]
N/A	[redacted]	[redacted]	[redacted]
T-Stage, n (%)			
T3a	[redacted]	[redacted]	[redacted]
T3b	200 (41.1)	201 (41.1)	401 (41.1)
T4a	113 (23.2)	116 (23.7)	229 (23.5)
T4b	172 (35.3)	172 (35.2)	344 (35.2)
Nodal Involvement, n (%)[§]			
NX	[redacted]	[redacted]	[redacted]
N0	[redacted]	[redacted]	[redacted]
N1C	[redacted]	[redacted]	[redacted]
Metastatic Staging, n (%)[¶]			
M0	[redacted]	[redacted]	[redacted]
M1C	[redacted]	[redacted]	[redacted]
M1D	[redacted]	[redacted]	[redacted]
Overall Cancer Stage, n (%)			
IIA	[redacted]	[redacted]	[redacted]

Characteristic	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
IIB	309 (63.4)	316 (64.6)	635 (64.0)
IIC	171 (35.1)	169 (34.6)	340 (34.8)
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Stratification, n (%)			
Paediatric Age (12–17)	[redacted]	[redacted]	[redacted]
IIB T3b >2.0–4.0 mm with ulceration	[redacted]	[redacted]	[redacted]
IIB T4a >4.0 mm without ulceration	[redacted]	[redacted]	[redacted]
IIC T4b >4.0 mm with ulceration	[redacted]	[redacted]	[redacted]

†ECOG is not applicable for paediatric patients.
‡KPS is not applicable for adult patients.
§NX indicates the regional lymph nodes cannot be evaluated; N0 indicated there is no cancer in regional lymph nodes; N1C indicates presence of in-transit, satellite, and/or microsatellite metastases.[9]
¶M0 indicates no metastatic spread; M1C indicates the cancer has spread to a non-CNS location; M1D indicates the cancer has spread to the CNS.[9]
Abbreviations: CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky performance status; N: number of patients; US: United States.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[42] Luke et al. 2021. Presented at Society for Melanoma Research congress.[44]

B.2.3.3 Concomitant medications

The majority of patients treated with pembrolizumab (95.4%) and placebo (92.0%) took concomitant medications.[42] Appendix L.4 shows the most common concomitant medications (incidence ≥5% in one or more treatment groups) in the 'all participants as treated' (ApaT) population.

B.2.4 *KEYNOTE-716: Statistical analysis and definition of study groups*

B.2.4.1 Analysis sets

The population sets used in the analysis of KEYNOTE-716 are presented in Table 9.

Table 9: Analysis sets used in the analysis of outcomes of the KEYNOTE-716 trial

Analysis set	Description
ITT population (N=976)	• Comprised all patients randomised to a treatment group • Patients were analysed according to the randomised treatment assignment following the ITT principle, irrespective of the study treatment received. • All efficacy analyses were performed on the ITT population and no patients

Analysis set	Description
	were excluded from the efficacy analysis • This included 487 patients in the pembrolizumab group and 489 patients in the placebo group
PRO FAS population (N=964)	• Comprised all patients who had at least one PRO assessment (EORTC QLQ-C30 or EQ-5D-5L questionnaire response) and received at least one dose of the study treatment • PRO analyses were performed in the PRO FAS population, which included • This included [redacted] patients in the pembrolizumab group and [redacted] patients in the placebo group
ApaT population (N=969)	• Comprised all patients who received at least one dose of study medication • Patients were included in the treatment group corresponding to the study treatment they actually received. Patients who take incorrect study treatment for the entire treatment period are included in the treatment group corresponding to the study treatment actually received, whereas, any patient who received the incorrect study treatment for one cycle, but received the correct treatment for all other cycles, were analysed according to the correct treatment group. • All safety analyses were performed on the ApaT population • This included 483 patients in the pembrolizumab group and 486 patients in the placebo group

Abbreviations: ApaT: all participants as treated; EORTC QLQ: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ: EuroQol; FAS: full analysis set; ITT: intention-to-treat; PRO: patient-reported outcome.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[42]

B.2.4.2 Patient disposition

At the time of IA2, [redacted] patients ([redacted]%) were ongoing in the pembrolizumab arm ([redacted] patients [[redacted]%] had discontinued the study) and [redacted] patients ([redacted]%) were ongoing in the placebo arm ([redacted] patients [[redacted]%] had discontinued the study). During Part 1, 162 patients (33.5%) in the pembrolizumab arm and 116 patients (23.9%) in the placebo arm had discontinued treatment. AE occurrence was the most common cause of patients in the pembrolizumab arm (n=85 [17.6%]) discontinuing a study drug, whereas recurrence was the most common cause in the placebo arm (n=60 [12.3%]). Reasons for patients discontinuing the trial and the study treatment are reported in Table 10.

Table 10. Disposition of patients in the ITT population at the time of IA2

	Pembrolizumab (N=487)	Placebo (N=489)
Trial disposition		
Discontinued	[redacted]	[redacted]
Death	[redacted]	[redacted]
Associated with COVID-19	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]

	Pembrolizumab (N=487)	Placebo (N=489)
Not associated with COVID-19, no further information	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Not associated with COVID-19, no further information	[redacted]	[redacted]
Not associated with COVID-19, subsequently died	[redacted]	[redacted]
Participants ongoing	[redacted]	[redacted]
Participant study medication disposition		
Started	483 (99.2)	486 (99.8)
Completed	[redacted]	[redacted]
Discontinued	162 (33.5)	116 (23.9)
AE	85 (17.6)	23 (4.7)
Associated with Covid-19	1 (0.2)	1 (0.2)
Lost to follow-up	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]
Physician decision	9 (1.9)	4 (0.8)
Associated with COVID-19	0 (0)	2 (0.4)
Protocol violation	4 (0.8)	1 (0.2)
Relapse/recurrence	25 (5.2)	60 (12.3)
Associated with COVID-19	0 (0)	1 (0.2)
Withdrawal by subject	39 (8.1)	26 (5.3)
Associated with COVID-19	6 (1.2)	7 (1.4)

Abbreviations: AE: adverse event.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[42] Luke et al. 2021. Presented at Society for Melanoma Research congress.[44]

B.2.4.3 Statistical analysis

The statistical analyses used for the primary endpoint, alongside the sample size calculations and methods for handling missing data are presented in Table 11.

Table 11: Summary of statistical analyses for the primary analysis in KEYNOTE-716

Hypothesis objective	The primary hypothesis of the study was to demonstrate if pembrolizumab is superior to placebo with respect to RFS as assessed by the site investigator
Statistical analysis	• A non-parametric Kaplan–Meier method was used to estimate the RFS curve in each treatment group. The treatment difference in RFS was assessed by the stratified log-rank test, with a stratified Cox proportional hazard model with Efron's method of tie handling used to assess the magnitude of the treatment difference between the treatment arms • The HR and 95% CI from the stratified Cox model with a single treatment covariate were reported. Kaplan–Meier estimates and the corresponding 95% CIs at specific follow-up time-points were provided for RFS • As disease assessment occurred periodically, and recurrence could occur at any time between assessments, the true date of the events occurring was

	approximated by the date of the first assessment at which event is objectively documented. Patients not experiencing a first recurrence event are censored at the last disease assessment • Two sensitivity analyses of RFS were conducted; one in which new primary melanomas were counted as RFS events, and another in which the following different censoring rules applied: o Patients experiencing recurrence or death after ≥2 consecutive missed disease assessments or after new anti-cancer therapy (if any), were censored at the last disease assessment prior to the date of that event occurring o Patients not experiencing recurrence or death and initiated on a new anti-cancer therapy, were censored at the last disease assessment prior to initiating the new anti-cancer therapy
Sample size, power calculation	• The study was designed to have 92% power to detect a 40% reduction in the risk of recurrence (HR of 0.60), using a log-rank test with 2-sided alpha level of 5% and 1:1 randomisation of pembrolizumab to placebo • It was calculated that 954 patients would need to be randomised 1:1 between pembrolizumab and placebo with the following assumptions: o RFS follows a cure model with a long-term RFS of 50% and the 60-month RFS estimated to be 68% o An enrolment period of 16 months and at least 32 months follow-up o A yearly drop-out rate of 4.7% • The final analysis of RFS in this the study was event driven, intended to be conducted after 179 RFS events were observed among all patients (expected to ~48 months after first patient was randomised)
Data management, patient withdrawals	The primary efficacy analysis and safety analysis used all available data from all patients in the respective populations (ITT and APaT), irrespective of premature discontinuation from the study medication

Abbreviations: ApaT: all participants as treated; CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; RFS: recurrence-free survival.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[42]

B.2.5 *KEYNOTE-716: Quality assessment*

A quality assessment of the KEYNOTE-716 trial was performed using the Cochrane risk-of-bias tool for randomised trials (ROB-2),[48] the results of which are presented in Table 12 and demonstrate low risk of bias across all areas for both efficacy (RFS) and safety (AE) outcomes. Full details of the SLR, including methods and the justification for each indicated risk of bias assessment made can be found in Appendix D.

Table 12: Quality assessment of the KEYNOTE-716 against ROB-2 criteria

Area of potential bias	Risk of bias within the specified outcome	
	RFS	AE
Randomisation process	Low	Low
Deviations from the intended interventions	Low	Low

Area of potential bias	Risk of bias within the specified outcome	
	RFS	AE
Missing outcome data	Low	Low
Measurement of the outcome	Low	Low
Selection of the reported result	Low	Low
Overall risk of bias	Low	Low

Abbreviations: AE: adverse event; RFS: recurrence-free survival.

B.2.6 *KEYNOTE-716: Clinical effectiveness*

The results presented in this submission are based on the second interim analysis (IA2), with 187 RFS events as of the data cut-off (21st June 2021). The median duration of follow-up for all participants (ITT population) was 20.5 months (range: 4.6 to 32.7 months) as of the data cut-off, with a similar median duration of follow-up across treatment groups.

B.2.6.1 Primary efficacy endpoint: RFS

At IA2, adjuvant pembrolizumab treatment resulted in a statistically significant improvement in RFS compared with placebo, demonstrating a 39% decreased risk of disease recurrence or death (hazard ratio [HR]=0.61 [95% CI: 0.45, 0.82]; nominal p=[redacted]). This IA2 supportive analysis was consistent with the primary RFS analysis at IA1 (HR=0.65 [95% CI: 0.46, 0.92]; p=[redacted]), where KEYNOTE-716 achieved the success criterion for the primary RFS endpoint.

As of the data cut-off, the median RFS was not yet reached in either treatment group. Main time-to-event analysis of RFS is presented for the ITT population in Table 13.

Table 13: Analysis of RFS (Primary Censoring Rule) (ITT Population)

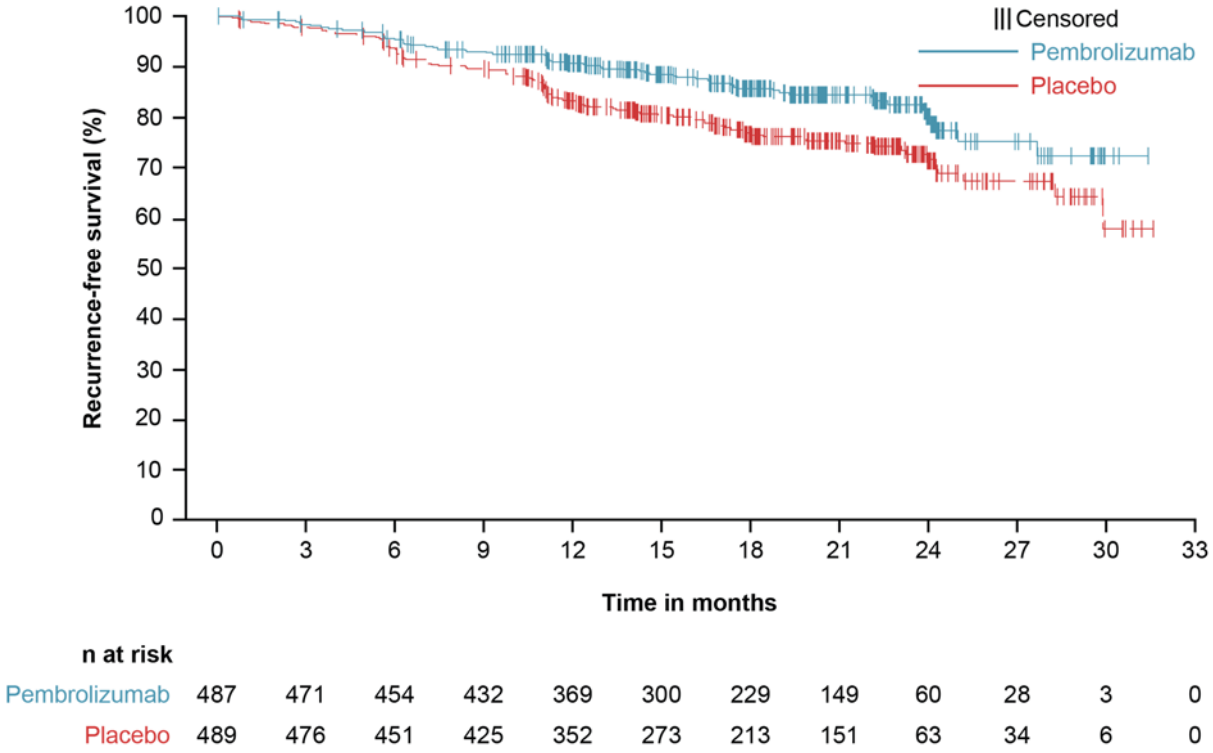
Treatment	N	Number of Events (%)	Person-month	Event Rate/100 Person-months	Median RFS† (months) (95% CI)	RFS Rate at 18 months† (%) (95% CI)
Pembrolizumab	487	72 (14.8)	[redacted]	[redacted]	NR (NR, NR)	85.8 (82.0, 88.9)
Placebo	489	115 (23.5)	[redacted]	[redacted]	NR (29.9, NR)	77.0 (72.6, 80.7)
Pairwise Comparisons					**HR‡, (95% CI)**	**Nominal p value§,¶**
Pembrolizumab vs. Placebo					0.61 (0.45, 0.82)	[redacted]

†From product-limit (Kaplan–Meier) method for censored data.
‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
§One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
¶ Statistical testing is nominal as RFS endpoint was met at IA1.

Abbreviations: CI: confidence interval; ITT: intention to treat; HR: hazard ratio; NR: not reached; RFS: recurrence-free survival.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

The Kaplan–Meier (KM) curves for RFS separated at Month 6 and remained separated through the period assessed (Figure 4) with RFS rates at 12, 18, and 24 months being higher in the pembrolizumab group compared with the placebo group (Table 14).

Figure 4: Kaplan–Meier estimates of RFS (primary censoring rule) (ITT population)



Abbreviations: ITT: intention to treat; RFS: recurrence-free survival.
Source: Luke et al. 2021. Presented at Society for Melanoma Research congress.[44]

Table 14: RFS rate over time

RFS rate at time point	Pembrolizumab (N=487), % (95% CI)†	Placebo (N=489), % (95% CI)†
6 months	95.6 [redacted]	93.6 [redacted]
12 months	90.8 [redacted]	83.3 [redacted]
18 months	85.8 [redacted]	77.0 [redacted]
24 months	80.5 [redacted]	71.7 [redacted]

†From product-limit (Kaplan–Meier) method for censored data.
Abbreviations: CI: confidence interval; NR: not reached; RFS: recurrence-free survival.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

Overall, fewer participants in the pembrolizumab group experienced disease recurrence during Part 1 of the study compared with the placebo group (Table 15). The most frequent type of recurrence was distant metastases, and the percentage of participants with this type

of recurrence in the pembrolizumab group (31 [6.37%] participants) was almost half compared with the placebo group (60 [12.27%] participants). The percentage of patients with Local/Regional/Locoregional recurrence was similar in the pembrolizumab and placebo groups (38 [7.80%] vs 50 [10.22%], respectively). Overall, 8 deaths contributed to the RFS events: 3 deaths in the pembrolizumab group ([redacted]), and 5 deaths in the placebo group ([redacted]) (Table 15).

Table 15: Type of First RFS Event (ITT Population)

Type of first event in RFS analysis	Pembrolizumab (N=487), n (%)	Placebo (N=489), n (%)
All events	72 (14.78)	115 (23.52)
Local/Regional/Loco-regional	38 (7.80)	50 (10.22)
Local†	[redacted]	[redacted]
Regional‡	[redacted]	[redacted]
Loco-regional§	[redacted]	[redacted]
Distant¶,††	31 (6.37)	60 (12.27)
Death	3 (0.62)	5 (1.02)

†Local: Tumour recurrence is in the immediate vicinity of primary tumour (i.e. skin, in transit lesions, micro-satellite metastases);
‡Regional: Regional Lymph node basin involvement;
§Loco-regional: Tumour recurrence is in the immediate vicinity of primary tumour and regional lymph node basin metastasis is noted. Tumour has not spread beyond regional lymph nodes;
¶Distant: Metastasis is beyond the regional lymph node basin;
††Includes distant event diagnosed within 30 days from Local/Regional/Locoregional event.
Abbreviations: ITT: intention to treat; RFS: recurrence-free survival.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[42] Luke et al. 2021. Presented at Society for Melanoma Research congress.[44]

B.2.6.2 Secondary efficacy endpoints

DMFS and OS

Analysis of DMFS and OS is event driven. As of IA2 data cut-off, insufficient events had occurred to enable analyses of these outcomes to be conducted. As noted in the protocol, these secondary endpoints (DMFS/OS) will be analysed at separate future IAs once the prespecified protocol criteria of target event numbers has been reached.[45] Reported events at IA2 have reached [redacted] DMFS events and [redacted] OS events, representing only [redacted] and [redacted] of the final number of events needed for analysis, respectively.[45] KEYNOTE-716 is ongoing and will continue to these endpoints.

Patient-reported outcomes (PROs)

HRQoL was measured in KEYNOTE-716 via the EQ-5D-5L and EORTC QLQ-C30 questionnaires, administered at baseline (Cycle 1), every fourth cycle (i.e. every 12 weeks)

during treatment in year 1, every 12 weeks during year 2, every 6 months during year 3, at the treatment discontinuation visit, and at the 30-day follow-up visit. Results for the EQ-5D-5L are presented below; results for the EORTC QLQ-C30 are presented in Appendix L.2.

EQ-5D-5L

At Week 48, the completion rates for the EQ-5D-5L were [redacted] and [redacted], in the pembrolizumab and placebo groups, respectively, and the compliance rates were [redacted] and [redacted], respectively.

Analysis of the EQ-5D-5L visual analogue scale (VAS) score at Week 48 showed [redacted] (nominal p value = [redacted]) (Table 16; Figure 5).

Table 16: Analysis of change from baseline in EQ-5D-5L VAS to Week 48 (FAS population)

Treatment	Baseline		Week 48		CFB to Week 48	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†,‡]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise Comparison	Difference in LS Means[†,‡] (95% CI)	Nominal p value[†,‡]
Pembrolizumab vs. Placebo	[redacted]	[redacted]

For baseline and Week 48, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
[†]Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction, stratification factor melanoma T stage (2B T3b greater than 2.0–4.0 mm with ulceration vs. 2B T4aCS greater than 4.0 mm without ulceration vs. 2C T4b greater than 4.0 mm with ulceration) as covariate.
‡ Statistical testing for PROs is nominal and is not adjusted for multiple testing.
Abbreviations: CFB: change from baseline; EQ-5D-5L: EuroQoL-5 Dimension Questionnaire; QoL: quality of life; PRO: patient-reported outcomes; LS: least squares; VAS: visual analogue scale.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

Figure 5: Empirical mean change from baseline and 95% CI for the EQ-5D VAS over time by treatment group (FAS population)

[redacted]

Abbreviations: EQ-5D-5L: EuroQoL-5 Dimension Questionnaire; FAS: Full analysis set; QoL: quality of life; VAS: visual analogue scale.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.7 *Subgroup analysis*

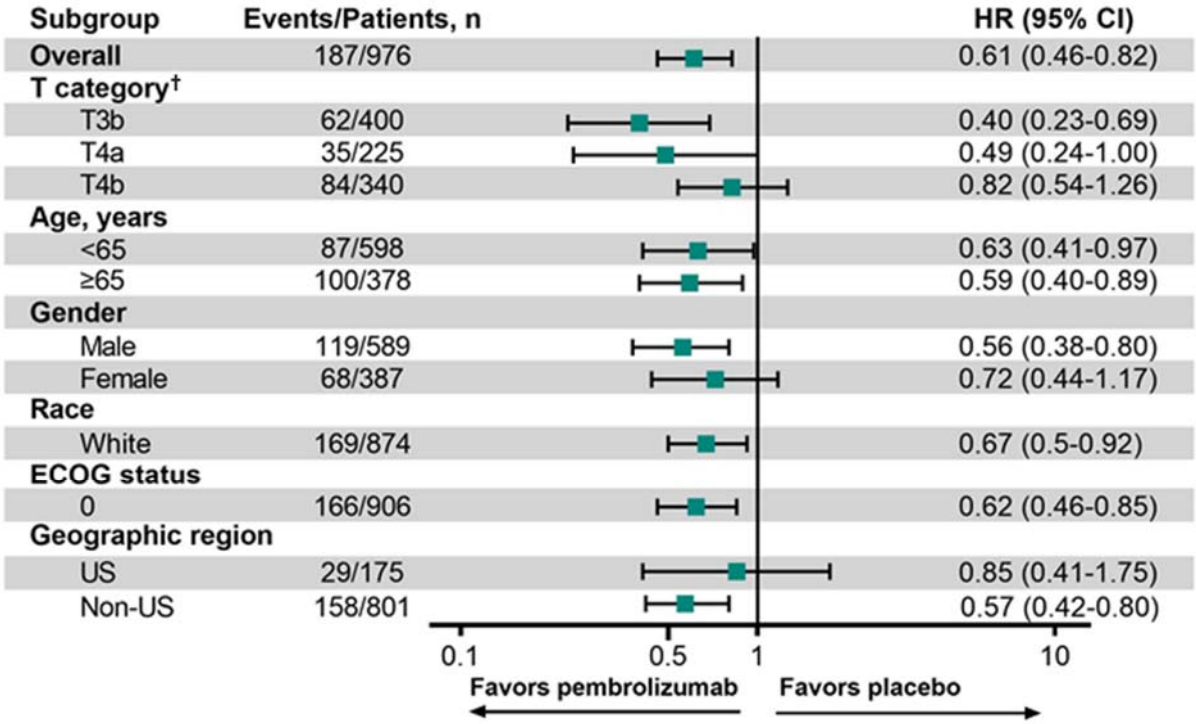
Pre-specified subgroup analyses of RFS were conducted to determine the consistency of treatment effect across the following variables:

- T-stage (T3b versus T4a versus T4b)
- Age (<65 years versus ≥65 years)
- Sex (male versus female)
- Race (White versus non-white)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) or equivalent Lansky Play-Performance Scale (LPS) status

The results of the subgroup analysis are reported in Figure 6. RFS results in prespecified demographic and clinical subgroups were generally consistent with the ITT analysis,

although certain subgroup factors (e.g. US participants) had a smaller number of participants and events, resulting in a wide 95% CI for the hazard ratio (HR).

Figure 6: RFS stratified by prespecified subgroups



The KEYNOTE-716 trial was not powered for these subgroup analyses. Small sample sizes led to large CIs for these analyses.
†Based on actual baseline tumour stages 2B and 2C collected on eCRF.
Abbreviations: CI: confidence interval; ECOG: European Cooperative Oncology Group; HR: hazard ratio; RFS: recurrence-free survival; US: United States.
Source: Luke et al. 2021. Presented at Society for Melanoma Research congress.[44]

B.2.8 *Meta-analysis*

Due to the identification of only one study evaluating the efficacy and safety of pembrolizumab for recurrence and survival in patients with surgically resected stage 2B and 2C cutaneous melanoma (i.e. the KEYNOTE-716 trial), no meta-analysis was performed.

B.2.9 *Indirect and mixed treatment comparisons*

Given the KEYNOTE-716 trial provides robust, head-to-head data for pembrolizumab versus routine surveillance, the comparator for this appraisal, no indirect or mixed treatment comparisons were conducted.

B.2.10 *Adverse reactions*

The overall frequency and type of adverse events (AEs) reported in KEYNOTE-716 were generally consistent with the established safety profile of pembrolizumab monotherapy.

B.2.10.1 Patient exposure

Table 17 gives a summary of drug exposure; Table 18 shows proportion of patients with exposure by duration.

Table 17: Summary of drug exposure (APaT population)

	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
Number of days on therapy			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of administrations			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Number of days on therapy is calculated as last dose date − first dose date +1.
Abbreviation: ApaT: all participants as treated; SD, standard deviation.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

Table 18: Exposure by duration (APaT population)

Duration of exposure	Patients, n (%)		
	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
>0 month	[redacted]	[redacted]	[redacted]
≥1 months	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]
≥9 months	[redacted]	[redacted]	[redacted]
≥10 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]

Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Abbreviation: ApaT: all participants as treated.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.10.2 Summary of AEs

Table 19 presents a summary of AEs in the KEYNOTE-716 trial.

Table 19: Overview of AEs (APaT population)

	Patients, n (%)†	
	Pembrolizumab, N=483	**Placebo, N=486**
Any AE	461 (95.4)	444 (91.4)
Any AE related to study drug‡	400 (82.8)	308 (63.4)
Any AE with toxicity grade 3–5	136 (28.2)	93 (19.1)
Any AE related to study drug‡ with toxicity grade 3–4§	82 (17.0)	21 (4.3)
Any SAE	[redacted]	[redacted]
Any SAE related to study drug‡	[redacted]	[redacted]
Death	[redacted]	[redacted]
Death related to study drug‡	0 (0.0)	0 (0.0)
Any AE leading to discontinuation	[redacted]	[redacted]
Any AE related to study drug‡ leading to discontinuation	79 (16.4)	12 (2.5)
Any SAE leading to discontinuation	[redacted]	[redacted]
Any SAE related to study drug‡ leading to discontinuation	[redacted]	[redacted]

Includes non-serious AEs up to 30 days after receiving the final dose of treatment (i.e. up to one year after initiating treatment in patients who completed the regimen) and serious AEs (SAEs) up to 90 days after receiving the final dose of treatment.
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
‡Related events as determined by the Investigator.
§No grade 5 treatment-related adverse events occurred.
Abbreviation: AE: adverse event; ApaT: all participants as treated; SAE: serious adverse event.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[42] Luke et al. 2021. Presented at Society for Melanoma Research congress.[44]

B.2.10.3 Adverse events

Table 20 presents AEs with an incidence ≥5% in one or more treatment arms. Most AEs were Grade 1 or 2; there were no grade 3–5 AEs with incidence ≥5% in one or more treatment arms.

Table 20: Participants with AEs (any grade) by decreasing incidence (incidence ≥5% in one or more treatment groups) (ApaT population)

AE, n (%)	Pembrolizumab, N=483	Placebo, N=486
Participants with one or more adverse event	461 (95.4%)	444 (91.4)
Fatigue	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]

AE, n (%)	Pembrolizumab, N=483	Placebo, N=486
Headache	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
Includes non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment.
Abbreviations: AE: adverse event; ApaT: all participants as treated.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.10.4 Drug related AEs

Table 21 shows specific drug-related AEs (any grade) with incidence ≥10% in one or both treatment arms. There were no drug related grade 3-5 AEs with incidence ≥5% in one or both treatment arms.

Table 21: Drug-related AEs (any grade) with incidence ≥10% in one or both treatment arms (ApaT population)

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Participants with one or more adverse event	400 (82.8)	308 (63.4)
Pruritus	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
Includes non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment.
Abbreviations: AE: adverse event; ApaT: all participants as treated.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.10.5 Serious adverse events (SAEs)

Table 22 shows SAEs with incidence ≥1% in one or both treatment arms. There were no drug-related SAEs with incidence ≥1% in one or both treatment arms.

Table 22: SAEs with incidence ≥1% in one or both treatment arms (ApaT population)

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Participants with one or more adverse event	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Squamous cell carcinoma of skin	[redacted]	[redacted]
Malignant melanoma in situ	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
Includes SAEs up to 90 days of last treatment.
Abbreviations: ApaT: all participants as treated; SAE: serious adverse event.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.10.6 AEs of special interest

Predefined AEs of special interest (AEOSI), corresponding to immune-mediated events and infusion-related reactions associated with pembrolizumab, were analysed. Overall, the type and severity of AEOSIs were consistent with the established pembrolizumab monotherapy safety profile. Most AEOSIs were Grade 1 or 2 and were generally manageable with corticosteroids and/or hormone replacement therapy, and/or with treatment interruption/discontinuation. Table 23 summarises the rates of AEOSIs (in which ≥1 event

occurred in either group); further details of the specific AESOI subtype and severity grade can be found in Appendix L.3.

Table 23: AEOSIs (any grade; ApaT Population)

Patients, N (%)[a]	Pembrolizumab, N=483	Placebo, N=486
Participants with one or more adverse event	182 (37.7)	44 (9.1)
Adrenal Insufficiency	12 (2.5)	0 (0)
Colitis	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypophysitis	12 (2.5)	0 (0)
Hypothyroidism	83 (17.2)	17 (3.5)
Infusion Reactions	[redacted]	[redacted]
Myasthenic Syndrome	[redacted]	[redacted]
Myelitis	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Sarcoidosis	[redacted]	[redacted]
Severe Skin Reactions	[redacted]	[redacted]
Thyroiditis	8 (1.7)	2 (0.4)
Type 1 Diabetes Mellitus	2 (0.4)	0 (0)
Uveitis	[redacted]	[redacted]

Abbreviation: AEOSI: adverse event of special interest.
Source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[42]

B.2.11 *Ongoing studies*

KEYNOTE-716 is an ongoing RCT which will continue until the number of DMFS and OS events reaches the criteria required for the analyses to be conducted. The final analyses of DMFS and OS will take place when [redacted] and [redacted] events have been observed, respectively. At IA2, [redacted] DMFS events and [redacted] OS events have been reported, representing only [redacted] and [redacted] of the final number of events needed for analysis, respectively.

Part 2 of KEYNOTE-716 will follow on from Part 1, in which eligible patients with disease recurrence are offered further treatment with pembrolizumab for 17 cycles after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis) or up to 35 cycles of pembrolizumab Q3W for unresectable disease

recurrence (unresectable local [regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases] or unresectable distant recurrence).

B.2.12 *Innovation*

Pembrolizumab has the potential to introduce an important step-change in the management of stage 2B and 2C melanoma in clinical practice in England.

As described in Section B.1.3.2**Error! Reference source not found.**, adjuvant immunotherapy after complete resection has shown increased benefits in both RFS and DMFS in patients with resected stage 3 melanoma and is now widely used in clinical practice.[18] Contrastingly, patients with resected stage 2 melanoma are not offered adjuvant therapy despite those with stage 2B and 2C melanoma having analogous survival and recurrence risks to those with stage 3 melanoma.[8, 49] Given the high risk of recurrence for patients with 2B and 2C melanoma, there is an unmet need for effective, preventative adjuvant treatment options that enable more patients to remain recurrence-free.

Introduction of pembrolizumab as an adjuvant therapy for patients with stage 2 melanoma would represent a step-change in the management of these patients, shifting treatment pathways towards proactively preventing metastasis, allowing more patients to benefit from reduced risk of recurrence. This approach is in line with the NHS long-term plan which sets out commitments for action that the NHS will take to improve prevention of disease.[19]

As an effective treatment for reducing recurrence of melanoma, adjuvant pembrolizumab may minimise the enduring fear of recurrence that many former melanoma patients experience and the corresponding negative impact this has on HRQoL.[36] As an adjuvant treatment, pembrolizumab aims to supplement potentially curative surgery by removing any remaining residual microscopic disease and therefore further reducing the risk of recurrence and progression to metastatic disease.[2] This preventative approach may provide patients with invaluable hope of sustained health, rather than awaiting recurrence, and worsening of their condition, before being treated. The benefits of this are already implied by the offering of adjuvant treatment in patients with stage 3 melanoma who are similarly at risk of recurrence and therefore may experience the same associated fear, but who are empowered with a greater range of treatment options.

The KEYNOTE-716 trial provides evidence that pembrolizumab is an effective treatment option, with a manageable side effect profile, for patients with stage 2B or 2C melanoma and who have undergone complete resection. Pembrolizumab would be the first adjuvant

treatment option available for these patients, enabling a greater proportion of patients to experience prolonged time without cancer and consequently reducing the overall burden of advanced melanoma treatment for the NHS.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principle findings from the clinical evidence base

Adjuvant pembrolizumab provided statistically significant improvements in RFS compared with placebo, enabling more patients to remain recurrence-free

The KEYNOTE-716 trial comprises the complete clinical evidence base for this submission. KEYNOTE-716 is a phase III, randomised, double-blind, multi-centre study of pembrolizumab monotherapy versus placebo for the adjuvant treatment of patients with resected high-risk stage 2 melanoma.

KEYNOTE-716 met its primary endpoint early at IA1, with adjuvant pembrolizumab demonstrating a significant 39% reduction in the risk of disease recurrence or death (hazard ratio [HR]=0.61 [95% CI: 0.45, 0.82]; nominal p=[redacted]) at the time of the latest data cut-off (21st June 2021; IA2). At IA2, the median duration of follow-up for all participants (ITT population) was 20.5 months (range: 4.6 to 32.7 months), with a similar median duration of follow-up across treatment groups. The Kaplan–Meier (KM) curves for RFS separated at Month 6 and remained separated through to Month 24, with RFS consistently improved in the adjuvant pembrolizumab arm compared with the placebo arm, thereby demonstrating the sustained effect of adjuvant pembrolizumab on RFS up to month 24.

Additionally, RFS results in prespecified demographic and clinical subgroups were broadly consistent with the primary analysis. Certain subgroup factors (e.g. US participants) had a smaller number of participants and events, resulting in wide 95% CI for the HR, however, overall, consistent improvements in RFS were seen with adjuvant pembrolizumab compared with placebo.

Analyses of DMFS and OS are event driven and as of IA2, insufficient events had occurred to enable analyses of these outcomes to be conducted. KEYNOTE-716 is ongoing, with DMFS and OS to be analysed at future IAs once the prespecified protocol criteria of target event numbers has been reached. Whilst OS data are not yet available from KEYNOTE-716, a significant survival advantage has been demonstrated by the use of adjuvant immunotherapy in resected high-risk stage 2 melanoma, with a recent study reporting a

significant improvement in 3-year OS for patients who received adjuvant immunotherapy compared with those who did not (82.5% versus 72.5%, p<0.001).[50] It is worth noting, however, that there are some differences in the eligible populations between this study and the KEYNOTE-716 trial, and due to a number of other identified limitations, it is not possible to draw any firm conclusions on OS benefit at this time.

HRQoL was measured in both treatment groups of KEYNOTE-716 (FAS population) by EORTC QLQ-C30 and EQ-5D-5L. At Week 48, completion rates of EQ-5D-5L were [redacted] and [redacted], in the pembrolizumab and placebo groups, respectively, and the compliance rates were [redacted] and [redacted], respectively. The difference in LS means of the EQ-5D-5L VAS at Week 48 of [redacted] showed [redacted].

Safety outcomes were consistent with the established safety profile of adjuvant pembrolizumab monotherapy

Overall, the proportion of patients experiencing any AE was comparable between the two treatment groups in KEYNOTE-716. Additionally, the type and severity of predefined AEOSIs, corresponding to immune-mediated events and infusion-related reactions associated with pembrolizumab, were consistent with the established pembrolizumab monotherapy safety profile. Most AEOSIs were Grade 1 or 2, and were generally manageable with corticosteroids and/or hormone replacement therapy, and/or with treatment interruption/discontinuation.[42]

B.2.13.2 Strengths and limitations of the evidence base

Internal validity

As discussed in Section B.2.5, the KEYNOTE-716 trial was methodologically robust and well-reported, with results considered to be of low risk of bias:

- Participants were appropriately randomised using an interactive response technology system, with concealed treatment allocation and participants as well as investigators administering treatment and/or performing clinical evaluations were blinded
- The sample size was sufficient to detect a difference in the primary objective of RFS between the two treatment groups
- Participant flow through the study was well reported. There were no meaningful differences in the rates of treatment discontinuation and drop-out between treatment

arms, and the sample size was significant to detect a difference in the primary objective of RFS between the two treatment groups

- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation, and participants experiencing a greater than 12-week delay between doses (due to treatment-related AE) were discontinued

External validity

The results of the KEYNOTE-716 trial can be considered generalisable to clinical practice in England and are well aligned with the decision problem specified in the NICE scope. The external validity of the KEYNOTE-716 trial is supported by the following:

- **Population** – the study population of KEYNOTE-716 was defined as patients with resected stage 2B or 2C melanoma in line with the decision scope, stratified to paediatric patients (≥12 years and <18 years of age) and adult patients (≥18 years of age) who were further stratified by T-stage. Based on feedback from clinical experts and data from Public Health England (Section B.1.3.1), the KEYNOTE-716 population can be considered relevant to the epidemiology of melanoma in England.[40, 47]

- **Intervention** – adjuvant pembrolizumab was directly evaluated as a treatment option for patients with surgically resected stage 2B and 2C melanoma, administered in line with the intended marketing authorisation.

- **Comparator** – the efficacy and safety of adjuvant pembrolizumab was directly compared with that of placebo. In this study, placebo was in line with routine surveillance which represents the current recommended management of patients with surgically resected stage 2B and 2C melanoma.[14, 51] As such, the comparison of adjuvant pembrolizumab to placebo in KEYNOTE-716 directly addresses the decision problem specified by the NICE scope.

- **Outcomes** – RFS, HRQoL and AEs were evaluated in KEYNOTE-716, all of which were outlined in the scope and are relevant to both patients and clinicians.

Limitations

A limitation of the KEYNOTE-716 study is the small numbers of patients who are aged 12 to 17 with one adolescent recruited to each arm. This may lead to insufficient data for robust modelling specifically for this group. The paediatric patients in the trial received pembrolizumab but as a modified dose of 2 mg/kg up to a maximum of 200mg Q3W.

The ongoing KEYNOTE-716 study has not yet reported OS and DMFS data. However, the absence of these data in studies of adjuvant therapies indicates that the intervention is achieving the aim of reducing the incidence of recurrence and therefore this should be considered a positive result for patients. These outcomes have therefore not been included in the submission as the prespecified number of either type of event required for analysis have not yet been reached. However, this should not be a barrier to effective decision-making given the significant benefit demonstrated in the RFS data from the KEYNOTE-716 trial, and the success of adjuvant therapies in the stage 3 setting. In prior NICE appraisals for adjuvant treatments in stage 3 melanoma (TA544, TA684, TA766) mature OS and DMFS data were not available, and improvements in RFS were considered by the committee to be associated with a DMFS and OS benefit.[2, 16, 17]

Whilst OS data are not yet available, a significant survival advantage has been demonstrated by the use of adjuvant immunotherapy in resected high-risk stage 2 melanoma, with a recent study reporting a significant improvement in 3-year OS for patients who received adjuvant immunotherapy compared with those who did not (82.5% versus 72.5%, $p<0.001$).[50] Additionally, the effect of pembrolizumab on RFS is well-established in KEYNOTE-716 and is quantified in the cost-effectiveness analysis to provide compelling evidence of the value of pembrolizumab in this population, based on RFS and the associated impact.

B.2.13.3 End-of-life criteria

Pembrolizumab does not meet the NICE end-of-life criteria in this indication.

B.2.13.4 Conclusion

The quality of the evidence provided by the KEYNOTE-716 trial is supported by robust and well-reported methodology, and the trial results are directly relevant to the treatment of patients with stage 2B or 2C melanoma and who have undergone complete resection in NHS clinical practice. Adjuvant pembrolizumab improved RFS compared with placebo in patients with surgically resected stage 2B or 2C melanoma, with a manageable safety profile.

Adjuvant pembrolizumab has the potential to introduce an important step-change in the management of stage 2B and 2C melanoma, particularly as there are currently no treatment options available for patients beyond resection to minimise recurrence for patients with stage 2B and 2C melanoma. Implementation of adjuvant pembrolizumab in this population would contribute towards a shift in focus within clinical practice in England to earlier prevention of melanoma recurrence and enabling more patients to be cancer-free.

B.3 Cost effectiveness

Summary

- A robust economic analysis produced an incremental cost-effectiveness ratio (ICER) of £4,616 per QALY for adjuvant pembrolizumab versus routine surveillance
- There was a 76.9% probability of being cost-effective at a willingness to pay of £30,000 per QALY
- Across a wide range of scenarios and sensitivity analyses, the ICERs remained stable and well below the £30,000 per QALY threshold

Overview of analysis

- A de novo economic model was developed to estimate the cost-effectiveness of adjuvant pembrolizumab versus routine surveillance, in patients with resected stage 2B and 2C melanoma based on the KEYNOTE-716 trial.
- A 4-state Markov state transition model was used, with health states designed to reflect the natural history of melanoma: recurrence-free (RF), locoregional recurrence (LRR), distant metastases (DM), and Death.
- The efficacy and safety of adjuvant pembrolizumab was informed by data from the RFS analysis, and adverse event findings, in KEYNOTE-716 (interim analysis 2, data cut-off 21st June 2021)
- Other inputs were sourced from real-world data, published studies, and publicly available sources of information.

- **The model demonstrates that the use of pembrolizumab for the adjuvant treatment of resected stage 2B/2C melanoma is a highly effective and cost-effective strategy versus routine surveillance:**
    - The incremental cost-effectiveness ratio (ICER) was £4,616 per QALY gained
    - There was a 76.9% probability of being cost-effective at a willingness to pay of £30,000 per QALY
- The use of adjuvant pembrolizumab reduces the risk of recurrence, and consequently reduces the downstream costs of treating and managing locoregional and metastatic recurrences.
    - Adjuvant pembrolizumab resulted in 1.45 additional life years compared with routine surveillance, which translated into [redacted] additional QALYs.
    - Due to reduced incidence of recurrence, downstream treatment costs following adjuvant pembrolizumab were reduced by [redacted] per patient.
- The ICER was largely insensitive to the parameters and assumptions tested in extensive sensitivity and scenario analyses, with all scenarios remaining <£30,000 per QALY

- **Pembrolizumab is shown to be a highly cost-effective use of NHS resources for patients with resected stage 2B/2C melanoma and therefore should be recommended to routine commissioning to address the high unmet need in this patient group.**

B.3.1 *Published cost-effectiveness studies*

A systematic literature review (SLR) was conducted on 6th October 2021 to identify studies reporting on the cost-effectiveness of adjuvant therapies for stage 2 melanoma. Seven studies evaluating the cost-effectiveness of adjuvant therapies were included, however no publications assessing the cost-effectiveness of pembrolizumab were identified. Full details of the search strategy, study selection process and results are presented in Appendix G.

B.3.2 *Economic analysis*

The cost-effectiveness analysis compared adjuvant treatment with pembrolizumab versus routine surveillance for patients with resected stage 2B/2C melanoma, from the perspective of the UK NHS and Personal Social Services (PSS) over a lifetime time horizon. No studies relevant to the current decision problem were identified in the SLR, therefore a de novo economic model was developed. The model used a Markov structure, populated with data from KEYNOTE-716 and supplemented by data from external sources where required.

B.3.2.1 Patient population

The economic model considered patients with stage 2B or 2C melanoma who have undergone complete resection, in line with the anticipated licence for pembrolizumab and the scope of the current appraisal. Baseline characteristics of the model patient cohort were set to reflect the patients enrolled in the KEYNOTE-716 trial (Luke et al, 2021).[42, 44] The proportion of patients with BRAF-mutation positive melanoma (used for later-stage modelling) was sourced from the KEYNOTE-054 trial of pembrolizumab for stage 3 melanoma[52] as BRAF mutation status was not captured in KEYNOTE-716 (Table 24).

Table 24: Baseline characteristics of patients in the economic model

Characteristic	Value	Source
Age	59.3 years	KEYNOTE-716[42, 44]
Age <18 years	0.2%	
Female	39.7%	
Stage 2B / 2C	64.8% / 35.2%	
Weight among adults, mean (SD)	[redacted] kg	
Weight among paediatrics, mean (SD)	[redacted] kg	
BRAF mutation positive†	43.3%	KEYNOTE-054[52]

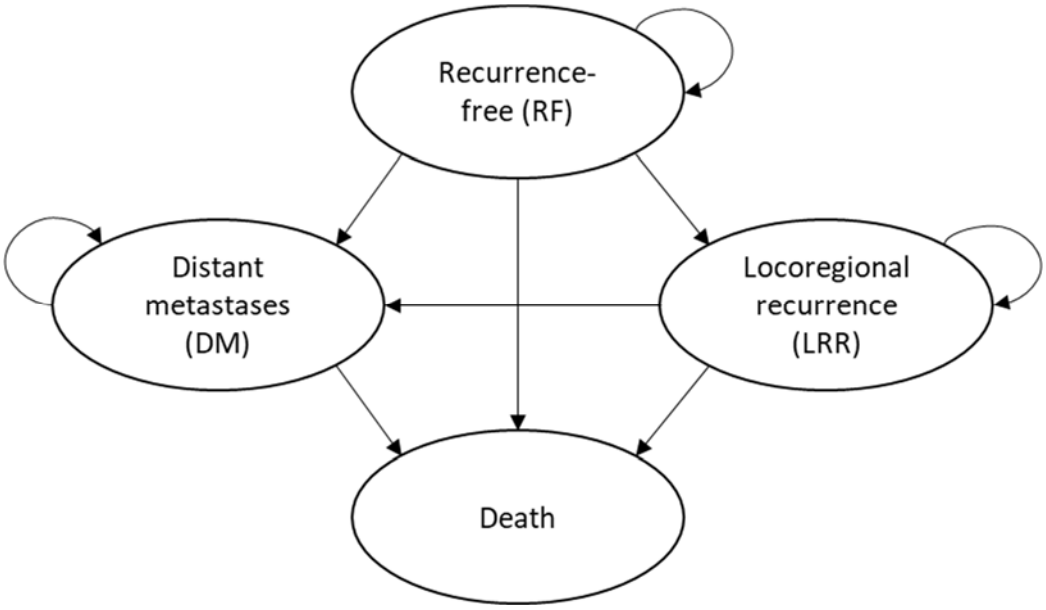
Abbreviations: SD, standard deviation.
† BRAF status was used in the modelling of locoregional recurrence and distant metastases sections of the model only, to ensure the market shares of BRAF-targeted agents did not exceed the proportion of patients who were BRAF mutation positive – it is not used to model the efficacy of pembrolizumab.

B.3.2.2 Model structure

A Markov cohort state-transition model was developed to estimate health outcomes and costs for patients with stage 2B or 2C melanoma treated with adjuvant pembrolizumab or followed with routine surveillance. The model consisted of four mutually exclusive health states designed to reflect the natural history of melanoma: recurrence-free (RF), locoregional recurrence (LRR), distant metastases (DM), and death (Figure 7). The model differentiated by type of recurrence (LRR or DM) as recurrence-type is a key prognostic factor affecting both outcomes and costs,[15, 53] and the KEYNOTE-716 trial encompasses both types of recurrence events. The DM state incorporated two sub-states (pre-progression and post-progression) to capture the costs and outcomes of subsequent therapies that patients may receive after DM recurrence. Survival time within the DM state, as well as the relative proportions of time spent in the pre- versus post-progression sub-states, depended upon the efficacy and market shares of first-line subsequent therapies in the advanced melanoma setting. Based on these relative proportions, utility in the DM state was computed as a weighted average of utilities in the pre- and post-progression sub-states. Similarly, per-cycle costs of healthcare resource use in the DM state were computed as a weighted average of per-cycle costs in these two sub-states.

The health states and allowable transitions were defined such that RFS, DMFS, and OS curves could be generated using the Markov trace. This facilitated validation of the model against observed Kaplan-Meier curves from the trial and long-term data from external sources.

Figure 7: Model structure



This structure has been commonly used for HTA submissions in adjuvant oncology indications, including the recent appraisal of adjuvant pembrolizumab in stage 3 melanoma (TA766),[2] as it allows indirect modelling of survival outcomes through relationships between intermediate health states. In the absence of DMFS and OS data from KEYNOTE-716, this approach enables the best use of the observed trial data and external evidence to estimate the implications of recurrence and explore the effects of the treatment pathway.

There is strong published evidence that improvements in RFS observed with adjuvant therapies in stage 3 melanoma will translate into improvements in DMFS and OS,[54-58] and it is reasonable to infer that a similar relationship could be observed in the stage 2B/2C setting. In particular:

- A significant OS benefit of adjuvant therapy versus routine surveillance has been reported in the EORTC-18071 trial in stage 3 melanoma, which has also 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).[58]

- An indirect treatment comparison (ITC) of adjuvant immunotherapy versus routine surveillance for stage 3 melanoma found that immunotherapy resulted in a statistically significant OS benefit, even after accounting for improvements in treatment options for metastatic disease in the last 10 years.[57] This was supported by another ITC which found that adjuvant pembrolizumab conveyed a significant OS benefit versus routine surveillance in the stage 3 setting.[2, 59]

- A meta-analysis of 13 clinical studies (n>5,000 patients) involving adjuvant interferon, and updated to include data for checkpoint inhibitors (in this case ipilimumab), for the treatment of resected stage 2–3 melanoma found that RFS was an appropriate and valid surrogate endpoint for OS.[54, 56]

- Wong et al, 2021 reported results from a retrospective US cohort that demonstrated that patients with resected stage 2B/2C melanoma who received adjuvant immunotherapy achieved a significant improvement in 3-year OS compared with patients who did not receive adjuvant immunotherapy,[50] although this may be confounded by potential differences in age and fitness between the two study groups.

Recurrence-free (RF) state

All patients entered the model in the RF health state, following complete surgical resection of their melanoma. Three transitions were estimated from the RF state: RF→LRR, RF→DM, and RF→Death. These transition probabilities were calculated using data from KEYNOTE-716 and used to estimate RFS over time.

Locoregional recurrence (LRR) state

Patients who had a LRR could either remain in the LRR health state, progress to the DM state, or move to the Death state. A proportion of patients entering the LRR state were assumed to undergo salvage surgery, as per KEYNOTE-716, and were eligible for systemic adjuvant therapy. Transitions from the LRR state were calculated using real-world evidence from the US Oncology Network (USON; Samlowski et al, 2021)[32, 60] as data are not yet available from KEYNOTE-716. The same transition probabilities were applied for both treatment arms therefore assuming that, after recurrence, the risk of progression or death was equal regardless of whether the patient received adjuvant pembrolizumab or routine surveillance. This is expected to be a conservative assumption, given the mechanism of action of pembrolizumab and the potential for immune memory [61-64] which is expected to confer an enduring benefit. Transitions from the LRR state were used in addition to the RF→DM and RF→Death transitions to estimate DMFS over time.

Distant metastases state

Transitions from the DM health state to Death were estimated using data from the published literature and a network meta-analysis (NMA). Patients in this health state were eligible for systemic therapy in line with current NICE recommendations for the metastatic melanoma setting, and therefore transitions and costs were dependent on the market shares of therapies used in this setting. As the use of adjuvant pembrolizumab may affect the treatment pathway after recurrence, the distribution of therapies may differ between model arms. However, as in the LRR state, there was conservatively assumed to be no ongoing benefit of pembrolizumab once patients entered the DM state, and survival from the DM state was calculated as a weighted average of survival based on market shares of treatments for first line metastatic melanoma. Costs of second line treatments were also included but did not influence survival calculations.

Death state

Death was an absorbing health state in which no costs or utilities were accrued.

Model parameters

A weekly cycle length was used to allow for precise calculation of the drug acquisition and administration costs, and half-cycle correction of outcomes and costs was applied to further increase precision. However, to ensure that costs incurred at the beginning of a model cycle (including adjuvant drug acquisition, administration, and adverse event costs) were fully captured, these costs were not half-cycle corrected. A lifetime time horizon (40.7 years, calculated as 100 minus the starting age [59.3 years]) was selected to comprehensively capture differences in costs and outcomes between pembrolizumab and routine surveillance. Key features of the economic model are presented in Table 25. Costs and effects were discounted at 3.5% per year, in line with the NICE reference case.[65]

Table 25: Features of the economic analysis

Factor	Chosen value	Justification
Time horizon	Lifetime (40.7 years)	A lifetime time horizon (100 minus starting age) was chosen to ensure all relevant direct costs and benefits of pembrolizumab were captured, in line with the NICE reference case[65]
Cycle length	1 week	To allow for precise calculation of the drug acquisition and administration costs
Half-cycle correction	Yes	Applied to costs and effectiveness (except costs specifically incurred at the beginning of a cycle) to increase precision, in line with the NICE reference case[65]
Discounting	3.5% for costs and effects	In line with the NICE reference case[65]
Treatment waning effect	Not applied	The treatment benefit of pembrolizumab is conservatively assumed to apply to patients in the RF health state only – no ongoing treatment effect is retained after disease recurrence. This is consistent with the recent appraisal of pembrolizumab for adjuvant treatment of stage 3 melanoma (TA766).[2] Due to the mechanism of action of pembrolizumab and the potential for immune memory, the treatment effect is expected to be maintained after stopping treatment. This is supported by long-term evidence from previous studies of pembrolizumab in the metastatic setting alongside other adjuvant IO studies.[61-64] Further, since the aim of adjuvant therapy is to supplement curative intent surgery and further prevent recurrences by clearing any residual micro-metastases, the treatment benefit is logically expected to be maintained.
Source of utilities	EQ-5D-5L utilities from KEYNOTE-716 mapped to EQ-5D-3L, and published literature	EQ-5D values collected from patients in the pivotal trial, in line with the NICE reference case.[65] These were supplemented by values from the literature where utilities from KEYNOTE-716 were not available for the DM post-progression health state.

Factor	Chosen value	Justification
Source of costs	MIMS, NHS Reference costs, PSSRU, previous NICE TAs, published literature	An NHS and PSS perspective was used, therefore only direct healthcare costs were considered, in line with the NICE reference case[65]

Abbreviations: MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal and Social Services; PSSRU, Personal Social Services Research Unit; RF, recurrence-free; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

Pembrolizumab was included in the model in line with the anticipated marketing authorization, based on a fixed dose intravenous (IV) infusion of 400 mg over 30 minutes every 6 weeks (Q6W) for adults and 2 mg/kg every 3 weeks (Q3W) for children. Treatment was continued for approximately 12 months (equivalent to 17 cycles of 200 mg Q3W) or until disease recurrence, toxicities leading to discontinuation, or physician/patient decision (as stated in the KEYNOTE-716 protocol).[45]

The SmPC for pembrolizumab allows treatment to be administered at a dose of either 200 mg Q3W or 400 mg Q6W across all monotherapy indications.[1] 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 with no increase in toxicity. As such, Q6W dosing is anticipated to be utilized by most clinics in UK practice and was used for the base case analysis.[40, 66] A scenario exploring Q3W dosing is explored in a scenario analysis.

Aligned with the NICE scope, the comparator arm of the model was routine surveillance (no active treatment).

B.3.3 *Clinical parameters and variables*

B.3.3.1 Transitions from the recurrence-free (RF) health state

For each treatment arm, transition probabilities starting from the RF health state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-716 trial, using the parametric multistate modelling approach described by Williams et al. (2017a & 2017b).[67, 68] Parametric models were used to estimate the cause-specific hazards of each transition (i.e. RF→LRR, RF→DM, and RF→Death) over time within the adjuvant pembrolizumab and routine surveillance arms. Within each cycle of the model, the

probabilities of each of these transitions (as well as the composite probability of any RFS failure event) were calculated as a function of all three cause-specific hazards.

Estimation of cause-specific hazards for each individual transition starting from the recurrence-free state

The cause-specific hazards of each transition in the pembrolizumab and routine surveillance arms were estimated based on parametric models fitted to patient-level data from the pembrolizumab and placebo arms of KEYNOTE-716. To fit parametric models to each of the three individual health state transitions, standard survival analysis methods were used with one modification to account for competing risks similar to the methodology employed in TA766.[2] When analysing time to each specific type of RFS failure, the two competing failure types were treated as censoring events and patients who experienced a censoring event were therefore treated as lost to follow-up at the time of the earlier competing event:[69, 70]

- RF→LRR: Patients who experienced a DM or death prior to LRR were censored
- RF→DM: Patients who experienced a LRR or death prior to DM were censored
- RF→Death: Patients who experienced a LRR or DM prior to death were censored

After these additional censoring criteria were applied to the patient-level time-to-event data for each transition, parametric curve fitting was performed using the survival analysis package *flexsurvreg* in R software,[71] similar to the process for fitting parametric functions for a standard partitioned survival model. Three parametric modelling approaches were tested to explore uncertainty in the estimation of transition probabilities starting from the RF state:

1. Parametric models separately fitted to each treatment arm:
   Under Approach #1, transition probabilities were estimated based on parametric models that were fitted individually to each treatment arm of the KEYNOTE-716 trial. Six different parametric functions were considered to model transitions from RF→LRR and from RF→DM in each treatment arm: exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions. Due to the small number of direct transitions from RF→Death observed in KEYNOTE-716, exponential distributions were fitted for this transition in each arm.

2. Parametric proportional hazards models with a time-constant treatment effect:
   Under Approach #2, transition probabilities in the pembrolizumab and routine surveillance arms were estimated based on jointly-fitted models from the proportional

hazards class (i.e. exponential, Weibull, or Gompertz) that incorporated a time-constant binary indicator equal to 1 in the pembrolizumab arm and 0 in the placebo arm. The models thus assumed a time-constant hazard ratio (HR) for pembrolizumab versus placebo in KEYNOTE-716. Due to the small number of direct transitions from RF→Death in the trial, an exponential model with a time-constant treatment effect was used for this transition.

3. Parametric proportional hazards models with a time-varying treatment effect (before and after year 1):
   Under Approach #3, transition probabilities in the pembrolizumab and routine surveillance arms were estimated based on jointly fitted models from the proportional hazards class that used a time-varying HR for pembrolizumab versus placebo. Specifically, the parametric models under Approach #3 incorporated a time-constant binary indicator equal to 1 in the pembrolizumab arm and 0 in the placebo arm, and a time-varying binary indicator equal to 1 in the pembrolizumab arm during the portion of follow-up after 1 year and 0 otherwise. The models thereby allowed the treatment effect to differ during versus after the first year following initiation of adjuvant therapy, based on the protocol-defined maximum treatment duration of 1 year. As in Approach #2, given the small number of events an exponential model with a time-constant treatment effect was used for transitions from RF→Death.

Parameter estimates associated with all parametric models for Approaches #1–3 are presented in Appendix M. For each treatment arm, probabilities of each transition from the RF state were calculated based on all three cause-specific hazard functions (RF→LRR, RF→DM, RF→Death). The predicted RFS curve over time in each treatment arm similarly depends upon all three cause-specific hazard functions. Therefore, to select the most suitable base-case parametric functions, all 54 (i.e. 6×6 + 3×3 + 3×3) possible combinations of parametric functions for RF→LRR and RF→DM were considered. However, given the availability of patient level data, in line with guidance from NICE DSU TSD 14 combinations produced using Approach #1 (independently fitted models) were generally preferred where plausible as these do not rely on the proportional hazards assumption.[72] As noted above, the cause-specific hazard of RF→Death was based on a constant exponential rate in each arm.

Calculation of transition probabilities based on cause-specific hazards

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

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

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

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

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

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

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

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

This represents the probability of having had an RFS failure of type *k* given that an RFS failure has occurred within the cycle.[73] The relative contribution of cause *k* was then multiplied by the probability of any RFS failure within the cycle to obtain the transition probability corresponding to cause *k*.

Within each cycle, the transition probability from RF→Death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in the UK were sourced from the Office for National Statistics (ONS) life tables 2017-2019.[74]

Reduction in risk over time

Patients with stage 2B/2C melanoma are recommended to be treated with surgery with "curative intent",[15, 75] therefore it is expected that a proportion of patients undergoing resection will have no further melanoma recurrences. The aim of adjuvant therapy with pembrolizumab is to remove any residual microscopic disease to further reduce the risk of recurrence and progression to metastatic disease.[2] It is therefore expected that adjuvant

pembrolizumab will increase the proportion of patients who will never have disease recurrence.

In current UK practice, patients with resected stage 2 or stage 3 melanoma are usually discharged from clinical follow-up if they remain recurrence-free at 5 years.[14] This management strategy reflects the evidence demonstrating that most melanoma recurrences, including in stage 2B/2C melanoma, occur in the first 5 years after resection; that 50% of recurrences occur in the first 2 years; and that the risk of recurrence after 5 years is relatively low and continues to decrease.[10, 13] This is supported by RFS Kaplan-Meier data from real-world studies in stage 2B/2C melanoma which show that the gradient of the RFS curve flattens over time.[12, 32, 60] In addition, UK clinical experts agreed, based on their experience, that the risk of recurrence decreases over time such that most patients are discharged at 5 years, and advised that the likelihood of disease recurrence after 10 years is extremely small, although would not reach zero. In other words, patients who remain recurrence-free at 10 years are highly unlikely to have a recurrence.[40, 66]

Given the short follow-up in the KEYNOTE-716 trial at IA2 (median 20.5 months) it is likely that the flattening of the curve observed in published real-world cohorts and described by clinical experts has not yet been reached in the trial. As such, the parametric functions fitted to the RF→LRR and RF→DM data from KEYNOTE-716 are unlikely to fully capture this reduction in recurrence risk that is expected to be observed with increased follow-up and therefore may underpredict true RFS for patients with stage 2B/2C melanoma. This is supported by clinical experts who felt that the long-term estimates after 10 years produced by the parametric functions were pessimistic and underestimated RFS.[40, 66]

To address this underprediction of RFS, the model applied an assumption that the per cycle risk of recurrence (i.e. transition probabilities for RF→LRR and RF→DM) for patients remaining in the RF health state after 10 years would reduce by 95% relative to the risk estimated by the parametric function. In addition, to further reflect the published evidence in stage 2,[10, 13] data from the study with the longest follow-up of adjuvant therapy at stage 3 melanoma,[58] and clinical opinion, it was assumed that the risk (relative to the parametric function) begins to linearly decrease from 7 years until a 95% risk reduction is reached at 10 years. This could be considered a conservative assumption, given the evidence showing that most stage 2B/2C melanoma recurrences occur in the first 5 years after resection, therefore this timepoint is explored in scenario analyses. The risk reduction was also applied to the RF→Death transitions, subject to the constraint that this risk must always be at least as high

as background mortality in each cycle. A risk reduction of 95% was selected to align with methodology applied in previous NICE oncology appraisals of adjuvant therapies (TA569, TA632, TA761),[76-78] and to reflect clinical opinion that the risk of recurrence after 10 years would be extremely small, but never zero.[40, 66]

Selection of base-case parametric functions

As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, assessing model fit is more challenging in the context of multistate models than in partitioned survival models, as the target outcomes of interest (i.e. the proportions of individuals experiencing the composite endpoint [e.g. RFS]) are determined by a combination of survival models rather than by a single survival model.[69] Therefore, to select base-case parametric functions, all 54 possible combinations of parametric functions for RF→LRR and RF→DM were considered. In accordance with recommendations in NICE DSU TSD 14,[72] base-case parametric functions were selected such that the same functional form was used to model each health state transition in both the pembrolizumab and routine surveillance arms. This prevents the extrapolated portion of the RFS curves from following drastically different trajectories between the two model arms.

Base-case parametric functions were chosen based on the following criteria:

1. Statistical fit:
   Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks.[67] Mean squared error (MSE) was therefore used as an alternative diagnostic test to assess fit of the predicted RFS curve versus the observed Kaplan-Meier curve during the within-trial period in each treatment arm. Specifically, MSE was calculated based on the average of the squared difference in predicted versus observed RFS at weekly intervals across the within-trial period, with weighting by number of patients at risk in each weekly interval (Table 26 and Table 27). In addition, the assumption of proportional hazards was assessed through formal statistical tests to evaluate the potential suitability of Approach #2 and #3. Namely, for each transition, the function *cox.zph()* in R was used to test for independence between time and the scaled Schoenfeld residuals from a Cox proportional hazards model with a time-constant treatment covariate. The proportional hazard assumption is supported by a non-significant relationship between residuals and time.

2. Visual assessment of fit:

   Predictions generated by different combinations of parametric functions were also visually verified against the observed data in each treatment arm, following the approach used by Williams et al, 2017.[67] Specifically, predicted versus observed cumulative incidence curves were plotted for each of the three individual transitions starting from the RF state (Appendix M).

3. Clinical plausibility of long-term extrapolations (external validity):

   Combinations of parametric functions that resulted in crossing RFS curves (i.e. higher long-term RFS under routine surveillance compared with pembrolizumab) were excluded from consideration due to clinical implausibility. This exclusion was supported by the available data from KEYNOTE-716, as well as longer-term RFS and DMFS data from the KEYNOTE-054 trial of pembrolizumab as an adjuvant treatment of resected high-risk stage 3 melanoma.[18] Combinations were further excluded if they resulted in lower 4-year RFS and/or DMFS for either pembrolizumab or routine surveillance than that reported for the corresponding arms of KEYNOTE-054, given the expectation of better prognosis in the stage 2B/2C population compared with stage 3.[9]

   Longer-term extrapolations of RFS, DMFS and OS in the routine surveillance arm were externally validated against observed data from several real-world studies reporting up to 10-year RFS, DMFS and/or OS in patients diagnosed with AJCC 8th edition stage 2B or 2C melanoma (Figure 8 to Figure 11). (Of note, predicted RFS depends only on transition probabilities starting from the RF state, while predicted DMFS depends on transition probabilities starting from the RF and LRR states. Predicted OS is a function of all transition probabilities in the model.) Clinical experts agreed that these external sources were generalizable to the UK and suggested that these sources be used as the key basis for external validation. Additional information on each of these studies is summarized in Appendix N. For each of these sources, the following steps were performed: (1) RFS, DMFS and/or OS were extracted separately for the stage 2B and 2C subgroups (using digitized Kaplan-Meier data where available); and (2) these subgroup-specific results were then pooled as a weighted average to obtain RFS, DMFS and/or OS for the combined stage 2B/2C target population, based on the percentages of patients with stage 2B vs. 2C melanoma in KEYNOTE-716.

Because empirical data were not available for adjuvant pembrolizumab, the plausibility of long-term extrapolations in the pembrolizumab arm was validated based on clinical expert opinion and comparison with 4-year data available for the stage 3 melanoma setting, and then explored in scenario analyses.

Statistical fit

Table 26 and Table 27 present the rankings of all 54 combinations of parametric functions from smallest to largest MSE in each treatment arm, for the routine surveillance and pembrolizumab arms, respectively. Long-term predictions of RFS, DMFS, and OS are also reported for each these different scenarios.

MSEs were generally higher for routine surveillance than for pembrolizumab, therefore the selection of base-case parametric functions prioritised statistical and visual fit in the routine surveillance arm. Long term predictions for both treatment arms were then checked for clinical plausibility against external sources and with clinical experts. In both treatment arms (and across Approaches #1–3) the 12 combinations that used exponential for RF→DM had larger MSEs relative to other combinations of functions.

The proportional hazards assumption could not be rejected for either RF→LRR ([redacted]) or RF→DM ([redacted]) based on statistical tests. Thus, no exclusions were made based on proportional hazards testing, and combinations of distributions under Approaches #2 and #3 were retained for further consideration as base-case or scenario analyses.

Visual assessment of fit

For the trial period, the observed cumulative incidence of transitions from RF→LRR in the routine surveillance and pembrolizumab arms, respectively, alongside the predicted cumulative incidence from different combinations of parametric functions, are presented in Appendix M. In both treatment arms, all combinations of parametric functions across all three approaches produced a close visual fit to the observed cumulative incidence of RF→LRR from KEYNOTE-716.

Analogous figures are presented for the cumulative incidence of RF→DM in each treatment arm (Appendix M). Consistent with MSE fit statistics, the 12 combinations of distributions that used exponential for RF→DM yielded slightly worse visual fit to this transition, particularly during the first 6 months; however, because these combinations generally fit well at the tails of the observed cumulative incidence curves, and the long-term projections appeared reasonable, they were further considered as potential scenario analyses.

Table 26: Comparison of different parametric functions used to model RFS in the routine surveillance arm: Fit with observed data and long-term extrapolations

Rank by MSE	Parametric functions		MSE vs. observed RFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
	RF → LR	RF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
Approach #1: Parametric models separately fitted to each treatment arm																					
1	Weibull	Gen. gamma	0.0000812	[redacted]																	
2	Log-logistic	Gen. gamma	0.0000828	[redacted]																	
3	Gompertz	Gen. gamma	0.0000834	[redacted]																	
4	Exponential	Gen. gamma	0.0000846	[redacted]																	
5	Gen. gamma	Gen. gamma	0.0000858	[redacted]																	
6	**Log-normal**	**Log-normal**	**0.0000987**	[redacted]																	
7	Log-normal	Gen. gamma	0.0000989	[redacted]																	
8	Gen. gamma	Log-normal	0.0001078	[redacted]																	
9	Log-logistic	Log-normal	0.0001129	[redacted]																	
10	Exponential	Log-normal	0.0001137	[redacted]																	
11	Gompertz	Log-normal	0.0001151	[redacted]																	
12	Weibull	Log-normal	0.0001168	[redacted]																	
13	Log-normal	Log-logistic	0.0001182	[redacted]																	
14	Log-normal	Weibull	0.0001248	[redacted]																	
15	Gen. gamma	Log-logistic	0.0001306	[redacted]																	
16	Log-logistic	Log-logistic	0.0001372	[redacted]																	
17	Gen. gamma	Weibull	0.0001390	[redacted]																	
18	Exponential	Log-logistic	0.0001395	[redacted]																	
19	Gompertz	Log-logistic	0.0001411	[redacted]																	
20	Weibull	Log-logistic	0.0001426	[redacted]																	
21	Log-logistic	Weibull	0.0001462	[redacted]																	
22	Exponential	Weibull	0.0001487	[redacted]																	
23	Gompertz	Weibull	0.0001506	[redacted]																	
25	Weibull	Weibull	0.0001522	[redacted]																	
27	Gen. gamma	Gompertz	0.0001562	[redacted]																	

Rank by MSE	Parametric functions		MSE vs. observed RFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
	RF → LR	RF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
28	Log-normal	Gompertz	0.0001562	[redacted]																	
30	Log-logistic	Gompertz	0.0001591	[redacted]																	
32	Weibull	Gompertz	0.0001633	[redacted]																	
35	Gompertz	Gompertz	0.0001673	[redacted]																	
36	Exponential	Gompertz	0.0001676	[redacted]																	
43	Weibull	Exponential	0.0002046	[redacted]																	
44	Log-logistic	Exponential	0.0002050	[redacted]																	
45	Gen. gamma	Exponential	0.0002102	[redacted]																	
46	Gompertz	Exponential	0.0002157	[redacted]																	
48	Exponential	Exponential	0.0002193	[redacted]																	
52	Log-normal	Exponential	0.0002342	[redacted]																	
Approach #2: Parametric proportional hazards models with a time-constant treatment effect																					
24	Gompertz	Weibull	0.0001509	[redacted]																	
29	Weibull	Weibull	0.0001581	[redacted]																	
31	Exponential	Weibull	0.0001609	[redacted]																	
37	Gompertz	Gompertz	0.0001726	[redacted]																	
39	Exponential	Gompertz	0.0001753	[redacted]																	
41	Weibull	Gompertz	0.0001763	[redacted]																	
49	Exponential	Exponential	0.0002193	[redacted]																	
51	Weibull	Exponential	0.0002293	[redacted]																	
53	Gompertz	Exponential	0.0002381	[redacted]																	
Approach #3: Parametric proportional hazards models with a time-varying treatment effect																					
26	Gompertz	Weibull	0.0001536	[redacted]																	
33	Weibull	Weibull	0.0001638	[redacted]																	
34	Exponential	Weibull	0.0001668	[redacted]																	
38	Gompertz	Gompertz	0.0001729	[redacted]																	
40	Exponential	Gompertz	0.0001760	[redacted]																	
42	Weibull	Gompertz	0.0001769	[redacted]																	

Rank by MSE	Parametric functions		MSE vs. observed RFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
	RF → LR	RF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
47	Exponential	Exponential	0.0002190	[redacted]																	
50	Weibull	Exponential	0.0002280	[redacted]																	
54	Gompertz	Exponential	0.0002418	[redacted]																	

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LRR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.
Red cells indicate that the survival estimate for routine surveillance is higher than the corresponding estimate for pembrolizumab (i.e. the curves cross). Red text indicates the 4-year RFS and/or DMFS estimates fall below the 4-year RFS and/or DMFS observed in KEYNOTE-054 (stage 3 melanoma). Green cells indicate the combinations considered in the base case and plausible relevant scenarios; **bold text** indicates the selected base case function.
Long-term predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years

Table 27: Comparison of different parametric functions used to model RFS in the pembrolizumab arm: Fit with observed data and long-term extrapolations

Rank by MSE	Parametric functions		MSE vs. observed RFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
	RF → LR	RF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
Approach #1: Parametric models separately fitted to each treatment arm																					
1	Exponential	Gompertz	0.0000490	[redacted]																	
2	Weibull	Gompertz	0.0000535	[redacted]																	
3	Gen. gamma	Gompertz	0.0000536	[redacted]																	
4	Log-logistic	Gompertz	0.0000539	[redacted]																	
5	Gompertz	Gompertz	0.0000556	[redacted]																	
6	Exponential	Weibull	0.0000557	[redacted]																	
7	Exponential	Log-logistic	0.0000567	[redacted]																	
8	Weibull	Weibull	0.0000569	[redacted]																	
9	Gen. gamma	Weibull	0.0000571	[redacted]																	
11	Log-logistic	Weibull	0.0000576	[redacted]																	
12	Weibull	Log-logistic	0.0000583	[redacted]																	
14	Gen. gamma	Log-logistic	0.0000585	[redacted]																	
15	Log-logistic	Log-logistic	0.0000590	[redacted]																	
16	Gompertz	Weibull	0.0000598	[redacted]																	

Rank by MSE	Parametric functions		MSE vs. observed RFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
	RF → LR	RF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
20	Gompertz	Log-logistic	0.0000615	[redacted]																	
22	Exponential	Log-normal	0.0000628	[redacted]																	
27	Log-normal	Gompertz	0.0000649	[redacted]																	
28	Weibull	Log-normal	0.0000659	[redacted]																	
29	Log-normal	Weibull	0.0000659	[redacted]																	
31	Gen. gamma	Log-normal	0.0000664	[redacted]																	
33	Log-logistic	Log-normal	0.0000672	[redacted]																	
34	Log-normal	Log-logistic	0.0000678	[redacted]																	
35	Exponential	Gen. gamma	0.0000709	[redacted]																	
36	Gompertz	Log-normal	0.0000712	[redacted]																	
37	Weibull	Gen. gamma	0.0000764	[redacted]																	
38	Gen. gamma	Gen. gamma	0.0000772	[redacted]																	
39	Log-logistic	Gen. gamma	0.0000784	[redacted]																	
40	**Log-normal**	**Log-normal**	**0.0000791**	[redacted]																	
43	Gompertz	Gen. gamma	0.0000841	[redacted]																	
45	Log-normal	Gen. gamma	0.0000948	[redacted]																	
47	Exponential	Exponential	0.0001184	[redacted]																	
50	Weibull	Exponential	0.0001475	[redacted]																	
51	Gen. gamma	Exponential	0.0001491	[redacted]																	
52	Log-logistic	Exponential	0.0001511	[redacted]																	
53	Gompertz	Exponential	0.0001621	[redacted]																	
54	Log-normal	Exponential	0.0001966	[redacted]																	
Approach #2: Parametric proportional hazards models with a time-constant treatment effect																					
10	Exponential	Weibull	0.0000574	[redacted]																	
13	Weibull	Weibull	0.0000584	[redacted]																	
17	Gompertz	Weibull	0.0000606	[redacted]																	
18	Exponential	Gompertz	0.0000606	[redacted]																	
24	Weibull	Gompertz	0.0000632	[redacted]																	

Rank by MSE	Parametric functions		MSE vs. observed RFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
	RF → LR	RF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
32	Gompertz	Gompertz	0.0000669	[redacted]																	
46	Exponential	Exponential	0.0001184	[redacted]																	
48	Weibull	Exponential	0.0001247	[redacted]																	
49	Gompertz	Exponential	0.0001336	[redacted]																	
Approach #3: Parametric proportional hazards models with a time-varying treatment effect																					
19	Exponential	Weibull	0.0000612	[redacted]																	
21	Weibull	Weibull	0.0000620	[redacted]																	
23	Exponential	Gompertz	0.0000631	[redacted]																	
25	Gompertz	Weibull	0.0000635	[redacted]																	
26	Weibull	Gompertz	0.0000646	[redacted]																	
30	Gompertz	Gompertz	0.0000663	[redacted]																	
41	Exponential	Exponential	0.0000809	[redacted]																	
42	Weibull	Exponential	0.0000828	[redacted]																	
44	Gompertz	Exponential	0.0000852	[redacted]																	

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LRR, locoregional recurrence; SE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.

Red cells indicate that the survival estimate for pembrolizumab is lower than the corresponding estimate for routine surveillance (i.e. the curves cross). Red text indicates the 4-year RFS and/or DMFS estimates fall below the 4-year RFS and/or DMFS observed in KEYNOTE-054 (stage 3 melanoma). Green cells indicate the combinations considered in the base case and plausible relevant scenarios; **bold text** indicates the selected base case function.

Long-term predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years

Clinical plausibility (external validity)

The plausibility of long- and short-term extrapolations for routine surveillance for the 54 combinations of parametric functions was assessed by comparing the projections of RFS, DMFS and OS with data from several external sources (Table 28). These sources were reviewed by UK clinical experts who felt that they were representative of stage 2 melanoma patients in the UK and were therefore suitable for use as validation sources;[40] further details on the characteristics of these studies are provided in Appendix N. As KEYNOTE-716 is the first trial of pembrolizumab in the stage 2 setting and immunotherapies are not currently used in clinical practice there were no available studies that reported analogous survival outcomes to validate the pembrolizumab arm. Instead, data from the KEYNOTE-054 and SWOG-S1404/KEYNOTE-053 trials of pembrolizumab in the stage 3 setting were used as lower bounds for the expected outcomes for patients with stage 2B/2C melanoma, and plausibility validated in discussion in clinical experts, and via scenario analyses.

Table 28: Sources used to validate modelled survival projections

Source	Description	Used to validate:
Bajaj et al, 2020[12]	Real world cohort study in 1,315 patients with melanoma (n=90 stage 2B/2C), 2010–2016, USA. Data available up to 7 years.	RFS, OS for **routine surveillance**
US Oncology Network (USON) study, Samlowski et al, 2021[32, 60]	Real world cohort study in 567 patients with stage 2B/2C resected melanoma, 2008–2017, USA. Data available up to 10 years.	RFS, DMFS and OS for **routine surveillance**
Bleicher et al, 2020[34]	Real world cohort study in 580 patients with stage 2 melanoma (n=300 stage 2B/2C), 2000–2017, USA. Data available up to 10 years.	OS for **routine surveillance** (not considered appropriate for validating RFS)†
Kanaki et al, 2019[33]	Real world cohort study in 1,462 patients with stage 2–4 melanoma (n=416 stage 2B/2C), 2003–2018, Germany Data available at 5 and 10 years.	OS for **routine surveillance**
KEYNOTE-054‡,18	*Phase 3 RCT of pembrolizumab versus placebo in stage 3 resected melanoma* *Data available up to 4.5 years.*	*RFS and DMFS **lower** bounds for **pembrolizumab and routine surveillance***
SWOG-S1404/KEYNOTE-053‡,79	*Phase 3 RCT of pembrolizumab versus ipilimumab or high-dose interferon (HDI) in stage 3 resected melanoma* *Data available up to 3.5 years*	*RFS and OS **lower** bounds for **pembrolizumab***

† Bleicher et al, 2020[34] also reported RFS for patients with stage 2B/2C melanoma up to ~10 years; however, the 2-year RFS (2B: 90.5%; 2C: 81.7%; pooled 2B/2C, using stage distribution from KEYNOTE-716: 87.4%) was ~16 percentage-points higher than 2-year RFS observed in the placebo arm of KEYNOTE-716 (71.7%) and ~7 percentage-points higher than that observed in the pembrolizumab arm (80.5%). The large difference in observed RFS between Bleicher et al, 2020 and KEYNOTE-716 suggested potential inconsistencies in the definition or measurements of RFS that could not be determined from the information provided in the publication. Further,

RFS from Bleicher et al, 2020 was substantially above the RFS reported in the other published sources,[34] and UK clinical experts advised that this RFS was not consistent with what is observed in UK clinical practice. However, as OS is a final endpoint and baseline characteristics were comparable to KEYNOTE-716, it was deemed appropriate to include Bleicher et al, 2020 as a validation source for OS.
‡ The KEYNOTE-054 and SWOG-S1404/KEYNOTE-053 trials in stage 3 melanoma were used as 'lower bounds' for the survival projections in the current stage 2 modelling, as outcomes for stage 2B/2C patients are expected to be better than for patients with stage 3 melanoma.

Twelve of the 54 combinations (all permutations where the Gompertz function was used to model RF→DM) produced 4-year RFS and/or DMFS estimates that fell below the 4-year RFS and/or DMFS observed in KEYNOTE-054 (stage 3 melanoma); six of these 12 combinations also resulted in implausible crossing of the survival curves for pembrolizumab and routine surveillance (Table 26 and Table 27). These 12 combinations of functions were therefore considered implausible and were excluded from consideration for the base case analysis.

Predicted RFS in the routine surveillance arm was validated against 7- to 10-year RFS data from two external studies. Across the Bajaj et al. (2020)[12] study and the US Oncology Network (USON) study,[32, 60] 7-year RFS ranged narrowly from 48.7% to 50.1% (simple average: 49.4%); 10-year RFS was only available from the USON study, at 23.2%, although there were a very small number at risk at 10 years ([redacted]).[32, 60] Given the close alignment of RFS and the generalisability to the UK of these two studies, and the fact that management of stage 2B/2C patients has not changed since these studies were conducted, further exclusions were applied based on the requirement that predicted RFS for routine surveillance must fall within the range of these studies ±5 percentage points over 10 years. Twelve of the 54 combinations of distributions met this external validity requirement (Appendix M), and all other combinations were tentatively excluded from further consideration for the base case analysis. Seven of these 12 combinations used exponential for RF→DM[a] and had a less optimal visual and statistical fit to the KEYNOTE-716 data, therefore the other five combinations that met this external validity requirement were prioritised (Weilbull-Generalised gamma; Gompertz-Generalised gamma; Lognormal-Lognormal; Generalised gamma-Lognormal; Log-logistic-Lognormal). The relative treatment benefit for pembrolizumab predicted using these prioritised combinations was smaller than that predicted using five of the seven deprioritised combinations. The deprioritised

[a] Log-logistic-exponential (Approach #1); Generalised gamma-exponential (Approach #1); Lognormal-exponential (Approach #1); Weibull-exponential (Approach #2); Gompertz-exponential (Approach #2); Weibull-exponential (Approach #3); Gompertz-exponential (Approach #3).

combinations were considered for relevance in scenario analyses (see Appendix M) to further explore the impact of this treatment effect on the cost-effectiveness results.

RFS estimates for the five prioritised combinations of interest are compared with estimates from the relevant external sources in Table 29 and Figure 8. The three curve combinations that used Lognormal for the RF→DM transition provided the best fit to the external data, and the Lognormal-Lognormal combination yielded RFS predictions that were closest to the external sources at the most timepoints over 10 years. The two functions that used Generalised gamma for the RF→DM transition produced RFS projections that were above the external data at all timepoints after 2 years.

In the pembrolizumab arm, the Gompertz-Generalised gamma combination produced an RFS curve that was substantially higher than all other curves and appeared to show a different trajectory after 5 years compared with the corresponding curve for routine surveillance, such that the benefit of pembrolizumab relative to routine surveillance continued to increase substantially over time. This combination was therefore deemed likely to overestimate the benefit of pembrolizumab. The four other curves provided projections that aligned with the shape of their corresponding routine surveillance curves. All five curves for both treatment arms over the full model time horizon are shown in Figure 9.

Table 29: External validation of modelled RFS

Source	RFS %, by year							
	1	2	3	4	5	6	7	10
Routine surveillance								
KEYNOTE-716, placebo	83.3	71.7	-	-	-	-	-	-
Bajaj et al. 2020[12]	87.4	64.6	56.7	48.7	44.2	41.4	33.6	-
USON study, 2021[32, 60]	85.6	70.9	58.0	50.1	43.2	37.5	35.0	23.2
Weibull-Generalized gamma (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz-Generalized gamma (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab								
KEYNOTE-716	90.8	80.5	-	-	-	-	-	-
KEYNOTE-054[†,18]	75.1	67.8	63.4	57.0	-	-	-	-

Source	RFS %, by year							
	1	2	3	4	5	6	7	10
Weibull-Generalized gamma (Approach #1)	[redacted]							
Gompertz-Generalized gamma (Approach #1)	[redacted]							
Log-normal-Lognormal (Approach #1)	[redacted]							
Generalized gamma-Lognormal (Approach #1)	[redacted]							
Log-logistic-Lognormal (Approach #1)	[redacted]							

Abbreviations: RFS, recurrence-free survival.
† Data represents patients with stage 3 melanoma – included here as a lower bound to the RFS estimates in the stage 2 setting.
Bold indicates the model selected for the base case analysis.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 8: External validation of modelled RFS

[redacted]

Abbreviations: PEM, pembrolizumab; RFS, recurrence-free survival; RS, routine surveillance.
In each colour group, the dark shade represents the pembrolizumab arm and the light colour represents the placebo (routine surveillance) arm.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 9: Predicted RFS for key parametric function combinations over lifetime horizon

Abbreviations: PEM, pembrolizumab; RFS, recurrence-free survival; RS, routine surveillance.
In each colour group, the dark shade represents the pembrolizumab arm and the light colour represents the placebo (routine surveillance) arm.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

As data on DMFS and OS were not available from KEYNOTE-716, the plausibility of the DMFS and OS estimates generated by the model was assessed using alternative external sources. The only source of DMFS data in the stage 2B/2C population was from the USON study (see details in Appendix N);[32, 60] although this study was used to inform modelling transitions from LRR→DM, it only partly informs the overall DMFS estimate as transitions from RF→DM were determined using KEYNOTE-716 data, and DM recurrences comprised >50% of all recurrences (i.e. most patients with recurrence transitioned directly to the DM state).[44] The three combinations that used Lognormal for the RF→DM transitions produced almost identical DMFS curves and fit this external data source exceptionally well over 10 years. When Generalised-gamma was used for this transition, the model estimates for DMFS far exceeded the USON data, indicating that these function combinations are unlikely to be appropriate for modelling this population (Table 30 and Figure 10). As expected, all five curves exceeded the DMFS observed in KEYNOTE-054 for stage 3 resected melanoma, for both routine surveillance and pembrolizumab.

For OS, the three curves that used Lognormal for the RF→DM transition were almost identical in terms of projections over 10 years. External OS data for routine surveillance were available from three sources.[12, 33, 34] As for DMFS and RFS, the three curves that used Lognormal for the RF→DM matched the external sources reasonably well in terms of curve shape, although generally predicted higher OS than reported in the external studies (

Table 31 and Figure 11). All curve combinations dropped below the OS estimates from Bajaj et al, 2020 after 5 years, however this should be interpreted with caution as the number at risk after this point in the Bajaj et al study was very small (n=42 at 4 years, n=26 at 6 years).[12] Also note that all studies (and in particular the study by Bleicher et al, 2020)[34] enrolled patients diagnosed before recent advances in treatment for stage 3 and metastatic melanoma were available. These advances have resulted in significantly improved survival rates therefore the OS estimates in these sources may be underestimated relative to current clinical practice.

In the absence of longer-term survival data for adjuvant pembrolizumab in stage 2B/2C melanoma, the plausibility of RFS, DMFS and OS predictions for pembrolizumab was assessed based on clinician opinion that, based on the RFS results observed in the KEYNOTE-716 trial and in the stage 3 setting, a continued benefit with pembrolizumab

would be expected after completion of adjuvant therapy.[2, 66] This was explored in scenario analyses.

Table 30: External validation of modelled DMFS

Source	DMFS %, by year							
	1	2	3	4	5	6	7	10
Routine surveillance								
USON study, 2021[32, 60]	[redacted]							
Weibull-Generalized gamma (Approach #1)	[redacted]							
Gompertz-Generalized gamma (Approach #1)	[redacted]							
Log-normal-Lognormal (Approach #1)	[redacted]							
Generalized gamma-Lognormal (Approach #1)	[redacted]							
Log-logistic-Lognormal (Approach #1)	[redacted]							
Pembrolizumab								
KEYNOTE-054†,[18]	82.8	73.5	68.2	62.9	-	-	-	-
Weibull-Generalized gamma (Approach #1)	[redacted]							
Gompertz-Generalized gamma (Approach #1)	[redacted]							
Log-normal-Lognormal (Approach #1)	[redacted]							
Generalized gamma-Lognormal (Approach #1)	[redacted]							
Log-logistic-Lognormal (Approach #1)	[redacted]							

Abbreviations: DMFS, distant metastases-free survival.
† Represents stage 3 melanoma – included here as a lower bound to the DMFS estimates in the stage 2 setting.
Bold indicates the model selected for the base case analysis.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 10: External validation of modelled DMFS

[redacted]

Abbreviations: DMFS, distant metastases-free survival; PEM, pembrolizumab; RS, routine surveillance.
In each colour group, the dark shade represents the pembrolizumab arm and the light colour represents the placebo (routine surveillance) arm.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Table 31: External validation of modelled OS

Source	OS %, by year							
	1	2	3	4	5	6	7	10
Routine surveillance								
Bajaj et al, 2020[12]	96.4	91.4	86.7	81.4	79.8	74.3	74.3	-
Bleicher et al, 2020[34]	96.6	88.5	78.3	72.1	67.6	60.3	54.8	52.9
USON study, 2021[32, 60]	96.8	92.1	84.1	79.2	71.9	64.1	61.5	42.2
Kanaki et al, 2019[33]	-	-	-	-	64.3	-	-	43.6
Weibull-Generalized gamma (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz-Generalized gamma (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab								
SWOG-S1404/KEYNOTE-053† [79]	97.8	92.1	86.3	84.1	82.36	-	-	-
Weibull-Generalized gamma (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz-Generalized gamma (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma-Lognormal (Approach #1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source	OS %, by year							
	1	2	3	4	5	6	7	10
Log-logistic-Lognormal (Approach #1)	[redacted]							

Abbreviations: OS, overall survival.
† Represents stage 3 melanoma – included here as a lower bound to the DMFS estimates in the stage 2 setting.
Bold indicates the model selected for the base case analysis.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 11: External validation of modelled OS

[redacted]

Abbreviations: OS, overall survival; PEM, pembrolizumab; RS, routine surveillance.
In each colour group, the dark shade represents the pembrolizumab arm and the light colour represents the placebo (routine surveillance) arm.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Base case

Based on the assessments described above, and in line with the guidance provided in NICE DSU TSD 14,[72] parametric models separately fitted to each treatment arm (Approach #1; independently fitted models) were preferred and appeared to provide the best balance between goodness of fit with observed data and plausibility of long-term extrapolations. When patient-level data are available, this approach is often preferred as it avoids reliance on an assumption of proportional hazards which is required for Approach #2 (constant proportional hazards) and involves fewer assumptions than are required for applying a time-varying treatment effect (Approach #3; proportional hazards with time-varying treatment effect). Amongst the combinations of models in Approach #1, the Lognormal-Lognormal combination for RF→LRR and RF→DM, respectively, was the most consistent with external sources for routine surveillance RFS over 10 years and provided a middle-ground estimate in terms of the treatment benefit of pembrolizumab versus routine surveillance. There was less scope to differentiate between the plausible curves for DMFS and OS, therefore RFS fit was prioritised in the selection process – however, DMFS and OS estimates were also aligned with the external sources available.

Consequently, the Lognormal-Lognormal parametric function combination was selected for the base case analysis. Alternative combinations of parametric functions, including the use of Approaches #2 and #3, were tested in scenario analyses to explore more optimistic and pessimistic extrapolations, including the size of the long-term treatment benefit with pembrolizumab. The long-term RFS, DMFS and OS projections for the Lognormal-lognormal combination are presented in Figure 12 and Table 32.

Figure 12: Predicted survival estimates over the modelled time horizon using Lognormal-lognormal to model transitions from the RF state

A) RFS

[redacted]

B) DMFS

[redacted]

C) OS

[redacted]

Table 32: Base case predicted survival estimates over the modelled time horizon

Outcome	Survival by year, %										
	1	2	3	4	5	6	7	10	20	30	40
Routine surveillance											
RFS	[redacted]										
DMFS	[redacted]										
OS	[redacted]										
Pembrolizumab											
RFS	[redacted]										
DMFS	[redacted]										
OS	[redacted]										

Abbreviations: DMFS, distant metastases-free survival; OS, overall survival; RFS, recurrence-free survival.

B.3.3.2 Transitions from the locoregional recurrence (LRR) health state

Given the available follow-up and the relatively small number of recurrence events to date, there were insufficient data from KEYNOTE-716 to enable transition probabilities from the LRR health state to be estimated from the trial. Transitions were instead informed using real-world data from the US Oncology Network (USON).[32, 60] Input from clinical experts indicated that, in current practice, patients with stage 2B/2C melanoma who had a LRR would be considered to have resectable stage 3 melanoma and would be eligible to receive systemic adjuvant therapy with one of three treatments recommended by NICE in the adjuvant setting: pembrolizumab, nivolumab, or dabrafenib + trametinib (if BRAF mutation positive [note that the proportion of BRAF mutation positive patients in the model was sourced from KEYNOTE-054, as this value was not available from KEYNOTE-716, and used to ensure the dabrafenib + trametinib market share did not exceed this value]).[75] The cause-specific hazards of LRR→DM and LRR→Death were therefore modelled to depend upon the market shares and relative efficacy of adjuvant treatments that patients may receive in the LRR state. It was conservatively assumed that after recurrence there was no ongoing benefit of adjuvant pembrolizumab in the stage 2 setting, therefore transition probabilities from the LRR state differed between treatment arms according only to the distributions of subsequent adjuvant therapies received in the LRR health state.

Estimation of cause-specific hazards of transitions starting from the LRR state, by subsequent adjuvant treatment

For patients who receive no adjuvant therapy in the LRR state, cause-specific hazards of LRR→DM and LRR→Death transitions were estimated using data from a real-world electronic medical records database. Specifically, an observational study was conducted using the US Oncology Network's (USON) iKnowMed (iKM) and electronic health record

(EHR) database as well as Limited Access Death Master File (LADMF).[32, 60] The analytical sample for this analysis included patients who underwent surgical resection of stage 2B or 2C melanoma and were subsequently identified as having a LRR – further details on this cohort are provided in Appendix M. Among the subset of these patients who had no adjuvant therapy, exponential parametric functions were fitted to observed data on time to distant metastases and time to death from the time of entry into the LRR state, accounting for competing risks (Table 33). 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.[80] When modelling each of these transitions, patients were censored at the end of follow-up or upon the occurrence of the competing transition type (i.e. Death for LRR→DM; DM for LRR→Death). Within each cycle, the transition probability from LRR→Death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality,[74] given the age and gender distribution of the cohort by that cycle.

Table 33: Weekly exponential rates of transitions starting from LRR among patients who receive no subsequent adjuvant treatment

Adjuvant regimen in LRR state	LRR→DM		LRR→Death		Source
	Exponential rate	SE	Exponential rate	SE	
No adjuvant treatment	[redacted]	[redacted]	[redacted]	[redacted]	US Oncology Network electronic health records[32, 60]

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; SE, standard error.

For patients who receive a subsequent adjuvant treatment in the LRR state, the model estimated transition probabilities using trial-based HRs of DMFS failure for each adjuvant treatment vs. placebo, as reported in the corresponding randomized controlled trials conducted in stage 3 melanoma.[18, 81, 82] This approach enabled the latest available data relating to the efficacy of each agent to be incorporated into the model based on market shares to reflect UK clinical practice as accurately as possible. Although a network meta-analysis (NMA) of HRs was not conducted to inform this transition, the difference in efficacy between adjuvant agents is negligible, therefore any effect on the ICER is expected to be minimal.[57, 83] These HRs (Table 34) were applied to the exponential rates of each transition (LRR→DM and LRR→Death) among patients who receive no adjuvant treatment in this setting (Table 33).

An alternative scenario was also explored whereby transition probabilities for patients receiving a subsequent adjuvant treatment in the LRR state were estimated using Electronic

Health Record (EHR) data. Exponential rates of these transitions were estimated through analyses of the subset of patients in the real-world EHR data from USON who received *any* adjuvant treatment. Under this approach, transition probabilities were not differentiated by specific adjuvant treatment received for stage 3 melanoma (Table 35).

Table 34: Weekly exponential rates of transitions starting from LRR among patients who receive subsequent adjuvant treatment – Base case

Adjuvant regimen in LRR state	HR of DMFS failure vs. no adjuvant treatment			Weekly exponential rate	
	HR	*SE of ln(HR)*	*Source*	*LRR→DM*	*LRR→Death*
Pembrolizumab	0.60	0.10	Eggermont et al., 2021 [KEYNOTE-054][18]	[redacted]	[redacted]
Nivolumab	0.60	0.10	Assumed equal to pembrolizumab†	[redacted]	[redacted]
Dabrafenib + trametinib	0.55	0.12	Dummer et al., 2020) [COMBI-AD][82]	[redacted]	[redacted]
No adjuvant treatment	1.00	1.00	Reference	[redacted]	[redacted]

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; HR, hazard ratio; LRR, locoregional recurrence; SE, standard error.
† In the CheckMate238 trial of nivolumab as an adjuvant treatment of resected stage III or IV melanoma, the comparator arm was an adjuvant ipilimumab regimen that differed from the ipilimumab regimen evaluated in the EORTC-18071 trial (i.e., the maximum duration of ipilimumab was 1 year in CheckMate 238 vs. 3 years in EORTC-18071). The HR of DMFS failure for nivolumab vs. no adjuvant treatment therefore could not be estimated directly or indirectly using results from CheckMate 238, so it was assumed that efficacy was equivalent to pembrolizumab.

Table 35: Weekly exponential rates of transitions starting from LRR among patients who receive subsequent adjuvant treatment – Scenario, using estimates from EHR

Adjuvant regimen in LRR state	LRR→DM		LRR→Death		Source
	Exponential rate	SE	Exponential rate	SE	
Any adjuvant treatment	[redacted]	[redacted]	[redacted]	[redacted]	US Oncology Network electronic health records[32, 60]

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LR, locoregional recurrence; SE, standard error.

Market shares of subsequent adjuvant treatments by initial adjuvant treatment

In each model arm, the exponential rates of LRR→DM and LRR→Death were calculated as a weighted average based on the exponential rates of these transitions for each subsequent adjuvant treatment regimen (Table 33 and Table 34) and the market shares of subsequent adjuvant treatments by model arm.

In the base case analysis, market shares of adjuvant treatment regimens for the routine surveillance arm were sourced from Ipsos Oncology Monitor market research[41] as this was the most robust source available for the UK setting. Data from KEYNOTE-716 on the use of subsequent treatments for patients who developed LRR were incomplete with respect to the use of combination regimens and were based on a small number of patients (n=[redacted]) (see Appendix P), therefore these were not suitable for informing the economic model. As the Ipsos dataset only included counts of treated patients, the estimated proportion of patients who received no systemic adjuvant therapy at LRR was obtained from market research of current UK treatment practices, conducted by MSD.[38] The market shares were validated by UK clinical experts who confirmed that they were reflective of current clinical practice in the stage 3 setting (Table 36).[66] Alternative sources of market share data, presented in Table 37, show trends consistent with the Ipsos data, indicating that the model inputs are likely to be representative of the current UK market.

For the pembrolizumab arm, clinical experts advised that they consider patients to have *'one shot'* at adjuvant therapy as there is currently no evidence on the efficacy of repeat treatment with adjuvant therapy, and they were not sure funding for further adjuvant therapy would be available; it was therefore deemed unlikely that patients treated with adjuvant pembrolizumab in the stage 2B/2C setting would receive further adjuvant therapy after LRR. However, they highlighted the benefits of giving adjuvant therapy in earlier disease stages in terms of reducing recurrence risk and thus reducing the burden of treating LRR and DM. [40, 66] Consequently, all patients in the pembrolizumab arm who had a LRR recurrence were assumed to have no further systemic adjuvant therapy. Despite this, there remains some uncertainty regarding retreatment with adjuvant therapy in the LRR setting, therefore a scenario analysis was included in which BRAF mutation positive patients in the pembrolizumab arm, adjusted for the proportion of the overall stage 3 population who have no adjuvant therapy, were able to receive adjuvant targeted therapy with dabrafenib + trametinib.

Table 36: Market shares of subsequent treatment in LRR health state

Stage 3 adjuvant treatment	Pembrolizumab		Routine surveillance
	Base case	Scenario	
Source:	*No further adjuvant therapy*	*BRAF positive patients eligible for targeted therapy*	*Ipsos Oncology Monitor, September 2021 & MSD market research, 2021*[38, 41]
Pembrolizumab	0%	0%	[redacted]
Nivolumab	0%	0%	[redacted]

Stage 3 adjuvant treatment	Pembrolizumab		Routine surveillance
	Base case	Scenario	
Dabrafenib + trametinib	0%	[redacted]	[redacted]
No systemic therapy	100%	[redacted]	[redacted]

Abbreviations: LRR, locoregional recurrence.
† Sourced from MSD market research, 2021[38];
‡ Capped at the proportion of BRAF-positive patients in the model (43.3%), adjusted for the proportion of the overall stage 3 population who have no adjuvant therapy ([redacted]).[38]

Table 37: Alternative for routine surveillance market share data for subsequent treatment in LRR health state

Stage 3 adjuvant treatment	Wilmington Specialist Share Data[84]	MSD market research[38]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
No systemic therapy	[redacted]	[redacted]

† Categorised as 'Other' in the Wilmington SSD dataset[84] – it is assumed that this corresponds to patients who were treated with surgery only, however this is uncertain.

B.3.3.3 Transitions from the distant metastasis (DM) health state

In each model arm, the transition probabilities from DM→Death were assumed to depend on the market shares of first-line treatments for advanced melanoma, which varied between arms. First-line treatment options included the following, based on the regimens currently approved by NICE and used in clinical practice for the treatment of advanced melanoma: pembrolizumab, nivolumab, nivolumab + ipilimumab, ipilimumab, dabrafenib + trametinib, encorafenib + binimetinib, and dacarbazine chemotherapy.[75] Second-line therapies for advanced melanoma were included in each adjuvant treatment arm but only with respect to their cost; survival within the DM state was therefore assumed to depend on the choice of first-line therapy only. As for the LRR state, it was conservatively assumed that there was no ongoing benefit of adjuvant pembrolizumab after recurrence, therefore the transition probabilities from the DM state differed between arms based only on the respective market shares of first-line treatments for advanced melanoma.

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

To estimate outcomes with pembrolizumab in the advanced melanoma setting, exponential models of OS and progression-free survival (PFS) were fitted to 5-year patient-level time-to-event data for patients receiving first-line treatment with pembrolizumab for metastatic melanoma from the KEYNOTE-006 trial, a multicentre, randomised, open-label phase 3 trial among ipilimumab-naïve patients with unresectable or advanced melanoma.[85, 86] The

resulting exponential curves were plotted alongside the corresponding Kaplan-Meier curves to assess fit, and are presented in Appendix M alongside the exponential model parameters.

The exponential distribution is typically 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.[80] Given the memoryless nature of Markov modelling, 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.

To estimate outcomes for other advanced treatment regimens, hazard ratios (HRs) for OS and PFS vs pembrolizumab were obtained from a network meta-analysis (NMA) of trials conducted in advanced melanoma.[87]

NMA of treatments for advanced melanoma

Eighteen RCTs reporting PFS and OS results for first-line treatment for advanced (unresectable stage 3 or 4) melanoma were identified in an SLR conducted on 15th October 2021. The feasibility for NMA using the identified studies was conducted based on between-study heterogeneity, presence of effect modifiers, and ability to generate connected evidence networks. A key assumption underlying the analysis was that BRAF status is only a relative treatment effect modifier for BRAF-targeted therapies (dabrafenib, encorafenib, and vemurafenib). As such, BRAF status is assumed to not be an effect-modifier for non-BRAF targeted therapies, and consequently separate NMAs were conducted to evaluate the efficacy in a BRAF all-comers population and a BRAF mutant population.

Each NMA synthesised reported HRs for PFS and OS assuming proportional hazards between treatments, which was shown to hold for >70% of treatment comparisons in the analysis. Whilst violation of this assumption in a small proportion of comparisons (mostly involving dacarbazine, cobimetinib + vemurafenib, and vemurafenib) is a limitation of the NMA, alternative NMA approaches using multidimensional models (i.e. time-varying HR NMA informed by both shape and scale parameters) would require extrapolation beyond the trial follow-up which may result in clinically implausible estimates and introduce concerns about overfitting. 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. Further, since the NMA was used to inform subsequent treatments only, and not the efficacy of adjuvant pembrolizumab, any limitations will apply to both treatment arms and therefore the impact on

the ICER is expected to be minimal. Consequently, the NMA based on proportional hazards was considered suitable for use in the economic model, and was aligned with the approach previously used in the recent appraisal for adjuvant pembrolizumab in stage 3 melanoma (TA766).[2] All analyses were performed in a Bayesian framework and involved a model with parameters, data and a likelihood distribution, and prior distributions. In each NMA, fixed- and random-effects models were explored; fixed-effects models were then selected as each treatment comparison across the network was primarily connected by a single trial. A limited number of trials precluded stable estimates of between-study heterogeneity from a random-effects model. Further details on the evidence networks and NMA methods are provided in Appendix O.

For nivolumab, ipilimumab, nivolumab + ipilimumab, and dacarbazine, HRs for the economic model were sourced from the BRAF all-comers NMA; for BRAF-targeted therapies (dabrafenib + trametinib and encorfenib + binimetinib), HRs were sourced from the BRAF-mutant NMA. The HRs of OS and PFS failure with other treatment regimens versus pembrolizumab obtained from the NMA and the resulting estimates of mean OS and PFS (in weeks) for each regimen, are presented in Table 38.

Table 38: HRs of OS and PFS failure with other treatment regimens vs. pembrolizumab in the advanced melanoma setting

Advanced regimen	OS HR vs. pembrolizumab		PFS HR h 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]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SE, standard error.
Note: HRs for OS and PFS vs. pembrolizumab were each obtained from an NMA of trials conducted in advanced melanoma.[87] For dabrafenib + trametinib and encorafenib + binimetinib, HRs were based on NMA results for the first-line BRAF-mutant population. For other treatments not targeting BRAF, HRs were based on NMA results for the first-line BRAF all-comers population.

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

In each model arm, the exponential hazard rate of DM→Death was assumed to depend on the market shares of first-line treatments received for advanced melanoma (Table 55) and the expected survival associated with each advanced melanoma treatment regimen (Table 38). Specifically, expected OS (starting from DM) was calculated in each model arm as a weighted average of expected OS associated with different first-line treatments for advanced melanoma based on the market shares of first-line advanced treatments in that arm.

Expected OS in each model arm was then translated into a weekly hazard rate. Expected PFS was similarly estimated for each model arm based on the distributions of first-line treatments received, and the ratio of mean PFS to mean OS was estimated for each arm. In each model arm, this ratio was used to calculate utility values (section B.3.4.5) and weekly disease management costs (section B.3.5.2) within the DM state (accounting for the proportion of time spent pre- vs. post-progression within this state).

The base case market share assumptions for first line treatment of advanced melanoma are described in section B.3.5.2 (Table 55). The estimated hazards of the transition from DM→Death with these base case market shares, along with the expected survival in the DM state, are shown in Table 39. The expected survival in the DM state predicted by the economic model ranged from [redacted] weeks ([redacted] years), based on the adjuvant treatment arm and eligibility for rechallenge. This is highly comparable to the 5.08 life years estimated for the pembrolizumab monotherapy arm in the economic model considered in the 2015 NICE appraisal of pembrolizumab monotherapy for untreated advanced melanoma (TA366).[88] As most deaths in the first half of the model occurred from the DM health state, based on this logic (which was the Evidence Review Group's [ERG's] preferred approach in TA766) this provides reassurance that the predicted OS is likely to be plausible.

Table 39: Hazards of death from DM state by model arm under base-case market shares of first-line treatments for advanced melanoma

Adjuvant regimen	**Eligibility for rechallenge (time from adjuvant treatment initiation)**	**Expected survival in DM state (weeks)†**			**DM→Death:** *Exponential hazard rate based on expected OS*
		OS	**PFS**	**Ratio of PFS to OS**	
Pembrolizumab	Ineligible (<24 months)	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	Eligible (≥24 months)	[redacted]	[redacted]	[redacted]	[redacted]

Routine surveillance	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; OS, overall survival; PFS, progression-free survival.
† Weighted average based on first-line advanced treatment market shares (Table 55).

B.3.3.4 Overview of health state transitions

An overview of the approaches used to estimate transitions between health states is provided in Table 40.

Table 40: Summary of health state transitions

Transition	Parameter assumptions		Source(s)	Justification
RF→LRR	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. Separate parametric models were fitted independently for each treatment arm of KEYNOTE-716, using the same functional form in each arm. A 95% risk reduction vs the parametric fitting was assumed from 10 years, with risk starting to decrease linearly from 7 years.	Lognormal both arms (Approach #1)†	• Treatment-specific patient-level data from the RFS analysis in KEYNOTE-716 IA2.[42] • Life tables for England & Wales (2017-2019) to ensure mortality ≥ general population mortality.[74]	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-716 RFS data and long-term plausibility of RFS, DMFS, and OS. This combination of parametric functions was validated using published external data sources. In line with guidance in NICE DSU TSD 14,[72] the same combination of parametric functions was used in both treatment arms. Published evidence and clinical opinion indicates that most recurrences occur in the first 5 years after resection, and the risk of recurrence after 10 years is extremely small.[13, 40] A 95% risk reduction, in line with methods used in previous NICE appraisals for adjuvant therapies,[76-78] was applied to capture this flattening of the RFS curves.
RF→DM		Lognormal both arms (Approach #1)†		
RF→Death		Exponential both arms†		Given the small number of deaths that occurred in the RFS analysis of KEYNOTE-716, exponential models were used as a conservative approach to modelling this transition.
LRR→DM	Exponential model fitted to real-world patient-level data from the US Oncology Network EHR to estimate the transitions for patients not receiving any adjuvant therapy for stage 3 melanoma. In each adjuvant treatment arm, the transition probability from LRR to DM or death was then assumed to depend on the expected mix of subsequent adjuvant treatments for stage 3 melanoma, and the efficacy of these treatments in terms of RFS and OS.		• US Oncology Network – patients with stage 2B/2C melanoma who had a LRR.[32, 60] • Market shares: Ipsos Oncology Monitor, 2021; MSD market research.[38, 41] • Life tables for England & Wales (2017-2019) to ensure mortality ≥ general population mortality.[74]	At the IA2 analysis of KEYNOTE-716, insufficient recurrence events had occurred to facilitate estimates of transitions from LRR, therefore real-world data were used instead. Note that the model does not apply any ongoing benefit after recurrence for patients who were treated with adjuvant pembrolizumab – this is considered a conservative assumption.
LRR→Death				

Transition	Parameter assumptions	Source(s)	Justification
DM→Death	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 first-line advanced melanoma); HRs for alternative subsequent treatments sourced from NMA of advanced melanoma treatments.	• Patient-level OS/PFS data from first-line treatment with pembrolizumab in KEYNOTE-006[85] • NMA of PFS/OS outcomes with treatments for advanced melanoma.[87] • Market shares: SACT 2021; Ipsos Oncology Monitor 2021; MSD market research.[38, 41, 89] • Life tables for England & Wales (2017-2019) to ensure mortality ≥ general population mortality.[74]	Survival for patients with advanced melanoma is dependent on the treatment they receive, which may differ based on whether they have previously been treated with pembrolizumab at stage 2. At the IA2 analysis of KEYNOTE-716, insufficient DM recurrence and subsequent death events had occurred to facilitate estimates of transitions from DM, therefore external sources were used instead. Note that the model does not apply any ongoing benefit after recurrence for patients who were treated with adjuvant pembrolizumab – this is considered a conservative assumption.

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; EHR, Electronic Health Records; IA2, interim analysis 2; LRR, locoregional recurrence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RF, recurrence-free; RFS, recurrence-free survival.
† Independently fitted to each adjuvant treatment arm.

B.3.3.5 Adverse events

The model considered grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial. Though risk at any grade was used to determine eligibility of inclusion for a certain type of AE, only grade 3 to 5 AEs were incorporated into the model due to their expected impact on resource utilization and quality of life. In addition to these grade 3+ AE types, diarrhoea of grades 2 or higher was also considered based on the high expected cost of managing this AE (i.e. need for hospitalisation) even for grade 2 events and to ensure consistency with previous NICE appraisals.[2, 90, 91] [redacted]

Risks of the included AEs for patients treated with pembrolizumab and routine surveillance were obtained from all-cause AE event rates observed in KEYNOTE-716 (Table 41). Mean durations of each AE per episode, and the mean number of episodes per patient with each AE, were collected from KEYNOTE-716 using pooled data from both treatment arms and were used within the model to estimate the duration of the disutility impact from each AE regardless of subgroup or adjuvant treatment arm. Consideration of AE-related disutility and cost is described in sections B.3.4.4 and B.3.5.3, respectively.

Table 41: Risks and durations of modelled adverse events, from KEYNOTE-716

AE type†	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with the AE (weeks)	Mean duration per episode (weeks)
	Pembrolizumab	Routine surveillance		
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]

AE type†	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with the AE (weeks)	Mean duration per episode (weeks)
	Pembrolizumab	Routine surveillance		
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia‡	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
† The model considered grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial, therefore AEs (such as colitis) that occurred in <5% of patients were not included; ‡ Selected for inclusion *a priori*, but not observed in the trial by the data cut-off.

B.3.4 *Measurement and valuation of health effects*

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

KEYNOTE-716

Health-related quality of life (HRQoL) was measured in KEYNOTE-716 using the EORTC-QLQ-C30 instrument and the EuroQoL EQ-5D-5L. The NICE STA guidelines state that the EQ-5D is the preferred tool to measure HRQoL and that the economic model should consider HRQoL data collected directly from patients in the relevant clinical study to inform the utility weights.[65]

In Part one of KEYNOTE-716, the EQ-5D-5L was administered at baseline (cycle 1), every fourth cycle while on treatment (cycles 5, 9, 13, 17; i.e. every 12 weeks), every 12 weeks during year 2 (week 60, 72, 84, and 96 from baseline), every 6 months during year 3 (month 30 and 36 from baseline), at the treatment discontinuation visit, and at the 30-day follow-up visit. In Part 2 (crossover/rechallenge after recurrence), measurements were collected at baseline (cycle 1 of Part 2), during treatment at cycles 9, 17 and 35, and at 24 and 48 weeks during the first year off treatment.

As per NICE's position statement for reference case analyses, the EQ-5D-3L value set is preferred for the reference case analysis,[92] therefore the EQ-5D-5L measurements collected in KEYNOTE-716 were mapped to the EQ-5D-3L tool using the crosswalk method developed by van Hout et al (2012).[93] The EQ-5D-3L UK value set, developed based on the time trade-off method,[94] was then used to derive utility values for the economic model. The EQ-5D-5L value set[37] was explored in a scenario analysis.

The EQ-5D analysis from KEYNOTE-716 was based on the IA2 data cut (21st June 2021) and consisted of the full analysis set (FAS), defined as all patients who received at least one

dose of study medication and had at least one EQ-5D measurement available. Compliance to the EQ-5D assessments in KEYNOTE-716 was very good and remained over [redacted] for all timepoints in both the pembrolizumab and placebo arms (see Appendix Q).

Utility values for the RF, LRR and DM health states were derived via repeated measures regression analyses of patient-level EQ-5D data from the KEYNOTE-716 trial (Table 42). At each visit where HRQoL was assessed, the corresponding EQ-5D score was used to estimate utility and visits with missing EQ-5D responses were excluded from the analysis. A linear mixed-effects model with patient-level random effects was used to account for the correlation among repeated measures within an individual. The analyses were pooled across treatment arms to estimate the average utility for all patients in the trial, as there was no clinically meaningful difference in HRQoL between the pembrolizumab and placebo arms of the KEYNOTE-716 trial.[95] Two regression models were conducted, with EQ-5D as the dependent variable:

- <u>RF utility and AE disutility:</u>
  Included patient visits with a utility measurement that occurred during each patient's RF period (N=[redacted] patients, with [redacted] unique patient-visits). Binary indicators for the absence of any AE during the patient-visit; and the presence of any other-grade (i.e. grade <3) AE during the patient-visit, were used to estimate utilities for patients with or without AEs. Further details on the calculation of AE disutilities are provided in section B.3.4.4 (Table 44).

- <u>LRR and DM utilities:</u>
  Considered all patient-visits with a utility measurement while patients were in the LRR or DM state (this included [redacted] patients with a LRR and [redacted] patients with a DM). Independent variables included binary indicators for: being in the LRR state during the patient-visit; and being in the DM state during the patient-visit. In contrast to the first regression model, this regression did not adjust for the presence/absence of AEs, as it was important to obtain LRR and DM utility estimates that incorporated any AE-related disutility associated with subsequent treatments, as the cost-effectiveness model did not separately apply AE-related disutility due to subsequent treatments within the LRR and DM states.

It was not possible to generate utility values for pre- versus post-progression in the DM health state as the available follow-up data from KEYNOTE-716 to date was too limited to capture the average utility over the entire post-progression disease course until death. In

addition, the utility values for the LRR and DM health states were informed by the relatively small number of patients who had a LRR or DM recurrence in the KEYNOTE-716 trial ([redacted] and [redacted] patients, respectively), and from a single time point shortly after recurrence. Consequently, the trial-based utilities for these health states should be interpreted with more caution.

Table 42: Summary of health state utility values derived from KEYNOTE-716

Health state	EQ-5D-3L		EQ-5D-5L (scenario)	
	Mean	SE	Mean	SE
RF†	[redacted]	[redacted]	[redacted]	[redacted]
RF (toxicity free)	[redacted]	[redacted]	[redacted]	[redacted]
RF with Grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]
LRR	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free; SE, standard error.
† Note that this utility value is not suitable for use in the economic model, as it includes effects of adverse events – it is shown here for completeness.

B.3.4.2 Mapping

EQ-5D-5L measurements collected in KEYNOTE-716 were mapped to the EQ-5D-3L tool using the crosswalk method developed by van Hout et al (2012),[93] as per the NICE position statement, to ensure the utility values were aligned with the NICE reference case.[92] The EQ-5D-3L UK value set, developed based on the time trade-off method, was then used to derive utility values for the base case economic model.[94]

B.3.4.3 Health-related quality-of-life studies

Early-stage melanoma

A systematic literature review (SLR) was conducted to identify studies reporting utility values for patients with early-stage melanoma. Details relating to the search strategy, study identification process, and the studies included in the SLR are presented in Appendix H. One study was identified: Tromme et al (2014) used the EQ-5D-5L (mapped to the EQ-5D-3L and valued using the Belgian value set) to obtain stage-specific utilities for patients on treatment (surgery and/or systemic therapy) versus patients in remission (Table 43).[96] This source was not consistent with the NICE reference case, as it did not report health states valued by the UK general population.[65] Further, the health states described did not correspond well to the health states considered in the current analysis (i.e. not stage 2B/2C), and the utilities reported for stage 3 melanoma were lower than those for patients with stage 4 melanoma, which is considered implausible.

Stage 3–4 melanoma

To identify HRQoL studies that reported utility values for stage 3 and stage 4 melanoma, the SLR was supplemented by reviewing the studies included in previous NICE appraisals of immunotherapies for melanoma (TA366, TA766 and TA684).[2, 16, 88] Four potential sources of utility values were identified (Table 43).

Health state utility values measured using the EQ-5D-3L from the KEYNOTE-054 RCT of adjuvant pembrolizumab for patients with resected stage 3 melanoma were available for the RF, LRR and DM health states (TA766).[2] These utilities were comparable, although slightly lower, compared with the utility values derived from KEYNOTE-716, which is logical given the differences in disease stage at baseline. Compared with KEYNOTE-716, at the latest database lock more patients in the KEYNOTE-054 trial had experienced a LRR or a DM and were therefore eligible for inclusion in the utility analyses and as such the utilities for these health states from KEYNOTE-054 may be more reliable. However, as in KEYNOTE-716 the utility for the DM state from KEYNOTE-054 does not distinguish between pre- and post-progression.

EQ-5D-3L utilities for pre- vs post-progression for advanced, ipilimumab-naïve melanoma were available from the KEYNOTE-006 trial in TA366 (0.8 and 0.7, respectively).[88] The progression-free utility from KEYNOTE-006 is lower than the DM utility obtained from KEYNOTE-716 (0.8 vs [redacted]) but similar to the DM utility from KEYNOTE-054 ([redacted]) which, given that only a small number of patients have had a DM in KEYNOTE-716 to date[44] and had utility results available (n=[redacted]), suggests that the DM utility from the KEYNOTE-716 trial may be slightly overestimated. Note that trial-based utility values in KEYNOTE-006 were collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit (i.e. immediately after progression), but no further; therefore trial utility data for post-progression typically does not capture the decrease in patients' HRQoL associated with toxic subsequent therapies and further disease progression. This could lead to an overestimate of the utility in the post-progression state from KEYNOTE-006.

Two alternative studies reporting UK utilities for health states that could be relevant to the current economic analysis were identified from these previous NICE TAs for melanoma. Beusterien et al (2009) and Middleton et al (2017) [97, 98] used SG methods to elicit societal preferences from the UK general population, for health states associated with advanced and stage 3 adjuvant melanoma, respectively. This is not fully aligned with the NICE reference case, [65] as health states were not described by patients with melanoma and time trade-off

methods are typically preferred, however they were valued by the UK population which is considered important. In both studies, the utilities that best corresponded to the DM health state in the current model ('stable disease' [0.77] and 'progressive disease' [0.59] from Beusterien et al;[97] 'recurrence-long term treatment/survival' [0.703] and 'recurrence' [0.581] from Middleton et al)[98] were all lower than the utilities obtained for the DM state from KEYNOTE-716 ([redacted]) and KEYNOTE-054 ([redacted]),[2] but do indicate that there is a substantial difference in utility between pre- and post-progression which is not captured in the KEYNOTE trials.

Table 43: Health state utility values from the literature

Study	Tool (Population)	Health state	Utility	
			Mean	SE (95% CI)
Tromme et al, 2014[96] (Belgium)	EQ-5D-5L mapped to 3L (Melanoma patients; Belgian value set)	Stage 1B–2, on treatment	0.579	0.047 (0.486, 0.671)
		Stage 1B–2, remission	0.802	0.019 (0.764, 0.839)
		Stage 3, on treatment	0.535	0.072 (0.395, 0.676)
		Stage 3, remission	0.703	0.022 (0.659, 0.746)
		Stage 4, from start of treatment	0.583	0.030 (0.524, 0.642)
		Stage 4, from start of remission	0.796	0.045 (0,708, 0.883)
KEYNOTE-054[2] (Global)	EQ-5D-3L† (Patients with stage 3 resected melanoma, UK value set)	RF (resected, stage 3 melanoma)	[redacted]	[redacted]
		LRR	[redacted]	[redacted]
		DM	[redacted]	[redacted]
KEYNOTE-006, TA366[88] (Global)	EQ-5D-3L (Patients with advanced melanoma, UK value set)	Progression-free‡	0.80	0.01 (0.78, 0.81)
		Progressed§	0.70	0.02 (0.67, 0.73)
Beusterien et al, 2009[97] (UK)	SG (UK general population)	Advanced melanoma: Partial response	0.85	0.02
		Advanced melanoma: Stable disease	0.77	0.02
		Advanced melanoma: Progressive disease	0.59	0.02
		Advanced melanoma: BSC	0.59	0.02
	SG	Adjuvant, no toxicities	0.840	NR

Study	Tool (Population)	Health state	Utility	
			Mean	SE (95% CI)
Middleton et al, 2017[98] (UK)	(UK general population)	Adjuvant, induction treatment	0.845	NR
		No adjuvant treatment	0.837	NR
		Recurrence-long term treatment/survival	0.703	NR
		Recurrence	0.581	NR

Abbreviations: BSC, best supportive care; CI, confidence interval; IFNa-2b, interferon alpha 2b; SD, standard deviation; SE, standard error; SG, standard gamble.
† Based on [redacted] patients, [redacted] measurements; ‡ Based on 432 patients, 1,141 measurements; § Based on 272 patients, 420 measurements.

B.3.4.4 Adverse reactions

As described in section B.3.3, the model considered Grade 3+ AEs that occurred at any grade in ≥5% of patients in either arm of the KEYNOTE-716 trial, in addition to Grade 2+ diarrhoea.

The disutility of an active Grade 3+ AE was estimated to be [redacted] and represents the difference in utility associated with recurrence-free (without toxicity) versus recurrence-free (during any grade 3+ AE) in KEYNOTE-716. This was obtained from the same regression model used to estimate EQ-5D RF health state utilities from the KEYNOTE-716 trial, based on the coefficient associated with the presence of any Grade 3+ AEs (Table 44). The same disutility was conservatively applied to Grade 2+ diarrhoea.

Table 44: Regression coefficients used to estimate AE disutility, from KEYNOTE-716

Covariate	EQ-5D-3L		EQ-5D-5L (scenario)	
	Estimate	SE	Estimate	SE
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
AE status at visit				
During Grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]
During other grade AE	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; SE, standard error.

The mean duration of each AE, pooled across treatment arms, was sourced from the KEYNOTE-716 trial and used to estimate the duration of the disutility impact for each AE (see section B.3.3.5, Table 41).

Disutilities associated with each AE were applied as a one-off utility decrement in the first model cycle and were therefore calculated as a function of treatment-specific AE risks; the

mean durations of these AEs per affected patient in KEYNOTE-716; and the estimated disutility associated with an active grade 3+ AE based on regression analyses of EQ-5D-5L data from the KEYNOTE-716 trial, mapped to EQ-5D-3L using the van Hout et al, 2012 algorithm[93].

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

As stated in the NICE methods guide, the preferred approach for incorporating HRQoL into the economic model is to collect health state measurements from patients relevant to the decision problem using the EQ-5D-3L tool, and the utility weights should be elicited from the UK general population.[65] Accordingly, for the RF, LRR, and pre-progression DM health states the base case analysis used utility values derived from the regression analyses of patient-level EQ-5D-5L data collected from the KEYNOTE-716 trial. The EQ-5D-5L measurements were mapped back to the EQ-5D-3L version of the tool using the algorithm developed by van Hout et al (2012)[93] and utilities derived using the UK value set. A disutility for AEs was also estimated from the KEYNOTE-716 trial and applied to patients in the RF state experiencing a AE (Table 45).[94]

In line with the model structure, the DM health state was comprised of two sub-states (pre-progression and post-progression) to capture differences in outcomes and costs of patients who develop advanced disease. As discussed above, EQ-5D data corresponding to post-progression were not available from KEYNOTE-716 as the available follow-up from the trial was too limited to enable a robust analysis of post-progression utility. Similarly, suitable post-progression utilities were not available from the other melanoma trials of pembrolizumab (KEYNOTE-054 and KEYNOTE-006) due to study follow-up methods.

Consequently, the utility value for the post-progression health state was sourced from the publication by Beusterien et al (2009) which used a SG approach to elicit utilities for advanced melanoma health states from the UK general population.[97] The use of this study is not fully aligned with the NICE reference case as health states were not measured by patients with melanoma, but it was deemed to be the best available source in the absence of data from the KEYNOTE-716 trial and was more conservative compared with the 'progressive disease' utility reported by Middleton et al, 2017.[98] It has also been used in previous NICE appraisals for melanoma (TA384 and TA766).[2, 99]

A summary of the utilities used in the base case analysis is provided in Table 45. These were validated with UK clinical experts, who confirmed that a decrease in HRQoL relative to RF would be expected for patients with a LRR, and a further decrease observed for patients with DM melanoma. However, clinical experts also indicated that the largest drop in HRQoL is typically observed on first recurrence, whether LRR or DM, and therefore that the utilities derived from KEYNOTE-716 for the LRR and DM health states are likely to be overestimated.[40] Given the limited availability of other sources of utilities meeting the NICE reference case, the KEYNOTE-716 values were retained for the base case analysis – this is considered to be a conservative approach. The impact of the utility values on the cost-effectiveness results was explored in scenario analyses which utilized alternative sources of utility values for the LRR and DM health states, in addition to a scenario that used EQ-5D-5L utilities derived from KEYNOTE-716.

Table 45: Summary of utility values used in the economic model

State	Utility value	SE	Source
RF (toxicity-free)	[redacted]	[redacted]	KEYNOTE-716
LRR	[redacted]	[redacted]	
DM (pre-progression)	[redacted]	[redacted]	
DM (post-progression)	0.59	0.02	Beusterien et al, 2009[97]
Death	0	-	-
AE†	[redacted]	-	KEYNOTE-716

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free; SE, standard error.
† This AE disutility was applied to the RF (toxicity free) utility, adjusted by the frequency of AEs, to estimate the utility for RF with toxicity.

The model then calculated a single utility value for the DM health state as a weighted average of the pre- and post-progression states, based on the proportion of time spent in each (i.e. the ratio of PFS:OS [Table 39]). This estimate of time spent in each substate was calculated based on market shares of first-line treatment regimens in the advanced setting (see section B.3.5), and the estimated efficacy of those treatment regimens in the advanced setting (see section B.3.3). As the market shares of subsequent treatments in the advanced setting affect the PFS:OS ratio and vary by adjuvant treatment arm, the weighted average utility will also differ for adjuvant pembrolizumab vs routine surveillance. The utility of the death state was set to zero.

Age-related disutility

To account for potential decreases in utility with age, age-adjusted utilities were applied in the model to account for the increasing age of the cohort over time using the algorithm

developed by Ara and Brazier (2010).[100] This approach uses a linear regression model to predict the mean utility for the general population, conditional based on age, age squared and sex (Table 46).

Table 46: Regression coefficients used to estimate age-related disutility

Parameter	Coefficient	Source
Age (years)	-0.0002587	Ara and Brazier, 2009[100]
Age^2	-0.0000332	
Male	0.0212126	
Intercept	0.9508566	

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

In line with the NICE reference case,[65] the model took a UK National Health Service (NHS) and Personal Social Services (PSS) perspective and therefore only direct healthcare costs related to the treatment and management of melanoma were considered. Evidence on resources used by patients in the treatment pathway were sourced from the KEYNOTE-716 trial and published literature and were verified by UK clinical experts.[40] Healthcare costs were obtained from publicly available sources which primarily included the Monthly Index of Medical Specialties (MIMS),[101] NHS Reference Costs,[102] and the Personal Social Services Research Unit (PSSRU)[103] to ensure the model used the most up to date costs relevant to UK practice. These were supplemented by costs from published studies where relevant inputs from the public sources were not available. All costs are reported in 2020 GBP.

B.3.5.1 Intervention and comparators' costs and resource use

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab, therefore the cost of treatment was estimated based on the drug acquisition costs and the cost of intravenous (IV) administration.

As per the anticipated licence, the model considered a 400 mg IV infusion of pembrolizumab every 6 weeks (Q6W) for adults, and weight-based dosing of 2 mg/kg Q3W for children. The list price of pembrolizumab was £2,630.00 per 100 mg vial,[101] therefore the list drug cost per administration was £10,520.00 for adults and [redacted] for children (based on mean paediatric weight in KEYNOTE-716 [Table 24]; note that 0.2% of the model cohort were paediatric). It was conservatively assumed that vial sharing was not permitted. To prevent over-dosing, it was assumed that the final dose of the pembrolizumab Q6W regimen within the 12-month treatment period would be 200 mg based on the available vial presentations for

pembrolizumab. A patient access scheme (PAS) is in place for pembrolizumab, which makes pembrolizumab available to the NHS at a discount (see Table 2). The relative dose intensity (RDI) observed in KEYNOTE-716 was applied to the drug acquisition cost per infusion of adjuvant pembrolizumab to account for any delays or interruptions in administration. Pembrolizumab is administered via a 30-minute IV infusion, which was costed based on Healthcare Resource Group (HRG) code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) from NHS Reference Costs 2019/20. This is consistent with the costing approach applied in previous NICE submissions for pembrolizumab (TA357, TA366, TA766) (Table 47).[2, 88, 104]

Table 47: Drug and administration cost of adjuvant pembrolizumab

Parameter	Value	Source
Acquisition cost per 100 mg vial (list price)	£2,630.00	MIMS[101]
Acquisition cost per administration (list price) - Adults	£10,520.00	Dosing schedule: 400 mg Q6W for up to 1 year[1]
Acquisition cost per administration (list price) - Children	[redacted]	Dosing schedule: 2 mg/kg Q3W (up to 200 mg) for up to 1 year[1]
Relative dose intensity (RDI)	[redacted]	KEYNOTE-716
RDI-adjusted cost per administration (list price)	[redacted]	-
Administration cost	£281.28	NHS Reference Costs 2019/20: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance (Total HRG)[102]

Abbreviations: HRG, Healthcare Resource Group; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; Q3W, every 3 weeks; Q6W, every 6 weeks; RDI, relative dose intensity.

There is no drug cost associated with the comparator, routine surveillance. Clinical monitoring activities for patients on adjuvant pembrolizumab are expected to follow current clinical practice for routine surveillance. Details of these activities are outlined in section B.3.5.2.

Treatment duration

The proportion of patients remaining on adjuvant pembrolizumab at each scheduled infusion was based on the observed Kaplan-Meier curve for time to treatment discontinuation in the KEYNOTE-716 trial (Figure 13). In the trial, patients randomized to adjuvant pembrolizumab received treatment for up to 1 year or until completion of 17 doses of 200 mg Q3W (i.e., the number of scheduled doses over 1 year). Based on this maximum duration, there was sufficient follow-up data from the trial to directly observe time on adjuvant treatment, without the need for extrapolation.

A small percentage of patients in the pembrolizumab arm of KEYNOTE-716 remained on adjuvant therapy beyond 1 year, as the protocol allowed patients to complete all scheduled doses past the 1-year point if there had been earlier delays in treatment. Within the economic evaluation, the costs of adjuvant pembrolizumab treatment were modelled based on a fixed interval of Q6W, and so the costs of the final dose were applied at t=48 weeks from baseline for the percentage of patients still on adjuvant treatment at this time point. Therefore, the model did not use the portion of the Kaplan-Meier curve beyond the scheduled 1-year treatment period (represented by the dashed line in Figure 13).

Figure 13: Adjuvant pembrolizumab observed time on treatment (KEYNOTE-716)

The KEYNOTE-716 protocol allowed patients to complete all scheduled doses past the 1-year point if there had been earlier delays in treatment. However, the model applied a fixed dosing interval and therefore considered adjuvant treatment dosing up to 1 year only, accounting for RDI. Consequently, the model did not use the portion of the Kaplan-Meier curve beyond the scheduled 1-year treatment period, indicated by the dashed line in this figure.

B.3.5.2 Health-state unit costs and resource use

Health state costs were based on resource use estimates sourced from the literature and were expected to be the same for patients on adjuvant pembrolizumab and routine surveillance. This was confirmed with UK clinical experts based on their experience using adjuvant pembrolizumab in the stage 3 resected melanoma setting.[40]

Recurrence-free (RF) health state

For patients remaining in the RF health state, medical resource use consisted of regular surveillance activities intended to identify tumor recurrences. The frequencies of clinical surveillance activities were based on NICE guideline 14 (NG14) and the surveillance policy for patients with stage 2B/2C resected melanoma outlined in a position paper developed by UK clinicians, which included clinic visits and imaging at specific intervals (Table 48).[14, 51] Based on clinical expert input, clinic visits were assumed to alternate between the plastic surgeon and dermatologist.[40]

Table 48: Resource use: Recurrence-free health state

Resource	Years 1-3		Years 4-5		Years 6+	Source
	% patients	No./year	% patients	No./year		
Clinic visits						
Medical oncologist	0%	0	0%	0	0	Larkin et al, 2013; NICE
Plastic surgeon	100%	2	100%	1	0	

Resource	Years 1-3		Years 4-5		Years 6+	Source
	% patients	No./year	% patients	No./year		
Dermatologist	100%	2	100%	1	0	NG14; Expert opinion[14, 40, 51]
Imaging						
CT scan – abdomen/pelvis/chest	50%	2	50%	1	0	Larkin et al, 2013; Expert opinion[40, 51]
MRI scan - brain	100%	2	100%	1	0	
PET-CT scan	50%	2	50%	1	0	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron-emission tomography.

Unit costs for each resource were sourced from NHS Reference Costs 2019/20 (Table 49),[102] applied to annual resource use estimates, and then converted to resource use cost per cycle for inclusion in the model.

Table 49: Unit costs: Regular surveillance activities

Resource	Unit price	Source[102]
Clinic visits		
Medical oncologist	£192.85	NHS Reference Costs 2019/20. Total outpatient attendances for 370 (medical oncology)
Plastic surgeon	£117.34	NHS Reference Costs 2019/20. Total outpatient attendances for 160 (plastic surgery)
Dermatologist	£121.15	NHS Reference Costs 2019/20. Total outpatient attendances for 330 (dermatology)
Imaging		
CT scan – abdomen/pelvis/chest	£78.66	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
MRI scan - brain	£147.78	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z
PET-CT scan	£147.78	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron-emission tomography.

Locoregional recurrence (LRR) health state

Upon entry to the LRR health state, a proportion of patients were assumed to undergo salvage surgery. The type of surgery, the proportion of patients having each surgery type, and the mean number of surgeries per patient, were calculated based on the frequency observed in the KEYNOTE-716 trial ([redacted] patients with a LRR as their first recurrence underwent salvage surgery, pooled across treatment arms). The frequency of regular surveillance activities was sourced from NG14 and the UK position paper used to inform the RF state (Table 50).[14, 51] In addition, UK clinical experts advised that patients who were

suspected of having a recurrence would undergo an image-guided biopsy (using CT or ultrasound imaging) to confirm the recurrence, therefore this resource was also included in the model.

Table 50: Resource use: Locoregional recurrence health state

Resource	One-off resource		Regular monitoring		Source
	% of patients	Average per patient	% of patients	Frequency per year	
Salvage surgery					
ITM resection or other surgery	[redacted]	[redacted]	-	-	[redacted] patients with LRR in KEYNOTE-716[42]
Lymphadenectomy	[redacted]	[redacted]	-	-	[redacted] patients with LRR in KEYNOTE-716[42]
Skin lesion resection	[redacted]	[redacted]	-	-	[redacted] patients with LRR in KEYNOTE-716[42]
Clinic visits					
Image-guided biopsy	100%	1.00	-	-	Expert opinion[40]
Medical oncologist	-	-	0%	0	Larkin et al, 2013; NICE NG14; Expert opinion[14, 40, 51]
Plastic surgeon	-	-	100%	2	
Dermatologist	-	-	100%	2	
Imaging					
CT scan – abdomen/pelvis/chest	-	-	50%	2	Larkin et al, 2013; Expert opinion[40, 51]
MRI scan - brain	-	-	100%	2	
PET-CT scan	-	-	50%	2	

Abbreviations: CT, computed tomography; ITM, in transit metastases; MRI, magnetic resonance imaging; PET, positron-emission tomography.

The costs of salvage surgeries were sourced from NHS Reference Costs 2019/20[102] and were applied as a one-off cost on entry to the LRR state (Table 51). Unit costs for clinic visits and imaging resources were sourced from NHS Reference Costs 2019/20 as per the RF health state (Table 49) and used to calculate the cost per cycle for inclusion in the model.[102] The HRGs selected were consistent with those used in the recent appraisal of adjuvant pembrolizumab for stage 3 melanoma (TA766).[2]

Table 51: Unit costs: Salvage surgery and biopsy

Resource	Unit price	Source[102]
ITM resection or other surgery	£2,868.21	NHS Reference Costs 2019/20 - Total HRG activity for JC41Z (major skin procedures)
Lymphadenectomy	£2,483.94	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for WH54A and WH54B

Resource	Unit price	Source[102]
Skin lesion resection	£526.62	NHS Reference Costs 2019/20 - Total HRG activity for JC42C (intermediate skin procedures, 19 years and over)
Image-guided biopsy	£550.61	NHS Reference Costs 2019/20 - Day case for YC01Z (Image Guided Core Needle Biopsy of Lesion of Neck), plus DAPS02 (Histopathology and histology)

Abbreviations: HRG, Healthcare Resource Group; ITM, in transit metastases; NHS, National Health Service.

In addition, patients in the routine surveillance arm who entered the LRR state were assumed to be eligible for systemic adjuvant therapy with one of the three agents currently recommended by NICE for resected stage 3 melanoma (pembrolizumab, nivolumab, or dabrafenib + trametinib). The proportions of patients receiving each adjuvant therapy are described in section B.3.3.2 (Table 36).

Drug acquisition and administration costs for adjuvant therapies were applied as lump-sum costs upon entry into the LRR state. The dosing schedule for each drug was based on the schedule included in the corresponding NICE recommendation and in line with the SmPC. For treatments where multiple dosing schedules are available (pembrolizumab and nivolumab), the schedule with longer dosing interval was selected for the base case in line with UK clinical expert advice regarding current clinical practice – the impact of shorter dosing schedules was explored in a scenario analysis. Unit costs per pack or vial of treatment were sourced from MIMS (Table 52); note that these are list prices, as the discounts in place for each therapy are confidential.

Table 52: Doses and drug acquisition costs for adjuvant therapies in LRR state†

Treatment	Dose	Pack size / vial volume	Cost per pack/vial	Sources
Pembrolizumab	400 mg Q6W	100 mg vial	£2,630	TA766; SmPC; MIMS[1, 2, 101]
Nivolumab	480 mg Q4W	40 mg vial 100 mg vial	£439 £1,097	TA684; SmPC; MIMS[16, 101]
Dabrafenib	150 mg BID	28 x 75 mg tablet	£1,400 (£50 per tablet)	TA544; SmPC; MIMS[17, 101]
Trametinib	2 mg QD	30 x 2 mg tablet	£4,800 (£160 per tablet)	

Abbreviations: BID, twice daily; MIMS, Monthly Index of Medical Specialties; Q4W, every 4 weeks; Q6W, every 6 weeks; QD, every day.
† Actual costs applied in the model are dependent on the market shares applied.

Drug administration costs for adjuvant therapies were sourced from NHS Reference Costs 2019/20 and the PSSRU 2021 (Table 53).[102, 103] As for adjuvant pembrolizumab therapy at

stage 2, IV infusions for pembrolizumab and nivolumab were costed based on HRG code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) and applied per administration. For oral therapies, the first administration was assumed to take place in hospital; subsequent doses were assumed to be taken at home, and therefore the subsequent administration cost included pharmacy dispensing costs every 28 days. This cost was calculated based on an average of 12 minutes of pharmacist time for dispensing each oral medicine,[103] applied to the hourly cost of a pharmacist time, consistent with the approach used in TA366.[88]

Table 53: Administration costs for adjuvant therapies in the LRR state

Treatment	Unit cost	Source[102, 103]
Pembrolizumab	£281.28	NHS Reference Costs 2019/20: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance (Total HRG)
Nivolumab	£281.28	NHS Reference Costs 2019/20: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance (Total HRG)
Dabrafenib + trametinib	First: £210.79	NHS Reference Costs 2019/20 - Total HRG activity for SB11Z (deliver exclusively oral chemotherapy)
	Subsequent: £9.60	12 minutes of pharmacist time. PSSRU 2021: Hospital based scientific and professional staff – Band 6 (Pharmacist)

Abbreviations: HRG, Healthcare Resource Group; LRR, locoregional recurrence; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

The mean duration of each adjuvant treatment in the stage 3 setting was estimated using observed time on treatment statistics reported from the corresponding clinical trial in this setting, which were used to calculate the exponential rate of discontinuation.[18, 82, 105] All adjuvant therapies were capped to account for the label-recommended maximum duration of each treatment (Table 54). Dose intensity was assumed to be 100% for all treatments in the LRR state.

Table 54: Treatment duration for adjuvant therapies in the LRR state

Treatment	Maximum ToT	Exponential rate of discontinuation	Dose intensity	Source
Pembrolizumab	52 weeks	[redacted]	100%	KEYNOTE-054[18]
Nivolumab	52 weeks	[redacted]	100%	Weber et al, 2017; CheckMate238[105]
Dabrafenib + trametinib	52 weeks	[redacted]	100%	Dummer et al, 2020; COMBI-AD[82]

Abbreviations: LRR, locoregional recurrence; ToT, time on treatment.

Distant metastatic (DM) health state

As outlined in the NICE pathway for melanoma, the primary treatment option for patients with advanced melanoma (i.e. unresectable or metastatic disease) is systemic therapy with immune-oncology (IO) or targeted agents.[75] All patients who entered the DM health state were assumed to be eligible for treatment in the advanced setting with one of the treatment regimens currently recommended by NICE and used in clinical practice. This is aligned with recent appraisals of IOs in adjuvant stage 3 melanoma (TA766, TA684).[2, 16]

UK clinical experts advised that, in current practice, IO combination therapy with nivolumab + ipilimumab would often be the preferred choice of first-line treatment for patients deemed to be fit enough, otherwise IO monotherapy, most often with pembrolizumab Q6W, would be given. Targeted therapies (dabrafenib + trametinib or encorafenib + binimetinib) would be options for patients with BRAF-mutation positive melanoma (43.3% of patients in KEYNOTE-054), although a substantial proportion of these patients would still receive first-line nivolumab + ipilimumab or single agent IO instead. They also highlighted some regional variation in prescribing patterns could be observed.[66]

In the adjuvant pembrolizumab arm, the proportions of patients in the DM first-line setting who received each therapy were sourced from the Systemic Anti-Cancer Treatment (SACT) report developed based on real-world use of adjuvant pembrolizumab in the stage 3 setting.[89] This is the only available dataset reporting subsequent treatment use specifically after adjuvant pembrolizumab in melanoma, as data from KEYNOTE-716 on the use of subsequent treatments for patients who developed DM were incomplete with respect to the use of combination regimens and were based on a small number of patients (n=[redacted]) (see Appendix P). The treatment regimens observed in SACT were reflective of the NICE guidance for systemic anticancer therapies in stage 4 melanoma,[75] with the exception that minimal use of IO monotherapy was observed. This suggests that, based on the 2-year follow-up reported by the SACT dataset, IO rechallenge for patients having a DM recurrence within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice in the absence of mature evidence on the efficacy of a rechallenge strategy. Clinical experts agreed with this, although advised that rechallenge with an IO monotherapy would be an option for patients who recurred >6 months after completing adjuvant treatment.[40, 66] Consequently, it was assumed that a small percentage of patients who entered the DM state more than 2 years after adjuvant treatment initiation (i.e. a conservative 12 months after completing adjuvant treatment) would receive rechallenge with pembrolizumab monotherapy

in the first line setting, and the SACT market shares of other non-targeted regimens were proportionally adjusted.

To maintain consistency in the source of market share data across treatment arms, the SACT data were also used for the routine surveillance arm. However as noted by clinical experts, IO monotherapies (pembrolizumab or nivolumab) are expected to be a common choice in the metastatic setting for patients who have not received adjuvant pembrolizumab, as they have good efficacy outcomes and a better tolerability profile compared with nivolumab + ipilimumab combination therapy so may be preferred for patients with lower fitness.[40, 66, 75] Therefore, the market share of pembrolizumab was sourced from market research data on current UK treatment patterns from Ipsos Oncology Monitor,[41] and shares of non-targeted agents from SACT were proportionally lowered to account for pembrolizumab usage.[89] The resulting first-line advanced melanoma market share distributions used in the model are presented in Table 55, and were confirmed by clinicians to be representative of UK practice.

Table 55: Market shares of therapies for advanced melanoma: First line DM

Treatment regimen	Pembrolizumab		Routine surveillance
	<24 months post-adjuvant treatment initiation	≥24 months post-adjuvant treatment initiation	
Source:	*SACT 1L from TA766* [89]	*SACT 1L from TA766, adjusted for pembrolizumab rechallenge*[89]	*SACT 1L from TA766, adjusted by Ipsos Oncology Monitor*[41, 89]
Pembrolizumab	0%	5.0%†	[redacted]
Nivolumab	2.6%	2.5%	[redacted]
Nivolumab + ipilimumab	55.0%	51.4%	[redacted]
Ipilimumab	19.2%	18.0%	[redacted]
Dabrafenib + trametinib	13.9%	13.9%	[redacted]
Encorafenib + binimetinib	8.6%	8.6%	[redacted]
Dacarbazine	0.7%	0.6%	[redacted]

Abbreviations: 1L, first line; DM, distant metastases; SACT, Systemic Anti-Cancer Therapy.
† Pembrolizumab market share based on clinical expert opinion to permit rechallenge, and market shares of other non-targeted therapies were proportionally adjusted;
‡ Pembrolizumab market share sourced from Ipsos Oncology Monitor as pembrolizumab rechallenge was not observed in the SACT dataset, and market shares of other non-targeted therapies were proportionally adjusted.

In addition, a subset of patients were assumed to go on to receive second-line therapy for advanced melanoma following progression on first-line therapy. The proportion of patients assumed to receive no active second-line therapy (due to death, deterioration of

performance status [fitness], patient/clinician choice, or participation in a clinical trial) was sourced from Ipsos Oncology Monitor (calculated as the ratio between the number of patients on second-line vs first-line regimens) and ratified by clinical experts.[41, 66]

In the second-line setting, clinicians advised that targeted therapy use, predominantly with dabrafenib + trametinib, would be expected for BRAF-mutation positive patients who had not received it at first line, while those deemed not fit enough or who had had targeted agents at first-line would likely have IO monotherapy. As in the first line setting, pembrolizumab monotherapy was preferred over nivolumab. BRAF-wild type patients have fewer available options and therefore ipilimumab, and less commonly chemotherapy, may see greater usage in this setting.

Data in the SACT report for stage 3 adjuvant pembrolizumab relating to 'further lines of therapy' were sparse and reflected 46 patients only, likely a result of the 2-year follow-up of patients in the SACT dataset meaning that very few patients had relapsed and reached the second-line setting within the observed period. The data also reported that 28/46 (60.87%) of these patients received nivolumab monotherapy which is not aligned with what is observed in clinical practice.[66] During the TA766 appraisal, the clinical experts explained that this could be a result of miscoding of nivolumab maintenance therapy for patients receiving nivolumab + ipilimumab at first line in the SACT dataset as further lines of therapy, which is skewing the data.[2] There are also several chemotherapy regimens presented in SACT which are not standard regimens for melanoma. As such, the SACT data were not considered suitable for informing market shares in the second-line setting.

Instead, the distribution of second-line regimens for the routine surveillance arm was sourced from Ipsos Oncology Monitor,[41] and confirmed by clinicians to be acceptable for the UK setting. In the pembrolizumab arm, market shares were also obtained from Ipsos Oncology Monitor.[41] However, as in the first-line setting, it was assumed that patients who reached the second-line setting less than 2-years after adjuvant pembrolizumab initiation would not be rechallenged with IO monotherapy. As such, the market shares of pembrolizumab and nivolumab monotherapy were set to 0% for the first 2 years and the shares of other non-targeted regimens were proportionately increased. After 2 years, a moderate share of pembrolizumab was permitted to reflect the rechallenge strategy described by clinical experts, and the shares of non-targeted agents (excluding dacarbazine, which is not extensively used in practice particularly when a rechallenge strategy is available) were proportionally adjusted (Table 56).

Table 56: Market shares of therapies for advanced melanoma: Second line DM

Treatment regimen	Pembrolizumab		Routine surveillance
	<24 months post-adjuvant treatment initiation	≥24 months post-adjuvant treatment initiation	
Source:	*Ipsos Oncology Monitor 2L[41], adjusted to 0% IO rechallenge*	*Ipsos Oncology Monitor 2L[41], adjusted to allow pembrolizumab rechallenge[66]*	*Ipsos Oncology Monitor 2L[41]*
Pembrolizumab	[redacted]†	[redacted]‡	[redacted]
Nivolumab	[redacted]†	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]
No systemic therapy	[redacted]§	[redacted]§	[redacted]§

Abbreviations: 2L, second line; DM, distant metastatic.
† Set to zero as IO monotherapy rechallenge not expected in the first 2-years post-adjuvant therapy initiation; Market shares of other non-targeted regimens were proportionally redistributed.
‡ Pembrolizumab market share assumption, based on clinical expert opinion,[66] to represent rechallenge with pembrolizumab, and market shares of other non-targeted therapies were proportionally adjusted (dacarbazine share was not adjusted vs Ipsos, as clinicians advised that this is not extensively used in practice particularly when IO rechallenge is an option).
§ Sourced from Ipsos Oncology Monitor and calculated as the ratio between the number of patients on second-line vs first-line regimens.

Drug acquisition and administration costs for the advanced melanoma setting were applied as one-off costs on entry to the DM health state. Based on the estimated discontinuation rate (and maximum duration of treatment where applicable), the model estimated the mean total cost of each treatment regimen in the first- and second-line setting, and then calculated the mean cost of treatment per adjuvant treatment arm as a weighted average of all treatment regimens using the first- and second-line market shares specified for each arm.

Unit costs per pack or vial of treatment were sourced from MIMS (Table 57);[101] note that these are list prices, as the discounts in place for each therapy are confidential. The dosing schedule for each therapy was based on the EMA label, and for pembrolizumab and nivolumab the schedules with the longest between-dose interval were used to reflect current UK clinical practice (Table 58). For agents where weight-based dosing is used, in the base case analysis it was conservatively assumed that vial sharing was not permitted. Therefore, the number of vials per infusion was calculated based on log-normal distributions of patient weight, using the means and standard deviations reported for patients in the KEYNOTE-716

trial. This approach calculated the proportion of patients requiring different number of vials based on the estimated percentage of patients who fall into the corresponding weight interval. This calculation is an accurate method of accounting for drug wastage which has been used in prior NICE submissions in the advanced melanoma setting (TA366).[88] However, clinicians have indicated that vial sharing does occur in practice, therefore a scenario was performed to explore this assumption. Under the scenario that vial-sharing is allowed, the number of vials required per infusion were calculated based on the average body weight or average body surface area of patients in the KEYNOTE-716 trial population.

Table 57: Drug acquisition costs for systemic therapies in DM state

Agent	Pack size / vial volume	Cost per unit (list price)	Sources
Pembrolizumab	100 mg vial	£2,630	MIMS[101]
Nivolumab	40 mg vial 100 mg vial	£439 £1,097	
Ipilimumab	50 mg vial 200 mg vial	£3,750 £15,000	
Dabrafenib	28 x 75 mg tablet	£50 per tablet	
Trametinib	30 x 2 mg tablet	£160 per tablet	
Encorafenib	42 x 75 mg tablet	£33.33 per tablet	
Binimetinib	84 x 15 mg tablet	£26.67 per tablet	
Dacarbazine	10 x 100 mg vial	£6.30 per vial	eMIT[106]

Abbreviations: BNF, British National Formulary.

Table 58: Dosing schedules for systemic therapies in DM state

Regimen	Dose	Frequency†
Pembrolizumab	400 mg IV	Q6W
Nivolumab	480 mg IV	Q4W
Nivolumab + ipilimumab	First 4 doses: Nivolumab: 1 mg/kg IV Ipilimumab: 3 mg/kg IV	Q3W‡
	After 4 doses: Nivolumab: 480 mg IV	Q4W
Ipilimumab	3 mg/kg IV	Q3W, up to 4 doses
Dabrafenib + trametinib	Dabrafenib: 150 mg oral Trametinib: 2 mg oral	BID QD
Encorafenib + binimetinib	Encorafenib: 450 mg oral Binimetinib: 45 mg oral	QD BID
Dabrafenib	150 mg oral	BID
Dacarbazine	250 mg/m^2/day IV	For 5 days, Q3W

Abbreviations: BID, twice daily; DM, distant metastatic; IV, intravenous; Q4W, every 4 weeks; Q6W, every 6 weeks; QD, every day.
† Dosing schedules based on EMA labels; ‡ Tue to ipilimumab dosing schedule, as per SmPC.

Drug administration costs for advanced melanoma therapies were sourced from NHS Reference Costs 2019/20 and the PSSRU 2021 (Table 59).[102, 103] Costs for intravenous infusions were applied per administration, and administration costs for oral therapies followed the approach applied for adjuvant therapies in the LRR health state whereby the first dose was assumed to be delivered in hospital, and subsequently pharmacy dispensing costs were applied every 28 days.

Table 59: Administration costs for systemic therapies in the DM state

Treatment	Unit cost	Source[102, 103]
Pembrolizumab	£281.28	NHS Reference Costs 2019/20: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance (Total HRG)
Nivolumab	£281.28	NHS Reference Costs 2019/20: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance (Total HRG)
Nivolumab + ipilimumab	First 4 doses: £475.67	NHS Reference Costs 2019/20: SB13Z Deliver More Complex Parenteral Chemotherapy at First Attendance (Total HRG)
	After 4 doses: £281.28	NHS Reference Costs 2019/20: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance (Total HRG)
Ipilimumab	£475.67	NHS Reference Costs 2019/20: SB13Z Deliver More Complex Parenteral Chemotherapy at First Attendance (Total HRG)
Dabrafenib + trametinib	First: £210.79	NHS Reference Costs 2019/20: SB11Z Deliver Exclusively Oral Chemotherapy (Total HRG)
	Subsequent: £9.60	12 minutes of pharmacist time. PSSRU 2021: Hospital based scientific and professional staff – Band 6 (Pharmacist)
Encorafenib + binimetinib	First: £210.79	NHS Reference Costs 2019/20: SB11Z Deliver Exclusively Oral Chemotherapy (Total HRG)
	Subsequent: £9.60	12 minutes of pharmacist time. PSSRU 2021: Hospital based scientific and professional staff – Band 6 (Pharmacist)
Dacarbazine	£2,378.35	Includes cost of five complex parenteral chemotherapy administrations (NHS Reference Costs 2019/20 - Total HRG activity for SB13Z) per 3-week cycle of dacarbazine treatment

Abbreviations: DM, distant metastases; HRG, Healthcare Resource Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Duration of treatment for first-line therapies was estimated using the exponential rates of progression-free survival (PFS) failure (as described in section B.3.3.3) to approximate treatment discontinuation rates, subject to any maximum treatment duration specified in the dosing schedules recommended by NICE (Table 60).[75] In the absence of robust data, relative dose intensity was assumed to be 100% for all agents.

In the second-line setting, mean time on treatment was assumed to be 21 weeks for all regimens, to be consistent with NICE TA319 and TA366 (ipilimumab and pembrolizumab in advanced melanoma, respectively) which assumed a fixed duration of 7 cycles at an interval of Q3W for second-line treatment.[88, 107] This assumption is also in line with the NICE submission for pembrolizumab in patients previously treated with ipilimumab (TA357), which considered a mean treatment duration of 6.86 cycles (20.57 weeks) based on mean PFS in the pembrolizumab arm of the KEYNOTE-002 trial.[104] The only exception was for ipilimumab (as monotherapy or in combination with nivolumab) which was capped at a maximum duration of 12 weeks as per the NICE guidance (Table 61).[107]

Table 60: Treatment duration for systemic therapies in the DM state: First line

Regimen	Maximum ToT[75]	Exponential rate of discontinuation‡	Dose intensity
Pembrolizumab	No maximum	[redacted]	100%
Nivolumab	No maximum	[redacted]	100%
Nivolumab + ipilimumab†	In combination: 12 weeks	[redacted]	100%
	Nivolumab maintenance: No maximum		100%
Ipilimumab	No maximum	[redacted]	100%
Dabrafenib + trametinib	No maximum	[redacted]	100%
Encorafenib + binimetinib	No maximum	[redacted]	100%
Dacarbazine	No maximum	[redacted]	100%

Abbreviations: DM, distant metastases; ToT, time on treatment.
† Nivolumab maintenance therapy was assumed to begin 12 weeks after initiation of the nivolumab + ipilimumab regimen for patients remaining on treatment after the initial course of nivolumab + ipilimumab;
‡ Exponential rates of discontinuation are based on the exponential rate of PFS failure estimated for the advanced melanoma regimens. Sources and derivation of exponential rates of PFS failure are described in section B.3.3.3.

Table 61: Treatment duration for systemic therapies in the DM state: Second line

Regimen	Mean ToT[88, 107]	Mean number of infusions or pharmacy dispensings
Pembrolizumab	21 weeks	3.5
Nivolumab	21 weeks	5.25
Nivolumab + ipilimumab†	In combination: 12 weeks	In combination: 4
	Nivolumab maintenance: 9 weeks†	Nivolumab maintenance: 2.25
Ipilimumab	12 weeks	4
Dabrafenib + trametinib	21 weeks	5.25
Encorafenib + binimetinib	21 weeks	5.25
Dabrafenib	21 weeks	5.25

Regimen	Mean ToT[88, 107]	Mean number of infusions or pharmacy dispensings
Dacarbazine	21 weeks	7

Abbreviations: DM, distant metastases; ToT, time on treatment.
† Assumes 21 weeks mean ToT for the regimen, comprised of 12 weeks on nivolumab + ipilimumab combination followed by 9 weeks (i.e. 21 minus 12 weeks) on nivolumab maintenance monotherapy.

Other medical resource use in the DM state consisted of outpatient clinic visits, inpatient stays, laboratory tests and imaging. Resource use frequencies were sourced from NICE TA319 (ipilimumab for untreated advanced melanoma), which based resource use on the MELODY study, a retrospective longitudinal survey study among patients with unresectable stage 3-4 melanoma (Table 62).[107] In addition, UK clinical experts advised that patients who were suspected of having a recurrence would undergo an image-guided biopsy to confirm the recurrence, therefore this resource has also been included in the model. Unit costs for each resource were sourced from NHS Reference Costs 2019/20 (Table 63),[102] applied to monthly resource use estimates, and then converted to resource use cost per cycle for inclusion in the model.

The DM state encompassed both pre- and post-progression DM, therefore, in each adjuvant treatment arm disease management costs per cycle for the distant metastases state were computed as a weighted average of resource use associated with pre- versus post-progression DM, based on the estimated proportion of time spent progression-free.

Table 62: Resource use: DM health state

Resource[40, 107]	Pre-progression: One-off resource use on DM state entry		Pre-progression: Subsequent monthly resource use		Post-progression: Monthly resource use	
	% patients	Average/ patient	% patients	Average/ patient	% patients	Average/ patient
Outpatient visits						
Medical oncologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiation oncologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General practitioner	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Plastic surgeon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Image-guided biopsy	100%	1.00	0%	0.00	0%	0.00
Inpatient stays						
Oncology/general ward	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory tests						
Complete blood count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete metabolic panel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lactate dehydrogenase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imaging						
CT scan of abdomen/pelvis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scan of chest	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scan of brain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI of brain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PET/CT scan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone scintigraphy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Echography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest x-ray	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CT, computed tomography; DM, distant metastases; MRI, magnetic resonance imaging; PET, positron emission tomography.
† Resource use estimates sourced from TA319, based on MELODY study.[107]

Table 63: Unit costs of medical resources for DM state

Resource	Unit price	Source[102, 103]
Clinic visits		
Image-guided biopsy	£550.61	NHS Reference Costs 2019/20 - Day case for YC01Z (Image Guided Core Needle Biopsy of Lesion of Neck), plus DAPS02 (Histopathology and histology)
Medical oncologist	£192.85	NHS Reference Costs 2019/20. Total outpatient attendances for 370 (medical oncology)
Radiation oncologist	£144.61	NHS Reference Costs 2019/20 - Total outpatient attendances for 800 (clinical oncology, previously radiotherapy)
General practitioner	£33.19	General practitioner costs – PSSRU 2021 - Unit Costs of Health and Social Care (Table 10.3b)
Psychologist	£200.97	Service Code 656 - Clinical Psychology - Total Outpatient Attendances - NHS Reference Costs 2019/20
Plastic surgeon	£117.34	NHS Reference Costs 2019/20 - Total outpatient attendances for 160 (plastic surgery)
Inpatient stays		
Oncology/general ward	£2,156.88	NHS Reference Costs 2019/20 - Elective inpatients for JC42C (intermediate skin disorders aged 19 years and over)
Laboratory tests		
Complete blood count	£2.56	NHS Reference Costs 2019/20 - Directly accessed pathology services for DAPS05 (haematology)
Complete metabolic panel	£1.20	NHS Reference Costs 2019/20 - Directly accessed pathology services for DAPS04 (clinical biochemistry)
Lactate dehydrogenase	£1.20	NHS Reference Costs 2019/20 - Directly accessed pathology services for DAPS04 (clinical biochemistry)
Imaging		
CT scan of abdomen/pelvis	£78.66	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z
CT scan of chest	£78.66	
CT scan of brain	£78.66	
MRI of brain	£147.78	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD01A, RD02A, and RD03Z
PET/CT scan	£147.78	
Bone scintigraphy	£289.65	NHS Reference Costs 2019/20 - Total HRG activity for RN16A (nuclear bone scan of other phases, 19 years and over)
Echography	£87.50	NHS Reference Costs 2019/20 - Total HRG activity for RD51A (simple echocardiogram, 19 years and over)
Chest x-ray	£122.44	NHS Reference Costs 2019/20 - Total HRG activity for RD30Z (contrast fluoroscopy procedures with duration of less than 20 minutes)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NHS, National Health Service; PET, positron emission tomography.

B.3.5.3 Adverse reaction unit costs and resource use

The description of AEs included in the model, and the corresponding frequencies of these AEs, are described in B.3.3.5, and the impact of AEs on HRQoL is described in B.3.4.4. Unit costs of AEs were sourced from NICE TA319 where available, which used the MELODY retrospective study of resource use in patients with advanced melanoma in the UK as the main data source.[107] These costs were inflated to 2020 using the health component of the Consumer Price Index from the ONS.[108] For AEs which did not have melanoma-specific costs available from TA319, costs were obtained from the NHS Reference Costs 2019/20 (Table 64).

Table 64: Unit costs of adverse events

Adverse event	Unit cost	Source[102, 107]
Diarrhoea	£805.64	Oxford Outcomes data reported in TA319, inflated to 2020 GBP
Hyperthyroidism	£557.96	Oxford Outcomes data reported in TA319 (endocrine disorders), inflated to 2020 GBP
Asthenia	£242.80	NHS Reference Cost 2019/20, WH17: Admission Related to Social Factors - Regular Day or Night Admissions (weighted average)
Fatigue	£204.81	Oxford Outcomes data reported in TA319, inflated to 2020 GBP
Alanine aminotransferase increased	£216.87	NHS Reference Cost 2019/20, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Aspartate aminotransferase increased	£216.87	NHS Reference Cost 2019/20, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Decreased appetite	£310.66	NHS Reference Cost 2019/20, FD04: Nutritional Disorders - Regular Day or Night Admissions (weighted average)
Hyperglycaemia	£216.87	NHS Reference Cost 2019/20, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Arthralgia	£273.69	NHS Reference Cost 2019/20, HD24: Non-Inflammatory, Bone or Joint Disorders - Regular Day or Night Admissions (weighted average)
Back pain	£316.15	NHS Reference Cost 2019/20, HC29: Inflammatory Spinal Conditions - Regular Day or Night Admissions (weighted average)
Myalgia	£138.02	NHS Reference Cost 2019/20, HD21: Soft Tissue Disorders - Regular Day and Night Admissions (weighted average)
Pain in extremity	£138.02	NHS Reference Cost 2019/20, HD21: Soft Tissue Disorders - Regular Day and Night Admissions (weighted average)
Basal cell carcinoma	£526.62	NHS Reference Costs 2019/20 - Total HRG activity for JC42C (intermediate skin procedures, 19 years and over)
Pruritus	£289.73	Oxford Outcomes data reported in TA319 (skin reaction), inflated to 2020 GBP

Adverse event	Unit cost	Source[102, 107]
Rash	£289.73	Oxford Outcomes data reported in TA319 (skin reaction), inflated to 2020 GBP
Rash maculo-papular	£289.73	Oxford Outcomes data reported in TA319 (skin reaction), inflated to 2020 GBP
Hypertension	£149.54	NHS Reference Cost 2019/20, EB04Z: Hypertension - Regular Day or Night Admissions

B.3.5.4 Miscellaneous unit costs and resource use

Terminal care

Patients who transitioned to the death health state were assumed to incur a one-off cost associated with palliative/terminal care if the death was melanoma-related. Within the model, deaths were considered melanoma-related if they occurred from the DM state, based on the assumption that all deaths occurring directly from the recurrence-free or locoregional recurrence states are attributable to causes other than melanoma. Consistent with TA366 and TA766, terminal care costs were based on costs during the last 90 days before death as reported by Georghiou & Bardsley (2014).[2, 88, 109] The costs of terminal care included services such as emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs. Reported costs were inflation-adjusted to 2020 GBP using the health component of the Consumer Price Index from the ONS (Table 65).[108]

Table 65: Terminal care costs

Terminal care cost	Cost	Source
District nurse	£345.51	Georghiou & Bardsley (2014), inflated to 2020 prices[108, 109]
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**	

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

B.3.6.1 Summary of base-case analysis inputs

The list of inputs used in the base case cost-effectiveness analysis is presented in Table 66, along with the parameters used to vary the base case inputs in sensitivity analyses, if applicable.

Table 66: Summary of base case model variables

Variable	Mean value	SE	Distribution for PSA	Section in submission
General				
Cycle length	1 week	-	Not varied	B.3.2.2
Time horizon, years	40.7	-	Not varied	
Discount rate: Costs	3.5%	-	Not varied	
Discount rate: Outcomes	3.5%	-	Not varied	
Patient characteristics				
Starting age, years	59.3	-	Not varied	B.3.2.1
Age <18 years, percent	0.2%	-	Not varied	
Female, percent	39.7%	-	Not varied	
BRAF mutation positive	43.3%	-	Not varied	
Adult weight, kg	[redacted]	-	Not varied	
Paediatric weight, kg	[redacted]	-	Not varied	
Parameter estimates for RF→LRR (using Log-Normal function)				
Parameter A, routine surveillance	[redacted]	-	Multivariate normal	B.3.3.1
Parameter B, routine surveillance	[redacted]	-	Multivariate normal	
Parameter A, pembrolizumab	[redacted]	-	Multivariate normal	
Parameter B, pembrolizumab	[redacted]	-	Multivariate normal	
Parameter estimates for RF→DM (using Log-Normal function)				
Parameter A, routine surveillance	[redacted]	-	Multivariate normal	B.3.3.1
Parameter B, routine surveillance	[redacted]	-	Multivariate normal	
Parameter A, pembrolizumab	[redacted]	-	Multivariate normal	
Parameter B, pembrolizumab	[redacted]	-	Multivariate normal	
Parameter estimates for RF→Death (using exponential function)				
Parameter A, routine surveillance	[redacted]	-	Normal	B.3.3.1
Parameter A, pembrolizumab	[redacted]	-	Normal	
Parameters for risk reduction over time				
Risk reduction starting timepoint, year	7	-	Not varied	B.3.3.1
Maximum risk reduction timepoint, year	10	-	Not varied	
Maximum risk reduction	95%	-	Not varied	
Exponential rates of LRR→DM (using exponential function)				
Adjuvant treatment	[redacted]	[redacted]	Normal	B.3.3.2
No adjuvant treatment	[redacted]	[redacted]	Normal	

Variable	Mean value	SE	Distribution for PSA	Section in submission
Exponential rates of LRR→Death				
Adjuvant treatment	[redacted]	[redacted]	Normal	B.3.3.2
No adjuvant treatment	[redacted]	[redacted]	Normal	
HR of DMFS failure vs. no stage 3 adjuvant treatment for LRR state				
Pembrolizumab, HR of DMFS vs. no stage 3 adjuvant treatment	0.6	[redacted]	Log-normal	B.3.3.2
Nivolumab, HR of DMFS vs. no stage 3 adjuvant treatment	0.6	[redacted]	Log-normal	
Dabrafenib + trametinib, HR of DMFS vs. no stage 3 adjuvant treatment	0.55	[redacted]	Log-normal	
Exponential rates of OS and PFS failure by treatment in the advanced melanoma setting				
Pembrolizumab, OS	[redacted]	[redacted]	Normal	B.3.3.3
Pembrolizumab, PFS	[redacted]	[redacted]	Normal	
Ipilimumab, HR of OS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Ipilimumab, HR of PFS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Nivolumab, HR of OS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Nivolumab, HR of PFS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Nivolumab + ipilimumab, HR of OS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Nivolumab + ipilimumab, HR of PFS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Dabrafenib + trametinib, HR of OS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Dabrafenib + trametinib, HR of PFS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Encorafenib + binimetinib, HR of OS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Encorafenib + binimetinib, HR of PFS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Dacarbazine, HR of OS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	
Dacarbazine, HR of PFS vs. pembrolizumab	[redacted]	[redacted]	Log-normal	

Variable	Mean value	SE	Distribution for PSA	Section in submission
Medical management costs by health state				
Medical management costs in RF state (per week, up to year 3)	19.15	3.83	Gamma	B.3.5.2 and B.3.5.4
Medical management costs in RF state (per week, years 3-5)	9.57	1.91	Gamma	
Medical management costs in RF state (per week, years 5-10)	0.00	0.00	Gamma	
Salvage surgery costs upon LRR state entry (one-time cost)	[redacted]	[redacted]	Gamma	
Medical management costs in LRR state (per week)	[redacted]	[redacted]	Gamma	
Medical management costs upon DM state entry (one-time cost)	[redacted]	[redacted]	Gamma	
Medical management costs in pre-progression DM state (per week)	[redacted]	[redacted]	Gamma	
Medical management costs in post-progression DM state (per week)	[redacted]	[redacted]	Gamma	
Terminal care cost (one-time cost)	8,486.01	1,697.20	Gamma	
Drug administration costs				
Unit cost of simple IV drug administration	281.28	56.26	Gamma	B.3.5.1 and B.3.5.2
Unit cost of complex IV drug administration	475.67	95.13	Gamma	
Unit cost of oral drug dispensing: First administration	210.79	42.16	Gamma	
Unit cost of oral drug dispensing: Second administration	9.60	1.92	Gamma	
Cost of AEs				
Pembrolizumab	91.83	18.37	Gamma	B.3.5.3
Routine surveillance	36.54	7.31	Gamma	
Utilities and disutilities				
Utility of RF (without toxicity)	[redacted]	[redacted]	Beta	B.3.4.5
Utility of LRR	[redacted]	[redacted]	Beta	
Utility of pre-progression DM	[redacted]	[redacted]	Beta	

Variable	Mean value	SE	Distribution for PSA	Section in submission
Utility of post-progression DM	0.59	0.02	Beta	
Disutility from AEs	[redacted]	[redacted]	Normal	
Disutility associated with age	-0.0002587	0.00005	Normal	
Disutility associated with age^2	-0.0000332	0.00001	Normal	
Utility associated with male gender	0.0212126	0.00424	Normal	

Abbreviations: AE, adverse event; DM, distant metastases; DMFS, distant metastases-free survival; HR, hazard ratio; IV, intravenous; LRR, locoregional recurrence; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; RF, recurrence-free.

B.3.6.2 Assumptions

A summary of the key parameters and assumptions used in the economic evaluation is provided in Table 67.

Table 67: Assumptions used in the economic evaluation

Parameter	Assumption	Justification
Transitions from the RF state	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. Separate parametric models were fitted independently for each treatment arm of KEYNOTE-716.	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-716 RFS data and long-term plausibility of RFS, DMFS, and OS. This combination of parametric functions was validated using published external data sources. In line with guidance in NICE DSU TSD 14,[72] the same combination of parametric functions was used in both treatment arms.
	Patients who remain in the RF health state after 10 years were assumed to have a 95% reduction in risk of recurrence relative to the risk estimated by the parametric function. It was assumed that the risk begins to linearly decrease gradually from 7 years until a 95% risk reduction is reached at 10 years.	Most recurrences occur in the first few years after resection and the risk of recurrence decreases over time. This is supported by real world evidence[12, 32, 60] and by UK clinical experts, who agreed that the risk of recurrence decreases over time such that most patients are discharged at 5 years, and the likelihood of disease recurrence after 10 years is extremely small.[40, 66] The risk reduction of 95% was aligned with methodology applied in previous NICE oncology appraisals of adjuvant therapies (TA569,

Parameter	Assumption	Justification
		TA632, TA761), and reflects clinical opinion that the risk of recurrence after 10 years would be extremely small, but never zero.[40, 66]
Transitions from the LRR state	Exponential model fitted to real-world patient-level data from the US Oncology Network EHR to estimate the transitions for patients not receiving any adjuvant therapy for stage 3 melanoma. The US Oncology Network cohort was assumed to be comparable to the KEYNOTE-716 population. In each adjuvant treatment arm, the transition probability from LRR to DM or death was then assumed to depend on the expected mix of subsequent adjuvant treatments for stage 3 melanoma, and the efficacy of these treatments. It was therefore also assumed that there was no ongoing benefit of adjuvant pembrolizumab after patients had a recurrence (i.e. had left the RF state), so differences between arms in transitions from the LRR state depended on the market shares of adjuvant treatments only.	At the IA2 analysis of KEYNOTE-716, insufficient recurrence events had occurred to facilitate estimates of transitions from LRR, therefore real-world data were used instead. The baseline characteristics of the US Oncology Network cohort were aligned with the KEYNOTE-716 population, and clinical experts confirmed that both were representative of UK melanoma patients. In line with TA766 and based on clinical expert opinion, given the mechanism of action of pembrolizumab it is considered a conservative assumption that there is no ongoing benefit of pembrolizumab after recurrence.
Transitions from the DM state	Transition probabilities depended on the distributions of first-line treatments received for advanced melanoma in each adjuvant treatment arm. It was assumed that there was no ongoing benefit of adjuvant pembrolizumab after patients had a recurrence (i.e. had left the RF state), so differences between arms in transitions from the DM state depended on the market shares of first-line treatments only. Exponential models fitted to patient-level OS data for all patients in the pembrolizumab arm of KEYNOTE-006 (trial in first-line advanced melanoma); HRs for alternative subsequent treatments sourced from NMA of advanced melanoma treatments.	Survival for patients with advanced melanoma is dependent on the treatment they receive, which may differ based on whether they have previously been treated with pembrolizumab. At the IA2 analysis of KEYNOTE-716, insufficient DM recurrence and subsequent death events had occurred to facilitate estimates of transitions from DM, therefore external sources were used instead.

Parameter	Assumption	Justification
Subsequent treatments for LRR	Patients who entered the LRR state were eligible for salvage surgery. Patients in the routine surveillance arm were assumed to be eligible for systemic adjuvant treatment for stage 3 melanoma; patients in the pembrolizumab arm were assumed to receive no further adjuvant therapy. Market shares of adjuvant therapies for the routine surveillance arm were sourced from Ipsos Oncology Monitor and MSD market research.	Clinical experts advised that patients with a LRR would be considered for systemic adjuvant therapy. However, patients who had already received adjuvant pembrolizumab at stage 2 were not expected to receive further adjuvant therapy, due to a lack of evidence of the efficacy of this approach and uncertainty regarding funding availability. This assumption was explored in a scenario whereby BRAF positive patients were eligible for BRAF targeted therapy. Data from KEYNOTE-716 on the use of subsequent treatments for patients who developed LRR were incomplete with respect to the use of combination regimens and were based on a small number of patients, therefore these were not suitable for informing the economic model.
Subsequent treatments for DM disease	Patients who entered the DM state were eligible for first-line systemic therapy for metastatic melanoma. Market shares of these first line therapies informed transition probabilities and therefore total health state costs. A proportion of these patients were also assumed to receive second-line treatment for metastatic disease, however these were only included in terms of costs. Subsequent therapies may differ by adjuvant treatment arm. Market shares for each treatment arm were sourced from the SACT dataset and Ipsos Oncology Monitor.	Data from KEYNOTE-716 on the use of subsequent treatments for patients who developed DM were incomplete with respect to the use of combination regimens and were based on a small number of patients, therefore these were not suitable for informing the economic model and alternative sources were explored. The market share assumptions were validated with UK clinical experts.
Rechallenge with pembrolizumab	Patients in the pembrolizumab arm who have a DM recurrence <2 years after adjuvant treatment initiation (i.e. <12 months after completion of adjuvant therapy) were not eligible for rechallenge with pembrolizumab monotherapy in the DM setting. A small proportion of patients who entered the DM state ≥2 years after adjuvant treatment initiation were assumed to receive rechallenge with pembrolizumab monotherapy.	UK clinical experts advised that rechallenge with IO monotherapy is an option that is used in current clinical practice for patients who recur ≥6 months after completing adjuvant IO therapy (i.e. 18 months after completion of adjuvant therapy. A threshold of 2 years was applied in the model as a conservative assumption, in line with TA684.

Parameter	Assumption	Justification
Safety	AE incidence rates were sourced from KEYNOTE-716 and assumed to be reflective of those observed in real world practice.	Safety data from KEYNOTE-716 were aligned with results from previous trials of pembrolizumab. The same method and criteria have been applied in several recent NICE oncology appraisals of pembrolizumab.
HRQoL	The HRQoL of patients in the model is appropriately captured using pooled utility values by health state and AE status. Estimates were derived using EQ-5D-5L measurements collected from patients in the KEYNOTE-716 and mapped to the 3L tool using the crosswalk algorithm. These were supplemented with published utilities where trial data were not available.	The source of utility estimates is consistent with the NICE reference case and the crosswalk algorithm developed by van Hout et al. is in line with the NICE position statement for reference case analyses.
AE disutility	The disutility associated with patients experiencing grade 3+ AEs was derived from KEYNOTE-716 and was also applied to grade 2+ AEs included in the economic model.	Use of KEYNOTE-716 ensures a consistent source for adverse events and impact on HRQoL.
Age-related disutility	Utility decreases observed with age in the general population were accounted for using a model for disutility from the UK population.	Based on the Ara and Brazier study suggesting the impact of age on HRQoL and in line with methodology used in previous appraisals.
Time on treatment	Time on treatment was estimated directly using Kaplan-Meier data from KEYNOTE-716.	Kaplan-Meier curves directly from the trial were used to inform the model inputs and account for early treatment discontinuation of patients as per the study protocol.
Healthcare resource use and costs	Disease management costs by health state were assumed to be equal between treatment arms.	Resource use estimates were sourced from the KEYNOTE-716 trial and public sources relating to the frequency of follow-up visits and imaging recommended in UK clinical practice and were validated with clinical experts.
Post-recurrence efficacy of adjuvant pembrolizumab	The treatment benefit of adjuvant pembrolizumab observed in KEYNOTE-716 is assumed to be maintained whilst the patient remains in the RF health state. However, this benefit is assumed to be lost after recurrence, therefore the risk of progressing from LRR→DM or Death, or from DM→Death is determined only by the market shares of subsequent therapies in each health state (which may differ by adjuvant treatment arm), and not by the adjuvant treatment arm itself.	Given the mechanism of action of pembrolizumab and the potential for immune memory, loss of treatment benefit after disease recurrence should be considered a conservative assumption.

Parameter	Assumption	Justification
Terminal care costs	Terminal care costs were only applied to people who die from metastatic melanoma (i.e. from the DM state).	It is assumed that deaths occurring directly from the RF or LRR states are attributable to causes other than melanoma and therefore will not be significantly different between treatment arms.
Vial sharing	No vial sharing was assumed.	In line with the NICE reference case.

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case cost-effectiveness results are presented in Table 68. The model estimated that adjuvant pembrolizumab resulted in [redacted] life years compared with 9.97 life years with routine surveillance. This translated into [redacted] and [redacted] QALYs for pembrolizumab and routine surveillance, respectively, and an incremental gain of [redacted] QALYs with pembrolizumab versus routine surveillance. The incremental cost-effectiveness ratio (ICER) was £4,616 per QALY gained. These results show that adjuvant treatment with pembrolizumab is a highly cost-effective strategy for the management of resected stage 2B/2C melanoma when considering the willingness to pay threshold of £30,000 per QALY.

Table 68: Base case cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,616
Routine surveillance	[redacted]	9.97	[redacted]	-	-	-	-

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

The disaggregated results for the base case analysis are presented in Appendix J. These results show that most of the costs in the model are incurred due to subsequent treatments in the DM health state, and most of the QALYs are gained in the RF health state. This illustrates that by reducing the incidence of recurrences, health outcomes are improved and most of the costs of adjuvant treatment with pembrolizumab can be offset by reducing the number of patients that need to be treated with expensive subsequent management strategies.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

To explore the uncertainty around the variables included in the economic model, probabilistic sensitivity analysis (PSA) was performed by running the analysis over 1,000 simulations. The distributions used to vary model parameters are presented in section B.3.6.1 (Table 66).

The cost-effectiveness results obtained from the PSA are shown in Table 69; the corresponding scatterplot of PSA results and cost-effectiveness acceptability curve (CEAC) are shown in Figure 14 and Figure 15, respectively. The probabilistic results are aligned to the deterministic base case and estimated that pembrolizumab was associated with [redacted] additional LYs and [redacted] additional QALYs, corresponding to a probabilistic ICER of £6,761 per QALY. The CEAC demonstrates that there is a 76.9% probability that adjuvant treatment with pembrolizumab is a cost-effective treatment strategy for patients with resected stage 2B/2C melanoma based on a WTP threshold of £30,000 per QALY.

Table 69: Probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6,761
Routine surveillance	[redacted]	9.98	[redacted]	-	-	-	-

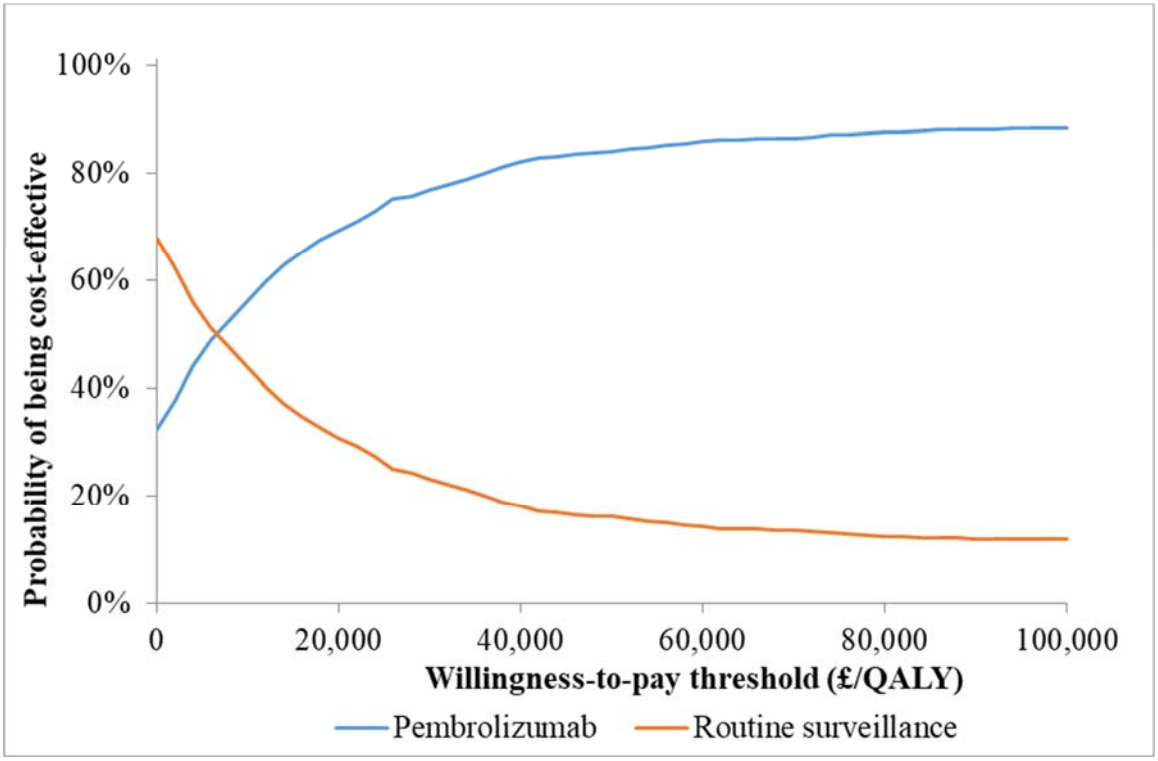
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 14: Scatterplot of PSA results

[redacted]

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 15: Cost-effectiveness acceptability curve



Abbreviations: QALY, quality-adjusted life year.

B.3.8.2 Deterministic sensitivity analysis

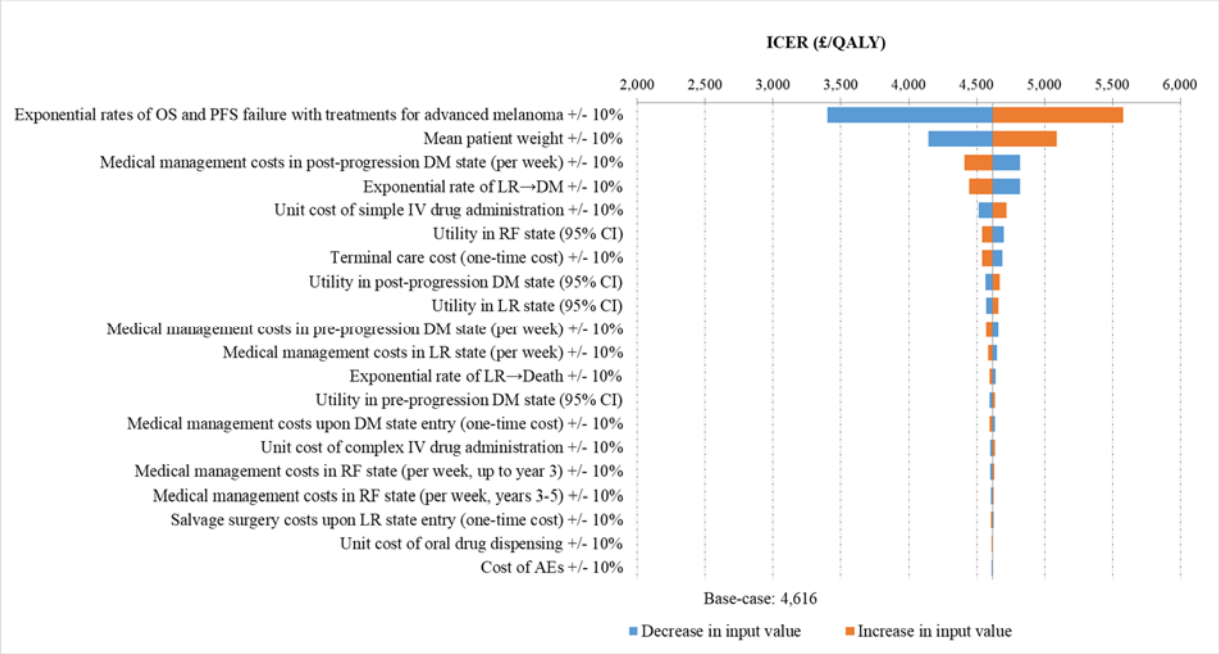
One-way deterministic sensitivity analyses (DSA) were conducted to explore the uncertainty in the cost-effectiveness results and identify key model drivers. Parameters were varied by their 95% confidence intervals, or by ±10% if measures of variance were not available. The following variables were explored in the DSA:

- Baseline weight
- Exponential rate of LRR→DM or Death
- Exponential rates of OS and PFS failure with treatments for advanced melanoma
- Drug administration, AE disease management, subsequent treatment and terminal care costs
- Adverse event disutility and age-related disutility
- Health state utility values

The results of the DSA are presented in a tornado diagram which illustrates the 20 parameters that had the most impact on the ICER. The biggest model drivers were the exponential rates used to model OS and PFS in the DM health state, and parameters that

impacted costs in the DM health state. Overall, the results show that the model is robust to changes in parameter inputs, and pembrolizumab remained cost-effective across all parameter variations.

Figure 16: Tornado diagram



Abbreviations: CI, confidence interval; DM, distant metastases; ICER, incremental cost-effectiveness ratio; IV, intravenous; LR, locoregional; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RF, recurrence-free.

B.3.8.3 Scenario analysis

A series of scenario analyses was conducted to explore the uncertainty around key structural and methodological assumptions, and sources of data used to inform model inputs. The results of all scenarios are presented in Table 70.

Table 70: Scenario analyses

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
-	**Base case**	**-**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**4,616**
1	Alternative functions for modelling of transitions from RF state (Approach #1)	Pessimistic RFS for pembrolizumab† RF→LRR: Log-logistic RF→DM: Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,483
2		Alternative pessimistic RFS for pembrolizumab† RF→LRR: Generalised gamma RF→DM: Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,890
3		Optimistic RFS for pembrolizumab‡ RF→LRR: Generalised gamma RF→DM: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	680
4	Alternative approaches for modelling transitions from RF state	Alternative modelling approach Approach #2 (time-constant HR): RF→LRR: Gompertz RF→DM: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	242
5		Alternative modelling approach Approach #3 (time-varying HR): RF→LRR: Gompertz RF→DM: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,294
6	Alternative risk reduction assumptions	For patients in the RF state, an 80% risk reduction is applied at 10 years, with gradual decrease starting from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,672
7		For patients in the RF state, the 95% risk reduction is applied at 10 years,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,195

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
		with gradual decrease starting from 5 years							
8		For patients in the RF state, the 95% risk reduction is applied at 5 years, with no gradual decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,029
9		For patients in the RF state, the 95% risk reduction is applied at 10 years, with no gradual decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,449
10	EHR data used to estimate transitions from LRR state	Transitions from the LRR state for patients receiving adjuvant therapy for stage 3 melanoma are estimated using data from the USON EHR database, rather than market shares and trial-based HRs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,780
11	Alternative market shares of adjuvant therapy for stage 3 resected disease in the LRR state	In the adjuvant pembrolizumab arm, BRAF mutation positive patients (43.3%) who enter the LRR state are eligible for adjuvant treatment with dabrafenib + trametinib, adjusted for the [redacted]% of patients in the overall cohort who are expected to receive no systemic adjuvant therapy.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,442
12	Alternative market shares of systemic therapy in the DM state	No rechallenge with pembrolizumab permitted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6,499
13	Only costs of first line systemic therapy in the DM state included	Costs of second line therapies in the DM state are excluded, as the model does not consider the efficacy of 2L15 agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,461
14	Alternative sources of utility values	EQ-5D-5L utilities sourced from KEYNOTE-716	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,387

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
15		Utilities sourced from KEYNOTE-054 for the LRR and pre-progression DM health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,561
16		Utilities for the DM state sourced from Middleton et al, 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,531
17	Alternative dosing schedule for IO therapies	Shorter dosing schedules used for pembrolizumab (200 mg Q3W) and nivolumab (240 mg Q2W) in all settings (conservative dosing scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,319
18		Shorter dosing schedules used for pembrolizumab (200 mg Q3W) in all settings (conservative dosing scenario) (nivolumab schedule as per base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,300
19	Vial sharing permitted	For agents where weight-based dosing is used, vial sharing is permitted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,121
20	Discount rate	Discounting of costs and effects set to 1.5%.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,927
21		Discounting of costs at 3.5% and effects at 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,415

Abbreviations: DM, distant metastases; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; QALY, quality-adjusted life year; QxW, every x weeks; RF, recurrence-free.

† Scenario estimates a smaller treatment benefit for pembrolizumab versus routine surveillance compared with the base case scenario; ‡ Scenario estimates a larger treatment benefit for pembrolizumab versus routine surveillance compared with the base case scenario.

B.3.8.4 Summary of sensitivity analyses results

Extensive sensitivity and scenario analyses were conducted to explore the robustness of the model and the impact of uncertainty around model parameters. The results of the PSA show that adjuvant pembrolizumab has a 76.9% probability of being cost-effective versus routine surveillance at a willingness to pay of £30,000/QALY and produced a probabilistic ICER comparable to the base case deterministic ICER. The DSA demonstrated that the key model drivers were related to parameters used to model the survival and costs in the DM health state, but that the model was robust to changes in key input parameters. The scenario analyses explored the impact of a range of difference modelling assumptions relating to efficacy and costs, considering more optimistic and more conservative scenarios. Across all the scenarios explored, the ICER remained well below the £30,000 per QALY willingness to pay threshold, ranging from £242 to £9,442 per QALY.

Taken together, these analyses indicate that adjuvant treatment with pembrolizumab is expected to be a highly cost-effective strategy for the management of resected stage 2B/2C melanoma in the UK.

B.3.9 *Subgroup analysis*

Subgroup analysis was not performed as it is not relevant for this indication.

B.3.10 *Validation*

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developer team to ensure that the mathematical calculations are being performed correctly and are consistent with the model's specifications. The model was also independently reviewed by two external health economists, who evaluated the model from an overall health economics perspective.

The internal validity of the model was also assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs. For example, the RFS curves predicted for the two arms of KEYNOTE-716 were plotted alongside the observed Kaplan-Meier curves for RFS to ensure that the curves are well-aligned during the trial period.

Model predictions were compared against observed data from three published external studies that reported long-term RFS and/or OS in real-world cohorts of patients diagnosed with AJCC 8th edition stage 2B or 2C melanoma.[12, 33, 34] These three external studies were

conducted in distinct patient cohorts (including two US-based cohorts[12, 34] and one European cohort[33]). Survival projections in the routine surveillance arm were also validated against long-term RFS, DMFS, and OS observed in a real-world study using US Oncology Network electronic health records.[32, 60] UK clinicians confirmed that these datasets were generalizable to the UK setting and therefore suitable for use as validation sources.

The modelled outputs were highly consistent with the RFS data observed in KEYNOTE-716, and RFS and DMFS outputs for routine surveillance were closely aligned with results reported in published real-world cohorts (Figure 8 and Figure 10). The estimated OS results for routine surveillance (Figure 11) were slightly higher than reported by the real-world evidence, however there have been significant improvements in the treatment of metastatic disease in the last 6–10 years which have substantially improved survival outcomes for patients with metastatic melanoma. For example, in the CheckMate-067 trial in untreated advanced melanoma, 5-year OS rates for nivolumab + ipilimumab (recommended by NICE in 2016) were 52% compared with 26% for ipilimumab monotherapy (recommended by NICE in 2014).[61] There have also been more recent advances in the management of stage 3 disease in terms of availability of adjuvant treatments, which is also expected to affect OS by improving outcomes for stage 2B/2C melanoma patients who have LRR. All the real-world studies enrolled patients who were diagnosed before these recent advances (i.e. before 2012; see Appendix N). Bleicher et al, 2020 enrolled patients between 2000–2017,[34] and therefore a large proportion of the cohort are likely to have recurred before these improvements were available. Note that the study by Bajaj et al, 2020 does represent a relatively more recent cohort (patients enrolled 2010–2016) which therefore may partly capture recent treatment improvements; however the study is limited by the small cohort size (n=90) and therefore the OS curve, particularly the second half, should be interpreted with caution. Consequently, it is likely that all the external studies somewhat underestimate the true OS for patients with contemporary diagnoses.

Clinical experts were consulted via an advisory board and through additional individual engagements to validate the efficacy inputs (e.g. the plausibility of long-term RFS, DMFS, and OS) and other key model decisions (e.g. assumptions about post-recurrence treatments) from a clinical perspective, to ensure that the model was reflective of the UK setting.[40, 66]

To provide further validation of the outcomes modelled from the DM state, which accounts for most deaths in the first half of the model, an additional check was conducted which considered the plausibility of the modelling assumptions in this health state, as per the

methods employed by the Evidence Review Group (ERG) during TA766.[2] The expected survival in the DM state predicted by the economic model was compared to the life years estimated for the pembrolizumab monotherapy arm in the economic model considered in the 2015 NICE appraisal of pembrolizumab monotherapy for untreated advanced melanoma (TA366).[88] In the current model, the expected survival ranged from [redacted] years, based on the first line market shares applied in each arm; this is highly comparable to the 5.08 life years in the TA366 model. This provides reassurance that the current modelling of this health state is reasonable, and thus the predicted OS is likely to be plausible.

In addition, to further validate that the competing risks approach to survival modelling employed in the economic model produced plausible composite RFS results, independent parametric survival analysis of the RFS data from KEYNOTE-716 was conducted based on fitting six standard parametric models (exponential, Weibull, Gompertz, lognormal, log-logistic, and Generalised gamma) to patient-level data from the pembrolizumab and placebo arms of KEYNOTE-716. Based on Bayesian Information Criterion (BIC) statistics and visual assessment, the log-logistic RFS distributions appeared to provide the best balance between goodness-of-fit in the pembrolizumab arm and goodness-of-fit in the routine surveillance arm, ranking as the third- and second best-fitting distributions in these arms, respectively. Comparison of the projections estimated by the log-logistic function in this independent analysis with the projected RFS estimated in the base case economic model demonstrates a close alignment in the 10-year RFS generated via these two approaches (i.e. until the 10-year risk reduction assumption is applied) (Figure 17A). In the scenario where the 10-year risk reduction is not applied (Figure 17B), the RFS predicted by the log-logistic function continues to align closely with the composite RFS estimated by the model. This provides further reassurance that the model produces credible results and that the parametric functions selected to model the intermediate health states are appropriate.

Figure 17: Validation of modelled RFS versus directly fitted parametric models

A) With 95% risk reduction implemented from 7–10 years (base case)

[redacted]

B) Without 95% risk reduction implemented from 7–10 years (scenario)

[redacted]

A targeted search for HTA submissions in adjuvant oncology settings did not identify any prior submissions for adjuvant treatments for high-risk stage 2 melanoma. Consequently, it was not possible to cross-validate the current model results against other, independently

developed economic evaluations in the same indication. However, prior HTAs and published cost-effectiveness studies in other adjuvant oncology indications provided support and precedence for the assumptions used in the current model.

B.3.11 *Interpretation and conclusions of economic evidence*

Over a lifetime model horizon, adjuvant pembrolizumab is expected to yield substantial improvements in QALYs and LYs relative to routine surveillance in patients with resected stage 2B or 2C melanoma. In the base case, the incremental cost per QALY gained was £4,616 for pembrolizumab vs. routine surveillance. Results from the DSA supported the base-case findings, with most variation observed in sensitivity analyses that varied RFS transitions, survival outcomes in the DM health state, and costs of subsequent treatments. In the PSA, the average ICER per QALY across all 1,000 iterations was consistent with the base-case ICER. At a willingness-to-pay threshold of £30,000 per QALY gained, pembrolizumab had a 76.9% probability of being cost-effective versus routine surveillance.

B.3.11.1 Strengths of the economic evaluation

The population included in the economic evaluation was consistent with the stage 2B/2C melanoma population eligible for pembrolizumab, as per the anticipated licence. Clinical efficacy estimates from the KEYNOTE-716 trial, which assessed patients in line with the anticipated licenced indication, were used in the model, therefore the economic evaluation is relevant to all patients who could potentially use pembrolizumab in the patient population under consideration. Further, the patient population in KEYNOTE-716 is reflective of UK patients with stage 2B/2C melanoma following complete resection, and the choice of comparator matches the current UK standard of care. The resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions for melanoma, incorporating the feedback provided by the ERGs in recent NICE appraisals. The results of the economic analysis are therefore directly applicable to clinical practice in England.

The Markov cohort structure is a well-established modelling approach that has been commonly used in published cost-effectiveness analyses and prior health technology appraisals of adjuvant/neoadjuvant therapies in other oncology indications.[2, 17, 76, 110] Previous HTA appraisals of pembrolizumab in a different adjuvant indication in melanoma (resected high-risk stage 3 melanoma) employed an analogous 4-state Markov model framework and used the same multi-state parametric modelling approach for the estimation of transition probabilities.[2]

Efficacy inputs for the pembrolizumab and routine surveillance arms were based on patient-level data from the randomized controlled KEYNOTE-716 trial which showed a statistically significant improvement in RFS. Consistent with methodological guidance from the NICE DSU,[69, 72] the selection of parametric functions to model transitions starting from the RF state was based on goodness of fit with the observed data, and clinical plausibility of long-term extrapolations was assessed using external data and clinical expert opinion. Long-term RFS, DMFS, and OS predictions in the routine surveillance arm closely aligned with external data from real-world cohorts of patients with stage 2B or 2C melanoma.

Given the 1-year maximum duration of adjuvant pembrolizumab, time on treatment in the adjuvant pembrolizumab arm was precisely estimated based on observed, mature Kaplan-Meier data from KEYNOTE-716, without the need for extrapolation.

Transition probabilities starting from both the LRR and DM states were modelled based on the market shares of subsequent treatments in these settings (i.e. subsequent adjuvant treatments for stage 3 melanoma in the LRR state and first-line treatments of advanced melanoma in the DM state). Consequently, it was possible to conduct meaningful sensitivity analyses that varied assumptions regarding the mix of subsequent treatments received in each adjuvant treatment arm. The base-case market shares of subsequent treatments were supported by clinical expert opinion and UK-specific market research data.

AE-related disutility, and most health state utility inputs, were directly obtained from the KEYNOTE-716 trial, and were measured using the EQ-5D, the utility measure preferred by NICE. The QALY decrement associated with AEs was considered in each treatment arm, accounting for the mean duration of each included AE and treatment-specific risk of each AE.

B.3.11.2 Limitations of the economic evaluation

As with any pharmacoeconomic evaluation, this model is subject to some limitations. Because DMFS and OS were not included as part of the pre-specified analyses at this early interim data cutoff, KEYNOTE-716 data were not available for use to model transition probabilities starting from the LRR and DM states. Supplemental data sources (an EHR database and results from clinical trials in the stage 3 adjuvant and advanced melanoma settings) were instead used to inform transition probabilities starting from LRR and DM. The model therefore conservatively assumed that adjuvant pembrolizumab would have no ongoing therapeutic benefit once patients experience either of these RFS failure events. OS is a model output and therefore modeled predictions should be validated against OS results

from KEYNOTE-716 when these data become available. However, considering the time required to collect OS data in the adjuvant setting, this is not expected within the timeframe of the current appraisal. Despite this, there is substantial published evidence that improvements in RFS, such as those observed with pembrolizumab relative to placebo in KEYNOTE-716, will translate into an OS benefit.[2, 54-56, 58, 59]

Another limitation was the need to extrapolate long-term RFS based on RFS data during the available follow-up period from KEYNOTE-716. Given the uncertainty inherent in the extrapolation of survival outcomes, alternative distributional assumptions were tested in scenario analyses, including conservative scenarios that assumed a smaller incremental RFS benefit of pembrolizumab vs. routine surveillance than that implied by the base-case parametric functions. Across all scenario analyses conducted on RFS, the resulting ICERs of pembrolizumab were well below the willingness-to-pay threshold, supporting the robustness of the base-case ICER.

Given the unique shape of the survival curves of immunotherapeutic agents which are now common practice for treatment of advanced melanoma, it is unlikely that the exponential distribution used to model the DM state is sufficiently flexible to characterize the plateau in OS which is now observed in advanced melanoma.[62, 111] It is possible that the approach underestimates the long-term OS benefit offered with contemporary regimens, and slightly overestimates the short term survival. However, given the Markov model structure, other more complicated survival modelling approaches to estimate transition probabilities from the DM state are extremely challenging to implement and would add significant additional complexity to the model. As this approach is implemented in both the pembrolizumab and routine surveillance arms however, the incremental effect should not have a significant impact on the overall result and conclusions of this cost-effectiveness analysis, as confirmed in sensitivity analyses.

Due to limited follow-up of patients after recurrence in KEYNOTE-716 as of the current data cutoff date, trial-based estimates of utility in the DM state may not accurately reflect HRQoL during the entire period from DM until death. Consequently, the base-case analysis used results from a published study to inform utility in the post-progression DM state.[97] Scenario analyses were also undertaken using several alternative sources for health state utilities, and the results supported the base-case cost-effectiveness conclusions.

Finally, the model reflects the anticipated license for pembrolizumab and includes patients aged ≥12 years. Although the paediatric cohort in the KEYNOTE-716 ITT population was

small, given then unique mode of action for anti-PD-1 therapies there is no evidence to suggest that pembrolizumab would not be an effective treatment in this population and therefore inferences regarding cost-effectiveness should be applicable to all patients covered by the license.

B.3.11.3 Conclusions

Patients with resected stage 2B/2C melanoma are recognized to have a high risk of disease recurrence, comparable to the risk seen in stage 3A/3B disease. There are currently no options available for systemic adjuvant treatment of resected stage 2B or 2C melanoma in the UK, therefore a strategy of routine surveillance continues to be the standard of care for this indication. In the KEYNOTE-716 trial, 28% of patients randomized to placebo experienced RFS failure (i.e., LRR, DM, or death) by 2 years. Among patients in the placebo arm who had a RFS failure by the end of follow-up, the majority (52%) experienced DM as their first RFS failure event. There is therefore an ongoing unmet need for effective adjuvant therapies to reduce the risk of disease recurrence and thereby improve outcomes in these patients. Adjuvant pembrolizumab has been proven to significantly reduce the risk of recurrence for patients with stage 2B/2C melanoma, including reducing the risk of developing metastatic melanoma which is associated with poor survival outcomes and complex and expensive management strategies.

This economic evaluation, conducted from the perspective of the UK NHS, found adjuvant pembrolizumab to be highly cost-effective over a lifetime horizon compared with the current standard of care, routine surveillance. The DSA demonstrated that the cost-effectiveness of pembrolizumab was robust across a range of plausible input values and alternative scenarios. In the PSA, pembrolizumab had a 76.9% probability of being cost-effective vs. routine surveillance at a willingness-to-pay threshold of £30,000 per QALY gained. Adjuvant therapy with pembrolizumab therefore represents a highly cost-effective strategy to reduce the risk of recurrence and consequently the need for expensive subsequent treatments, thus addressing the high unmet need for patients with resected stage 2B/2C melanoma.

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Appendices

See the following Appendix documents provided alongside this document:

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Checklist of confidential information
- Appendix L: Additional data from the KEYNOTE-716 trial
- Appendix M: Transition probabilities
- Appendix N: External validation sources
- Appendix O: Network meta-analysis for advanced melanoma treatments
- Appendix P: Subsequent treatments from KEYNOTE-716
- Appendix Q: Utility analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence

[ID3908]

Clarification questions

March 2022

File name	Version	Contains confidential information	Date
ID3908 Pembrolizumab-in-Stage2-melanoma_Clarifications_MSD_FINAL_23-03-2022_[REDACTED].docx	1.0	NO	23 March 2022

Section A: Clarification on effectiveness data

Literature searches

A1. All search methods (appendix D, G, H & I) report a single search strategy for both Medline and Embase searches. Please confirm if this is a simultaneous search of both resources using a single strategy or a single search of the Embase database conducted on the understanding that it now contains all records from Medline.

For the clinical systematic literature review (SLR) (Appendix D), Medline and Embase were searched simultaneously via the OvidSP platform, using a single strategy. The search strategy was designed so that the free-text keywords and subject heading could be used in both databases. Scottish Intercollegiate Guidelines Network (SIGN) filters of study types for Medline and Embase were combined in the single search strategy.

For the cost-effectiveness studies, health-related quality-of-life (HRQoL) and costs and resource use SLRs (Appendices G, H and I, respectively), Medline and Embase were searched simultaneously via the Embase.com interface, using a single search strategy.

A single search strategy was chosen based on the understanding that the Emtree indexing system utilised by the Embase database is now inclusive of all Medical Subject Headings (MeSH) terms used by Medline. Thus, this single search strategy can be considered inclusive of all records from both Medline and Embase.

A2. Appendix D mentions an additional search of ClinicalTrials.gov. Whilst details of the filters and keywords used are given, the number of records retrieved is not reported, nor do they appear in the PRISMA flow chart. Please provide full details of this search including date searched and hits retrieved.

As described in Appendix D, search terms for the ClinicalTrials.gov website search were “Melanoma”, “Stage II”, and “adjuvant”; one search was run using all three terms. This search was conducted on 21st December 2021 and focused on trials without study results since trials with results were captured in other searches. Filters were applied to limit search results to “active/recruiting trials” among adults and records were reviewed manually.

The search returned 70 results, which are detailed in Table 1. No additional randomised controlled trials (RCTs) relevant to the decision problem were identified.

Table 1: Results of the ClinicalTrials.gov search (clinical SLR)

#	Title	Status	Conditions	Interventions	URL
1	Vaccine Therapy in Treating Patients With Primary Stage II Melanoma	Unknown status	Melanoma (Skin)	Biological: GM2-KLH vaccine Biological: QS21 Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00005052
2	Tiragolumab Plus Atezolizumab Versus Atezolizumab in the Treatment of Stage II Melanoma Patients Who Are ctDNA-positive Following Resection	Not yet recruiting	Stage II Melanoma	Drug: Atezolizumab Drug: Tiragolumab Device: Signatera Assay	https://ClinicalTrials.gov/show/NCT05060003
3	Vaccine Therapy in Treating Patients With Stage II Melanoma That Can Be Removed by Surgery	Completed	Melanoma (Skin)	Biological: gp100 antigen Biological: incomplete Freund's adjuvant Biological: sargramostim Biological: tyrosinase peptide	https://ClinicalTrials.gov/show/NCT00003274
4	Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)	Active, not recruiting	Melanoma	Biological: Pembrolizumab Other: Placebo	https://ClinicalTrials.gov/show/NCT03553836
5	Adjuvant Nivolumab Treatment in Stage II (IIA, IIB, IIC) High-risk Melanoma	Recruiting	Malignant Melanoma Stage II	Drug: Nivolumab	https://ClinicalTrials.gov/show/NCT04309409
6	Evaluation of Oncoxin-Viusid® in Cutaneous Melanoma	Completed	Cutaneous Melanoma, Stage II Malignant Cutaneous Melanoma Cutaneous Melanoma, Stage III	Dietary Supplement: Oncoxin-Viusid	https://ClinicalTrials.gov/show/NCT03541148

7	Vaccine Therapy and Resiquimod in Treating Patients With Stage II, Stage III, or Stage IV Melanoma That Has Been Completely Removed by Surgery	Completed	Melanoma (Skin)	Drug: resiquimod	https://ClinicalTrials.gov/show/NCT00470379
8	Vaccine Therapy and GM-CSF With or Without Low-Dose Aldesleukin in Treating Patients With Stage II, Stage III, or Stage IV Melanoma	Completed	Melanoma (Skin)	Biological: MART-1 antigen Biological: IL-2 Biological: gp100 antigen Biological: GM-CSF Biological: MART-1a peptide	https://ClinicalTrials.gov/show/NCT00470015
9	Vaccine Therapy With or Without Imiquimod in Treating Patients Who Have Undergone Surgery for Stage II, Stage III, or Stage IV Melanoma	Completed	Melanoma (Skin)	Biological: incomplete Freund's adjuvant Biological: multi-epitope melanoma peptide vaccine Biological: sargramostim Biological: tetanus toxoid helper peptide Drug: dimethyl sulfoxide Drug: imiquimod Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00118313
10	Adjuvant Therapy of Pegylated Interferon- 2b Plus Melanoma Peptide Vaccine	Completed	Melanoma	Drug: Pegylated Interferon-Alfa 2b (PEG Intron) Drug: GP-100 Peptide Vaccine	https://ClinicalTrials.gov/show/NCT00861406
11	Vaccine Therapy With or Without Sargramostim in Treating Patients With Stage IIB, Stage IIC, Stage III, or Stage IV Melanoma	Completed	Melanoma (Skin)	Biological: incomplete Freund's adjuvant	https://ClinicalTrials.gov/show/NCT00089193

				Biological: multi-epitope melanoma peptide vaccine Biological: sargramostim	
12	Interferon Alfa-2b in Treating Patients With Melanoma and Early Lymph Node Metastasis	Completed	Melanoma (Skin)	Biological: recombinant interferon alfa Procedure: lymphangiography Drug: Observation	https://ClinicalTrials.gov/show/NCT00004196
13	Vaccination With 6MHP, With or Without Systemic CDX-1127, in Patients With Stage II-IV Melanoma	Recruiting	Melanoma	Biological: 6MHP Drug: Montanide ISA-51 Drug: polyICLC Drug: CDX-1127	https://ClinicalTrials.gov/show/NCT03617328
14	Interferon Alfa or No Further Therapy Following Surgery in Treating Patients With Stage II, Stage III, or Recurrent Melanoma	Completed	Melanoma (Skin)	Biological: recombinant interferon alfa	https://ClinicalTrials.gov/show/NCT00002892
15	PegIntron Versus IntronA in CMAJCC Stage II (EADO 2001/CMII Trial)	Completed	Melanoma Neoplasm Metastasis	Drug: PegIntron Drug: intron A	https://ClinicalTrials.gov/show/NCT00221702
16	Phase II/III Clinical Study CSF470 Plus BCG Plus GM-CSF vs IFN Alpha 2b in Stage IIB, IIC and III Melanoma Patients	Unknown status	Cutaneous Melanoma	Biological: CSF470 vaccine, BCG, Molgramostim Drug: interferon alpha 2b	https://ClinicalTrials.gov/show/NCT01729663
17	GM-CSF as Adjuvant Therapy of Melanoma	Completed	Malignant Melanoma	Drug: Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	https://ClinicalTrials.gov/show/NCT00350597
18	Neoadjuvant PD-1 Blockade in Patients With Stage IIB/C Melanoma	Recruiting	Melanoma	Drug: Pembrolizumab	https://ClinicalTrials.gov/show/NCT03757689

				Procedure: Wide Excision and Sentinel Lymph Node (SLN) Biopsy	
19	Injection Of AJCC Stage IIB, IIC, III And IV Melanoma Patients With A Multi-Epitope Peptide Vaccine Using GM-CSF DNA As An Adjuvant: A Pilot Trial To Assess Safety And Immunity	Completed	Melanoma	Biological: GM-CSF DNA, NSC 683472 gp100: 209-217(210M), NSC 699048 Tyrosinase: 368-376(370D)	https://ClinicalTrials.gov/show/NCT00580060
20	Pegylated Interferon-alpha-2a in Patients With Malignant Melanoma Stage IIA-IIIB	Completed	Melanoma	Drug: pegylated interferon-alpha-2a Drug: interferon-alpha-2a	https://ClinicalTrials.gov/show/NCT00204529
21	Vaccine Therapy in Treating Patients With Melanoma	Completed	Melanoma (Skin)	Biological: aldesleukin Biological: gp100 antigen Biological: incomplete Freund's adjuvant Biological: tyrosinase peptide	https://ClinicalTrials.gov/show/NCT00020358
22	Effectiveness Study of Nivolumab Compared to Placebo in Prevention of Recurrent Melanoma After Complete Resection of Stage IIB/C Melanoma	Active, not recruiting	Melanoma	Biological: Nivolumab Other: Placebo	https://ClinicalTrials.gov/show/NCT04099251
23	Nivolumab in Treating Patients With Stage IIB-IIC Melanoma That Can Be Removed by Surgery	Active, not recruiting	Melanoma (Skin)	Biological: Nivolumab	https://ClinicalTrials.gov/show/NCT03405155
24	Immunotherapy After Surgery in Treating Patients With Breast Cancer, Colon Cancer, or Melanoma	Unknown status	Breast Cancer Colorectal Cancer Melanoma (Skin)	Biological: Corynebacterium granulosum P40 Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00002455
25	Vaccine Therapy in Treating Patients With Advanced Melanoma	Completed	Intraocular Melanoma	Biological: incomplete Freund's adjuvant	https://ClinicalTrials.gov/show/NCT00705640

			Malignant Conjunctival Neoplasm Melanoma (Skin)	Biological: multi-epitope melanoma peptide vaccine Biological: tetanus toxoid helper peptide Procedure: biopsy	
26	Efficacy of Propranolol Treatment to Prevent Melanoma Progression	Suspended	Stages III Skin Melanoma Stages II Skin Melanoma Stage IB Skin Melanoma	Drug: Propranolol hydrochloride Drug: Placebo pill	https://ClinicalTrials.gov/show/NCT01988831
27	Vaccine Therapy and Interleukin-12 With Either Alum or Sargramostim After Surgery in Treating Patients With Melanoma	Completed	Intraocular Melanoma Melanoma (Skin)	Biological: MART-1 antigen Biological: gp100 antigen Biological: incomplete Freund's adjuvant Biological: recombinant interleukin-12 Biological: sargramostim Biological: tyrosinase peptide Drug: alum adjuvant Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00031733
28	MART-1 Antigen With or Without TLR4 Agonist GLA-SE in Treating Patients With Stage II-IV Melanoma That Has Been Removed by Surgery	Completed	Stage IIA Skin Melanoma Stage IIB Skin Melanoma Stage IIC Skin Melanoma	Biological: MART-1 Antigen Drug: TLR4 Agonist GLA-SE Other: Laboratory Biomarker Analysis	https://ClinicalTrials.gov/show/NCT02320305

			Stage IIIA Skin Melanoma Stage IIIB Skin Melanoma Stage IIIC Skin Melanoma Stage IV Skin Melanoma		
29	Vaccine Therapy With or Without Sargramostim in Treating Patients Who Have Undergone Surgery for Melanoma	Completed	Ciliary Body and Choroid Melanoma, Medium/Large Size Extraocular Extension Melanoma Iris Melanoma Stage IIB Melanoma Stage IIC Melanoma Stage IIIA Melanoma Stage IIIB Melanoma Stage IIIC Melanoma Stage IV Melanoma	Biological: tyrosinase peptide Biological: gp100 antigen Biological: MART-1 antigen Biological: incomplete Freund's adjuvant Drug: Montanide ISA 51 VG Biological: sargramostim Other: laboratory biomarker analysis	https://ClinicalTrials.gov/show/NCT00089063
30	Adjuvant PEG Intron in Ulcerated Melanoma	Unknown status	Ulcerated Melanomas	Biological: PEG IFN alfa-2b	https://ClinicalTrials.gov/show/NCT01502696
31	Nivolumab or Expectant Observation Following Ipilimumab, Nivolumab, and Surgery in Treating Patients With High Risk Localized, Locoregionally Advanced, or Recurrent Mucosal Melanoma	Withdrawn	Cervical Carcinoma Esophageal Carcinoma Mucosal Melanoma Mucosal Melanoma of the Head and Neck	Procedure: Conventional Surgery Biological: Ipilimumab Other: Laboratory Biomarker Analysis Biological: Nivolumab	https://ClinicalTrials.gov/show/NCT03220009

			Oral Cavity Mucosal Melanoma Recurrent Melanoma Stage II Vulvar Cancer AJCC v7 Stage III Vulvar Cancer AJCC v7 Stage IIIA Vulvar Cancer AJCC v7 Stage IIIB Vulvar Cancer AJCC v7 Stage IIIC Vulvar Cancer AJCC v7 Stage IV Oral Cavity Cancer AJCC v6 and v7 Stage IV Vulvar Cancer AJCC v7 Stage IVA Oral Cavity Cancer AJCC v6 and v7 Stage IVB Oral Cavity Cancer AJCC v6 and v7 Stage IVC Oral Cavity Cancer AJCC v6 and v7 Vaginal Carcinoma	Other: Patient Observation Radiation: Radiation Therapy	
32	Adjuvant Sunitinib or Valproic Acid in High-Risk Patients With Uveal Melanoma	Recruiting	Ciliary Body and Choroid Melanoma, Medium/Large Size Ciliary Body and Choroid Melanoma, Small Size|Iris Melanoma	Drug: Sunitinib Drug: Valproic Acid	https://ClinicalTrials.gov/show/NCT02068586

			Stage I Intraocular Melanoma Stage IIA Intraocular Melanoma Stage IIB Intraocular Melanoma Stage IIIA Intraocular Melanoma Stage IIIB Intraocular Melanoma Stage IIIC Intraocular Melanoma		
33	Using Nivolumab Alone or With Cabozantinib to Prevent Mucosal Melanoma Return After Surgery	Not yet recruiting	Anal Melanoma Bladder Melanoma Cervical Melanoma Esophageal Melanoma Gallbladder Melanoma Mucosal Melanoma Mucosal Melanoma of the Head and Neck Mucosal Melanoma of the Urinary System Oral Cavity Mucosal Melanoma Penile Mucosal Melanoma Rectal Melanoma	Drug: Cabozantinib Biological: Nivolumab Drug: Placebo Administration	https://ClinicalTrials.gov/show/NCT05111574

			Recurrent Mucosal Melanoma Sinonasal Mucosal Melanoma Stage II Vulvar Cancer AJCC v8 Stage IIIC Vulvar Cancer AJCC v8 Stage IV Vulvar Cancer AJCC v8 Stage IVA Vulvar Cancer AJCC v8 Stage IVB Vulvar Cancer AJCC v8 Urethral Melanoma Vaginal Melanoma Vulvar Melanoma		
34	Experimental Therapeutic Cancer Vaccine Created In-situ in Patients With Stage II-Stage IV Cancer	Completed	Solid Tumors Stage II, Stage III and Stage IV Breast Cancer Colorectal Cancer Prostate Cancer Melanoma Ovarian Cancer Sarcoma Non-small Cell Lung Cancer	Biological: AlloStim Procedure: Cryoablation	https://ClinicalTrials.gov/show/NCT01065441

35	Vaccination of Melanoma Patients With Dendritic Cells Loaded With Allogeneic Apoptotic-Necrotic Melanoma Cells	Completed	Melanoma	Biological: DC/Apo-Nec	https://ClinicalTrials.gov/show/NCT00515983
36	Trial for the Evaluation of the Effect of Systemic Low-dose Interleukin-2 (IL-2) on the Immunogenicity of a Vaccine Comprising Synthetic Melanoma Peptides Administered With Granulocyte-macrophage Colony-stimulating Factor (GM-CSF)-In-Adjuvant, in Patients With High Risk Melanoma	Completed	Melanoma	Drug: low-dose IL-2 Biological: melanoma vaccine	https://ClinicalTrials.gov/show/NCT00928902
37	A Phase II Study of Neoadjuvant Pembrolizumab & Lenvatinib for Resectable Stage III Melanoma	Active, not recruiting	Melanoma Stage III	Drug: Pembrolizumab Drug: Lenvatinib	https://ClinicalTrials.gov/show/NCT04207086
38	Phase I/II Trial of a Long Peptide Vaccine (LPV7) Plus TLR Agonists	Active, not recruiting	Melanoma Metastatic Melanoma Mucosal Melanoma	Biological: Peptide Vaccine (LPV7) + Tetanus peptide Other: PolyICLC Other: Resiquimod|Other: IFA	https://ClinicalTrials.gov/show/NCT02126579
39	A Phase II Study of Imatinib Versus Interferon as Adjuvant Therapy in KIT-mutated Melanoma	Unknown status	Melanoma	Drug: imatinib Drug: Interferon	https://ClinicalTrials.gov/show/NCT01782508
40	Postoperative Adjuvant Treatment of Completely Resected Mucosal Melanoma Phase II Study	Recruiting	Mucosal Melanoma	Combination Product: Toripalimab Combination Product: Temozolomide	https://ClinicalTrials.gov/show/NCT04462965
41	BrUOG 324: Adjuvant Nivolumab and Low Dose Ipilimumab for Stage III and Resected Stage IV Melanoma: A Phase II Brown University Oncology Research Group Trial	Unknown status	Melanoma	Drug: Ipilumumab Drug: Nivolumab	https://ClinicalTrials.gov/show/NCT02656706

42	Monoclonal Antibody Therapy in Treating Patients With Stage III or Stage IV Melanoma	Completed	Melanoma (Skin)	Biological: monoclonal antibody 4B5 anti-idiotype vaccine Biological: sargramostim Drug: alum adjuvant	https://ClinicalTrials.gov/show/NCT00004184
43	Vaccine Therapy in Treating Patients With Stage III or Stage IV Melanoma That Cannot Be Removed With Surgery	Unknown status	Melanoma (Skin)	Biological: D1/3-MAGE-3-His fusion protein Biological: SB-AS02B adjuvant Biological: SB-AS15 adjuvant	https://ClinicalTrials.gov/show/NCT00086866
44	Sorafenib, Tamoxifen, and Cisplatin in Treating Patients With High-Risk Stage III Melanoma	Unknown status	Melanoma (Skin)	Drug: cisplatin Drug: sorafenib tosylate Drug: tamoxifen citrate Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00492505
45	Vaccine Therapy in Treating Patients With Stage IV Melanoma	Completed	Melanoma (Skin)	Biological: D1/3-MAGE-3-His fusion protein Biological: SB-AS02B adjuvant	https://ClinicalTrials.gov/show/NCT00042783
46	Complementary Vaccination With Dendritic Cells Pulsed With Autologous Tumor Lysate in Resected Stage III and IV Melanoma Patients.	Terminated	Malignant Melanoma Adjuvant Drug Therapy Vaccine Therapy	Biological: Autologous Dendritic Cell vaccine	https://ClinicalTrials.gov/show/NCT02718391
47	Vaccine Therapy in Treating Patients With Stage IIC-IV Melanoma	Completed	Ciliary Body and Choroid Melanoma, Medium/Large Size Ciliary Body and Choroid Melanoma, Small Size	Biological: gp100 antigen Biological: tyrosinase peptide	https://ClinicalTrials.gov/show/NCT00085189

			Extraocular Extension Melanoma Iris Melanoma Metastatic Intraocular Melanoma Mucosal Melanoma Recurrent Intraocular Melanoma Recurrent Melanoma Stage IIC Melanoma Stage IIIA Intraocular Melanoma Stage IIIA Melanoma Stage IIIB Intraocular Melanoma Stage IIIB Melanoma Stage IIIC Intraocular Melanoma Stage IIIC Melanoma Stage IV Intraocular Melanoma Stage IV Melanoma	Biological: recombinant MAGE-3.1 antigen Biological: multi-epitope melanoma peptide vaccine Biological: incomplete Freund's adjuvant Drug: Montanide ISA 51 VG Drug: agatolimod sodium Other: laboratory biomarker analysis	
48	Immunotherapy With Nivolumab or Nivolumab Plus Ipilimumab vs. Double Placebo for Stage IV Melanoma w. NED	Completed	Malignant Melanoma	Drug: Nivolumab + Placebo Drug: Nivolumab + Ipilimumab Drug: Double Placebo Control	https://ClinicalTrials.gov/show/NCT02523313

49	Sunitinib, Tamoxifen, and Cisplatin in Treating Patients With High-Risk Ocular Melanoma	Unknown status	Intraocular Melanoma	Drug: cisplatin Drug: sunitinib malate Drug: tamoxifen citrate Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00489944
50	A Randomized Controlled Phase II Trial With Intradermal IMO-2125 in Pathological Tumor Stage (p) T3-4 cN0M0 Melanoma	Recruiting	Malignant Melanoma	Drug: Tilsotolimod Drug: Saline (0.9% sodium chloride)	https://ClinicalTrials.gov/show/NCT04126876
51	A Study to Compare the Administration of Pembrolizumab After Surgery Versus Administration Both Before and After Surgery for High-Risk Melanoma	Recruiting	Acral Lentiginous Melanoma Clinical Stage III Cutaneous Melanoma AJCC v8 Clinical Stage IV Cutaneous Melanoma AJCC v8 Mucosal Melanoma Pathologic Stage IIIB Cutaneous Melanoma AJCC v8 Pathologic Stage IIIC Cutaneous Melanoma AJCC v8 Pathologic Stage IIID Cutaneous Melanoma AJCC v8 Pathologic Stage IV Cutaneous Melanoma AJCC v8	Biological: Pembrolizumab Procedure: Therapeutic Conventional Surgery	https://clinicaltrials.gov/ct2/show/NCT03698019

52	Vaccine Therapy With or Without Interleukin-12 in Treating Patients With Stage III or Stage IV Melanoma	Completed	Intraocular Melanoma Melanoma (Skin)	Biological: gp100 antigen Biological: incomplete Freund's adjuvant Biological: recombinant interleukin-12 Biological: tyrosinase peptide	https://ClinicalTrials.gov/show/NCT00003339
53	Post-Operative Adjuvant Radiotherapy With Concurrent Interferon-Alfa	Completed	Melanoma (Skin)	Biological: Interferon alfa Radiation: Radiation therapy	https://ClinicalTrials.gov/show/NCT00005615
54	Phase I/II Study of Chemo-Immunotherapy Combination in Melanoma Patients	Completed	Melanoma	Biological: Melan-A Other: Melan-A plus Dacarbazine	https://ClinicalTrials.gov/show/NCT00559026
55	Evaluation of the Immunogenicity of Vaccination With Multiple Synthetic Melanoma Peptides With Granulocyte-macrophage Colony-stimulating Factor (GM-CSF)-In-Adjuvant, in Patients With Advanced Melanoma	Completed	Melanoma	Biological: 4-peptide and 12-peptide melanoma vaccines	https://ClinicalTrials.gov/show/NCT00938223
56	Ipilimumab With or Without Vaccine Therapy in Treating Patients With Previously Treated Stage IV Melanoma	Withdrawn	Melanoma (Skin)	Biological: gp100:209-217(210M) peptide vaccine Biological: gp100:280-288(288V) peptide vaccine Biological: incomplete Freund's adjuvant Biological: ipilimumab	https://ClinicalTrials.gov/show/NCT00357461
57	Trial of Ipilimumab After Isolated Limb Perfusion, in Patients With Metastases Melanoma	Completed	In-transit Metastases Melanoma Stage IIIB and IIIC	Drug: Ipilimumab	https://ClinicalTrials.gov/show/NCT02094391

58	Interleukin-2 and Sargramostim After Chemotherapy in Treating Patients With Stage III or Stage IV Melanoma	Withdrawn	Melanoma (Skin)	Biological: aldesleukin Biological: sargramostim Procedure: adjuvant therapy	https://ClinicalTrials.gov/show/NCT00085579
59	LMB-2 Immunotoxin and Vaccine Therapy in Treating Patients With Metastatic Melanoma That Cannot Be Removed By Surgery	Completed	Melanoma (Skin)|Non-melanomatous Skin Cancer	Biological: LMB-2 immunotoxin Biological: MART-1 antigen Biological: gp100 antigen Biological: incomplete Freund's adjuvant	https://ClinicalTrials.gov/show/NCT00295958
60	Vaccine Therapy With or Without Interleukin-2 After Chemotherapy and an Autologous White Blood Cell Infusion in Treating Patients With Metastatic Melanoma	Terminated	Recurrent Melanoma Stage IV Melanoma	Drug: cyclophosphamide Drug: fludarabine phosphate Biological: therapeutic autologous lymphocytes Procedure: in vitro-treated peripheral blood stem cell transplantation Biological: gp100 antigen Biological: MART-1 antigen Biological: incomplete Freund's adjuvant Biological: filgrastim Biological: aldesleukin	https://ClinicalTrials.gov/show/NCT00303836
61	Vaccine Therapy With High-Dose Interleukin-2 in Treating Patients With Metastatic Melanoma	Completed	Melanoma (Skin)	Biological: aldesleukin Biological: gp100 antigen	https://ClinicalTrials.gov/show/NCT00003568

				Biological: incomplete Freund's adjuvant	
62	Vaccine Therapy and GM-CSF in Treating Patients With Recurrent or Metastatic Melanoma	Completed	Melanoma (Skin)	Biological: autologous tumor cell vaccine Biological: sargramostim Biological: therapeutic autologous dendritic cells	https://ClinicalTrials.gov/show/NCT00436930
63	Vaccine Therapy With or Without Biological Therapy in Treating Patients With Metastatic Melanoma	Completed	Melanoma (Skin)	Biological: MART-1 antigen Biological: gp100 antigen Biological: incomplete Freund's adjuvant Biological: recombinant interferon alfa Biological: sargramostim Biological: tyrosinase peptide	https://ClinicalTrials.gov/show/NCT00006385
64	A Study Evaluating Whether Pembrolizumab Alone or in Combination With CMP-001 Improves Efficacy in Patients With Operable Melanoma	Recruiting	Clinical Stage III Cutaneous Melanoma AJCC v8 Melanoma of Unknown Primary Pathologic Stage IIIB Cutaneous Melanoma AJCC v8 Pathologic Stage IIIC Cutaneous Melanoma AJCC v8	Biological: Pembrolizumab Procedure: Surgical Procedure Drug: VLP-encapsulated TLR9 Agonist CMP-001	https://ClinicalTrials.gov/show/NCT04708418

			Pathologic Stage IIID Cutaneous Melanoma AJCC v8 Recurrent Cutaneous Melanoma		
65	Testing Treatment With Encorafenib and Binimetinib Before Surgery for Melanoma With Lymph Node Involvement	Not yet recruiting	Melanoma of Unknown Primary Metastatic Malignant Neoplasm in Lymph Node Pathologic Stage IIIB Cutaneous Melanoma AJCC v8 Pathologic Stage IIIC Cutaneous Melanoma AJCC v8 Pathologic Stage IIID Cutaneous Melanoma AJCC v8 Recurrent Cutaneous Melanoma	Drug: Binimetinib Procedure: Computed Tomography Procedure: Conventional Surgery Drug: Encorafenib Other: Fluorothymidine F-18 Procedure: Positron Emission Tomography	https://ClinicalTrials.gov/show/NCT04221438
66	Neoadjuvant Vemurafenib + Cobimetinib + Atezolizumab in Melanoma: NEO-VC	Terminated	Malignant Melanoma	Drug: Vemurafenib Drug: Cobimetinib Drug: Atezolizumab	https://ClinicalTrials.gov/show/NCT02303951
67	Interleukin-12 and Interferon Alfa in Treating Patients With Metastatic Malignant Melanoma	Completed	Recurrent Melanoma Stage IV Melanoma	Biological: recombinant interleukin-12 Biological: recombinant interferon alfa Other: laboratory biomarker analysis	https://ClinicalTrials.gov/show/NCT00026143

68	flt3L With or Without Vaccine Therapy in Treating Patients With Metastatic Melanoma or Renal Cell Cancer	Completed	Stage IV Melanoma Stage IV Renal Cell Cancer Recurrent Renal Cell Cancer Recurrent Melanoma	Drug: flt3 ligand Drug: gp100 antigen Drug: MART-1 antigen Drug: Montanide ISA-51 Drug: tyrosinase peptide	https://ClinicalTrials.gov/show/NCT00019396
69	Vaccine Therapy Followed by Biological Therapy in Treating Patients With Stage III or Stage IV Melanoma	Terminated	Melanoma (Skin)	Biological: MART-1 antigen Biological: aldesleukin Biological: gp100 antigen Biological: recombinant CD40-ligand Biological: recombinant interferon gamma Biological: recombinant interleukin-4 Biological: sargramostim Biological: therapeutic autologous dendritic cells Biological: therapeutic tumor infiltrating lymphocytes Biological: tyrosinase peptide Radiation: Candida albicans skin test reagent	https://ClinicalTrials.gov/show/NCT00006113
70	Vaccine Therapy and Interleukin-12 in Treating Patients With Metastatic Melanoma	Completed	Melanoma (Skin)	Biological: MART-1 antigen Biological: recombinant MAGE-3.1 antigen	https://ClinicalTrials.gov/show/NCT00002952

				Biological: recombinant interleukin-12	

Abbreviations: 6MHP: 6 melanoma helper peptide; AJCC: American Joint Cancer Committee; BCG: bacillus Calmette-Guérin; BrUOG: Brown University Oncology Group; ctDNA: circulating tumour deoxyribonucleic acid; DC/Apo-Nec: dendritic cells with apoptotic and necrotic melanoma cell lines; GLA-SE: glucopyranosyl lipid adjuvant-stable emulsion; GM-CSF: granulocyte-macrophage colony-stimulating factor; GP: glycoprotein; IL: interleukin; MAGE: melanoma antigenic epitope; MART: melanoma antigen recognised by T-cells; NEO-VC: neoadjuvant vemurafenib and cobimetinib; PD: programmed cell death protein; PEG IFN: pegylated interferon; SLN: sentinel lymph node; SLR: systematic literature review; TLR: toll-like receptor; VG: vegetable grade; VLP: virus-like particle.

A3. Given the low number of results retrieved for each search in the clinical effectiveness section, please explain the rationale behind not searching more broadly. The clinical searches combined terms for (Melanoma + (Stage 2 or resected) + adjuvant), This is in contrast to the economic searches which searched more broadly, combining terms for (Melanoma + adjuvant) only.

The clinical searches were concluded in line with the anticipated marketing authorisation of pembrolizumab as [redacted]. These searches were performed in alignment with the preferred methods of evidence synthesis outlined by NICE. To ensure the comparability of the identified studies with the KEYNOTE-716 trial, and to assess the feasibility of conducting a network meta-analysis with pembrolizumab, the SLR population was chosen to be similar to the study population in KEYNOTE-716.

In contrast, the economic searches were wider in scope because their purpose was to identify modelling approaches more broadly and manually assess assumptions/structures.

A4. Please provide justification for the 10 year date limit applied to the clinical effectiveness searches.

The search was conducted among articles published after 2011 since evidence in the target population is limited before 2011. For approximately 40 years prior to 2011, treatment options for patients with metastatic melanoma or high-risk stage 2 disease were limited and no significant impact on survival was observed.[1] Since 2011, there have been marked changes in the management of metastatic melanoma or high-risk stage 2 disease including adjuvant treatment options and, as such, the limit applied in the searches is appropriate.

A5. Appendix G (Published cost-effectiveness studies), reports additional searches of both conference proceedings and HTA websites, but details of keywords used and the number of records retrieved is not included in the tables in section G.2.2. or recorded in the PRISMA flow chart. Where appropriate please provide full strategies, date searched and number of records retrieved.

Additional searches of conference proceedings for the published cost-effectiveness studies review were conducted on 6 April 2021 and updated on 18 October 2021. Keywords used are presented in Table 2, along with the number of hits from each search. Results were reviewed manually for relevance to the decision problem. From these, no relevant abstracts were retrieved.

Table 2: Conference searches conducted during the published cost-effectiveness studies review

Conference name	Year	Keywords	Hits	Number of relevant abstracts found
ISPOR 2019, New Orleans, LA, USA	2019	Melanoma	18	0
		Economic	342	0
ISPOR 2019, Latin America, Bogota, Colombia		Melanoma	10	0
		Economic	65	0
ISPOR 2019, Europe, Copenhagen, Denmark		Melanoma	49	0
		Economic	575	0
ISPOR 2020, Orlando, FL, USA	2020	Melanoma	15	0
		Economic	383	0
ISPOR 2020, Asia Pacific, Seoul, South Korea		Melanoma	16	0
		Economic	276	0
ISPOR 2020, Europe, Milan, Italy		Melanoma	61	0
		Economic	1048	0
ISPOR 2021, Montreal, Canada	2021	Melanoma	0	0
		Economic evaluations	0	0
SITC 2019	2019	Melanoma, economic, cost, resource, utility	0	0
SITC 2020	2020	Melanoma, economic, cost, resource, utility	0	0
SITC 2021	2021	Conference not conducted yet	NA	0
Society for melanoma research	2019	Conference abstracts paid	NA	0
	2020	Conference abstracts paid	NA	0
	2021	Conference abstracts paid	NA	0
ASCO	2019	Melanoma and economic	7	0
		Melanoma and cost	21	0
		Melanoma and resource	13	0
		Melanoma and utility	28	0
	2020	Melanoma and economic	4	0
		Melanoma and cost	21	0
		Melanoma and resource	7	0
		Melanoma and utility	18	0
	2021	Melanoma and economic	0	0
		Melanoma and cost	0	0
		Melanoma and resource	0	0
		Melanoma and utility	0	0
ESMO	2019	Melanoma	204	0
	2020	Melanoma	157	0
	2021	Conference not conducted yet	NA	0

AACR	2019	Melanoma, economic, cost, resource, utility	0	0
	2020	Melanoma, economic, cost, resource, utility	0	0
	2021	Conference not conducted yet	NA	0

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

In addition, health technology assessment (HTA) website searches were conducted in April 2021 and updated in October 2021, as detailed in Table 3. The searches did not identify any HTA submission available for patients with stage 2 melanoma.

Table 3: HTA website searches conducted during the published cost-effectiveness studies review

HTA databases	URL	Keywords searched	Identified hits
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	Melanoma, Stage II	0
Canadian Agency for Technology and Drugs in Health (CADTH)/ The pan-Canadian Oncology Drug Review (pCODR)	https://www.cadth.ca/index.php/en/hta	Melanoma, Stage II	0
Haute Autorité de Santé (HAS)	http://translate.google.co.uk/translate?hl=en&sl=fr&u=http://www.has-sante.fr/&ei=ylxaTLnrI8KYrAey2dS9DA&sa=X&oi=translate&ct=result&resnum=1&ved=0CCcQ7gEwAA&prev=/search%3Fq%3Dhas%2Bfrance%26hl%3Den%26prmd%3Dn	Melanoma, Stage II	0
Institute for Quality and Efficiency in Healthcare (IQWIG)/Gemeinsamer Bundesausschuss (G-BA)	http://www.iqwig.de/	Melanoma, Stage II	0
Pharmaceutical Benefits Advisory Committee (PBAC)	http://www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Advisory+Committee-1	Melanoma, Stage II	0
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	Melanoma, Stage II	0
All Wales Medicines Strategy Group (AWMSG)	https://awttc.nhs.wales/	Melanoma, Stage II	0
National Centre for Pharmacoeconomics (NCPE)	https://www.ncpe.ie/	Melanoma, Stage II	0

A6. The search strategies for the HRQoL literature review (Appendix H) and Resource use (Appendix I), appear to have been mixed up. The numbers of hits per resource reported in the PRISMA flow charts for each section appear to tally with this assumption. Please confirm that this is the case for all searches listed in each appendix and provide a corrected version.

MSD can confirm the Evidence Assessment Group's (EAG) assumption here that the search strategies for the HRQoL literature review (Appendix H) and costs and resource use have been mixed up and apologise for this error. Tables 18–21 (Appendix H) should be switched with Tables 25–29 (Appendix I) to rectify this. The PRISMA flow charts for each review are reported within the correct appendices.

A7. Appendix O reports an additional SLR used to inform a network meta-analysis for advanced melanoma treatments. Searches are listed for Medline, Embase and CENTRAL databases as well as additional searches of clinical trial.gov and manual searches of 4 conference proceedings. No search strategies appear to be provided. Please could you send full strategies for each search.

Predefined search strategies for the Embase, Medline and the Cochrane Register of Controlled Trials are detailed below in Table 4, Table 5 and Table 6, respectively. All searches were conducted on 15 October 2021. The study design filters recommended by SIGN for Medline and Embase were used to identify randomised clinical trials. Key terms related to both the generic and brand name of the interventions of interest were used.

Table 4: Search strategy for EMBASE (EMBASE 1974 to 2021 October 14 searched on 15 October 2021)

#	Strings	Hits
1	exp skin tumor/ or exp Skin Neoplasms/	193698
2	exp melanoma/	173120
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	284590
4	1 or 2 or 3	380904
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	2624040
6	4 and 5	135992
7	exp atezolizumab/	8458
8	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	9176
9	exp binimetinib/	1202
10	exp NKTR-214/	148
11	(bempegaldesleukin OR NKTR-214).mp.	214
12	(binimetinib OR Mektovi OR MEK162).mp.	1265

13	exp cobimetinib/	1698
14	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	1837
15	exp dabrafenib/	5235
16	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	5601
17	exp dacarbazine/	21116
18	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	21713
19	exp daromun/	7
20	(daromun).mp.	6
21	exp encorafenib/	832
22	(encorafenib or LGX818 or Braftovi).mp.	891
23	exp Ipilimumab/	17853
24	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	18570
25	exp lenvatinib/	3620
26	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	3808
27	exp Nivolumab/	24985
28	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	26160
29	exp Pembrolizumab/	22984
30	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	24191
31	(PV-10).mp.	201
32	exp relatlimab/	140
33	(relatlimab OR BMS-986016).mp.	189
34	exp talimogene laherparepvec/	1098
35	(Talimogene laherparepvec OR T-VEC OR Imlygic or Oncovex).mp.	1258
36	exp tilsotolimod/	38
37	(tilsotolimod OR IMO-2125).mp.	98
38	exp trametinib/	6464
39	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	6714
40	exp vemurafenib/	8372
41	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	9049
42	or/7-41	80355
43	Clinical Trial/	1017097
44	Randomized Controlled Trial/	680077
45	controlled clinical trial/	464161
46	multicenter study/	303227
47	Phase 3 clinical trial/	56729
48	Phase 4 clinical trial/	4500
49	exp RANDOMIZATION/	92307
50	Single Blind Procedure/	44029

51	Double Blind Procedure/	188690
52	Crossover Procedure/	68395
53	PLACEBO/	372403
54	randomi?ed controlled trial$.tw.	268561
55	rct.tw.	43853
56	(random$ adj2 allocat$).tw.	47898
57	single blind$.tw.	27682
58	double blind$.tw.	224144
59	((treble or triple) adj blind$).tw.	1436
60	placebo$.tw.	332879
61	Prospective Study/	719073
62	or/43-61	2579705
63	Case Study/	81780
64	case report.tw.	464299
65	abstract report/ or letter/	1213414
66	Conference proceeding.pt.	0
67	Conference abstract.pt.	4223186
68	Editorial.pt.	705377
69	Letter.pt.	1194192
70	Note.pt.	868756
71	or/63-70	7483785
72	62 not 71	1886510
73	6 and 42 and 72	2604

Table 5: Search strategy for MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to October 14, 2021; searched on 15 October 2021)

#	Strings	Hits
1	exp Skin Neoplasms/	132019
2	exp melanoma/	100728
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	235364
4	1 or 2 or 3	239465
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	1766371
6	4 and 5	73603
7	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	1903
8	(binimetinib or Mektovi or MEK162).mp.	272
9	(bempegaldesleukin OR NKTR-214).mp.	30
10	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	360
11	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	1415
12	exp dacarbazine/	8469
13	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	8900

14	(daromun).mp.	2
15	(encorafenib or LGX818 or Braftovi).mp.	204
16	exp ipilimumab/	2291
17	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	4463
18	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	1209
19	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	7160
20	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	6216
21	(PV-10).mp.	60
22	(relatlimab OR BMS-986016).mp.	5
23	(Talimogene laherparepvec OR T-VEC OR Imlygic or Oncovex).mp.	344
24	(tilsotolimod OR IMO-2125).mp.	9
25	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	1612
26	exp vemurafenib/	1456
27	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	2650
28	or/7-27	28781
29	Randomized Controlled Trials as Topic/	148987
30	randomized controlled trial/	546185
31	Random Allocation/	106012
32	Double Blind Method/	167584
33	Single Blind Method/	30993
34	clinical trial/	531482
35	clinical trial, phase i.pt	22438
36	clinical trial, phase ii.pt	35987
37	clinical trial, phase iii.pt	19210
38	clinical trial, phase iv.pt	2198
39	controlled clinical trial.pt	94453
40	randomized controlled trial.pt	546185
41	multicenter study.pt	305497
42	clinical trial.pt	531482
43	exp Clinical Trials as topic/	364771
44	or/29-43	1464476
45	(clinical adj trial$).tw	413768
46	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	183483
47	PLACEBOS/	35715
48	placebo$.tw	229389
49	randomly allocated.tw	32031
50	(allocated adj2 random$).tw	35526
51	or/45-50	698400

52	44 or 51	1763691
53	case report.tw	345632
54	letter/	1155057
55	historical article/	365887
56	or/53-55	1849369
57	52 not 56	1723666
58	6 and 28 and 57	2057

Table 6: Search strategy for Cochrane Register of Controlled Trials (EBM Reviews - Cochrane Central Register of Controlled Trials September 2021; searched on 15 October 2021)

#	Strings	Hits
1	exp Skin Neoplasms/	1663
2	exp melanoma/	1910
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	8404
4	or/1-3	8405
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	176343
6	4 and 5	4677
7	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	1029
8	(binimetinib OR Mektovi OR MEK162).mp.	118
9	(bempegaldesleukin OR NKTR-214).mp.	20
10	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	158
11	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	275
12	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	1479
13	(daromun).mp.	1
14	(encorafenib or LGX818 or Braftovi).mp.	89
15	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	1512
16	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	417
17	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	2246
18	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	2109
19	(PV-10).mp.	15
20	(relatlimab OR BMS-986016).mp.	38
21	(Talimogene laherparepvec OR T-VEC OR Imlygic or Oncovex).mp.	94
22	(tilsotolimod OR IMO-2125).mp.	17
23	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	337
24	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	275
25	or/7-24	7575

26	6 and 25	1906

Abbreviations: EBM: evidence-based medicine.

Additional searches were performed for select relevant conference proceedings to identify any new RCTs not yet published but potentially eligible for inclusion:

- American Association for Cancer Research (AACR; 2020–2021)
- American Society of Clinical Oncology (ASCO; 2020–2021)
- European Society of Medical Oncology (ESMO; 2020–2021)
- Society of Melanoma Research (SMR; 2019–2020)

Search strategies used in the Northern Light Life Sciences Conference Abstracts database are presented in Table 7–Table 10.

Table 7: Search strategy for AACR 2021 (Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 41; searched on 23 October 2021)

#	Strings	Hits
1	exp Skin Neoplasms/	6269
2	exp melanoma/	35502
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	38979
4	or/1-3	39069
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	234940
6	4 and 5	11722
7	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	888
8	(binimetinib OR Mektovi OR MEK162).mp.	135
9	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	148
10	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	402
11	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	1071
12	(encorafenib or LGX818 or Braftovi).mp.	80
13	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	4012
14	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	495
15	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	6919
16	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	3211
17	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	617

18	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	1715
19	or/7-18	15457
20	American Association for Cancer Research.cf.	65183
21	6 and 19 and 20	152
22	Limit 21 to yr = 2021	3

Abbreviations: AACR: American Association for Cancer Research.

Table 8: Search strategy for ASCO 2021 (Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 41; searched on 23 October 2021)

#	Strings	Hits
1	exp Skin Neoplasms/	6269
2	exp melanoma/	35502
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	38979
4	or/1-3	39069
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	234940
6	4 and 5	11722
7	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	888
8	(binimetinib OR Mektovi OR MEK162).mp.	135
9	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	148
10	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	402
11	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	1071
12	(encorafenib or LGX818 or Braftovi).mp.	80
13	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	4012
14	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	495
15	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	6919
16	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	3211
17	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	617
18	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	1715
19	or/7-18	15457
20	American Society of Clinical Oncology.cf.	70119
21	6 and 19 and 20	1006
22	Limit 21 to yr = 2021	91

Abbreviations: ASCO: American Society of Clinical Oncology.

Table 9: Search strategy for ESMO 2021 (Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 41; searched on 23 October 2021)

#	Strings	Hits

1	exp Skin Neoplasms/	6269
2	exp melanoma/	35502
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	38979
4	or/1-3	39069
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	234940
6	4 and 5	11722
7	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	888
8	(binimetinib OR Mektovi OR MEK162).mp.	135
9	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	148
10	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	402
11	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	1071
12	(encorafenib or LGX818 or Braftovi).mp.	80
13	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	4012
14	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	495
15	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	6919
16	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	3211
17	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	617
18	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	1715
19	or/7-18	15457
20	European Society for Medical Oncology.cf.	20805
21	6 and 19 and 20	503
22	Limit 21 to yr = 2021	0

Abbreviations: ESMO: European Society for Medical Oncology.

Table 10: Search strategy for SMR 2021 (Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 41; searched on 23 October 2021)

#	Strings	Hits
1	exp Skin Neoplasms/	6269
2	exp melanoma/	35502
3	((skin adj (neoplasm$ or cancer$ or tumo?r* or carcinoma$ or adenocarcinoma$ or sarcoma$)) or melanoma).mp.	38979
4	or/1-3	39069
5	(advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).mp.	234940
6	4 and 5	11722
7	(Atezolizumab or MPDL3280A or MPDL-3280A).mp.	888
8	(binimetinib OR Mektovi OR MEK162).mp.	135

9	(cobimetinib or cotellic or GDC-0973 or XL518).mp.	148
10	(dabrafenib or gsk 2118436$1 or gsk2118436$1).mp.	402
11	(dacarbazine or dtic or dacarbazin or deticene or detimedac).mp.	1071
12	(encorafenib or LGX818 or Braftovi).mp.	80
13	(ipilimumab or bms 734016 or bms734016 or mdx 101 or mdx101 or "mdx 010" or mdx010 or Yervoy or MDX CTLA 4).mp.	4012
14	(lenvatinib or Lenvima or lenvanix or kisplyx E7080 or E 7080 or E-7080).mp.	495
15	(Nivolumab or Opdivo or ONO-4538 or ONO4538 or ONO 4538 or BMS-936558 or BMS936558 or BMS 936558 or MDX-1106 or MDX1106 or MDX 1106 or L01XC17).mp.	6919
16	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	3211
17	(trametinib or gsk 1120212 or gsk 1120212b or gsk1120212 or gsk1120212b or jtp 74057 or jtp74057).mp.	617
18	(vemurafenib or plx 4032 or plx4032 or r 7204 or r7204 or rg 7204 or rg7204 or ro 5185426 or ro5185426 or zelboraf).mp.	1715
19	or/7-18	15457
20	Society for Melanoma Research.cf.	1175
21	6 and 19 and 20	171
22	Limit 21 to yr = 2021	0

Abbreviations: SMR: Society of Melanoma Research.

The ESMO and SMR conference websites were also hand-searched for abstracts not yet indexed in Northern Light database. Search strategies are presented in Table 11.

Table 11: Hand search strategy for ESMO and SMR conference websites

Conference	Website	Filter/Search term	Hits	Comment
ESMO 2021	https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021?hit=ehp	melanoma	79	--
SMR 2021	NA	NA	NA	SMR 2021 resources not published yet

Abbreviations: ESMO: European Society for Medical Oncology; NA: non-applicable; SMR: Society of Melanoma Research.

ClinicalTrials.gov was also searched to identify clinical trials not yet published that met the screening criteria with results available. The search strategy is presented in Table 12.

Table 12: Search strategy used to identify clinical trials from ClinicalTrials.gov (NMA SLR)

Search term	Hits
Condition or disease: Advanced melanoma Recruitment status: Recruiting; Active, not recruiting and Completed Study Results: With Results	64

Abbreviations: NMA: network meta-analysis; SLR: systematic literature review.

Decision problem

A8. Priority question. According to the company submission, the anticipated marketing authorisation is for a dose of pembrolizumab in adults of either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W). However, in KEYNOTE-716 adult patients received only 200 mg every 3 weeks (Q3W). Please discuss the implications on effectiveness and safety of the difference in dosing regimen, supported by evidence where available.

The summary of product characteristics (SmPC) for pembrolizumab was amended to include the alternative dosing regimen of 400mg every 6 weeks (Q6W) for all approved monotherapy indications in March 2019. This change was made after initiation of the (ongoing) KEYNOTE-555 trial in September 2018, and as such, patients only received 200mg Q3W.[2, 3]

Pembrolizumab doses of 2 mg/kg every 3 weeks (Q3W), 10 mg/kg Q3W, and 10 mg/kg every 2 weeks (Q2W) were evaluated in melanoma or previously treated non-small cell lung cancer (NSCLC) clinical trials. Based on the pharmacokinetic modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg Q3W, 2 mg/kg Q3W, and 400 mg Q6W as monotherapy.[4, 5] The regulatory authority was satisfied that this was the case when the posology changes were approved.

A9. Please further justify that routine surveillance as observed in the KEYNOTE-716 trial is reflective of routine surveillance in the NHS in England.

According to the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of cutaneous melanoma, there is no consensus on the frequency of follow-up examinations and the use of imaging techniques and blood tests for patients with resected melanoma.[6] In the KEYNOTE-716 trial, routine surveillance of disease involved tumour imaging for the abdomen, pelvis and brain. The protocol stipulated that the preferred method of imaging for the abdomen and pelvis was by computerised tomography (CT) scan. For the brain, magnetic resonance imaging (MRI) was preferred. This is in line with imaging surveillance guidance published by Melanoma Focus for the follow-up of high risk cutaneous melanoma in the UK, which recommends imaging by CT for the chest, abdomen and pelvis, plus imaging by MRI for the head.[5, 7]

Furthermore, the guidance from Melanoma Focus recommends imaging should occur at baseline and then be repeated 6 monthly to 3 years, then annually to 5 years. Clinical experts confirmed that in UK clinical practice, patients receiving adjuvant treatment undergo general surveillance

post-treatment in line with these current guidelines.[8] This is reflected in the KEYNOTE-716 trial, where tumour scans were prespecified at the following intervals:

- Initial tumour scans were performed at Screening, within 28 days of randomisation
- The first on-study scan time point was performed 6 months (26 weeks ± 7 days) from the date of randomisation
- Subsequent tumour scans were then performed every 6 months (26 weeks ± 7 days) while on treatment
- A further scan was performed at the end of treatment
- Tumour scans were then performed every 6 months (26 weeks ± 14 days) from years 2 to 4 after randomisation
- Finally, a scan was performed once in year 5 (365 ± 28 days) from randomisation or until recurrence, whichever occurred first.[7]

As such, routine surveillance as observed in the KEYNOTE-716 can be considered reflective of routine surveillance in the NHS in England.

A10. Please perform subgroup analyses of RFS, OS and DMFS, one with patients with stage 2B and the other with patients with stage 2C disease.

Randomised patients in KEYNOTE-716 were stratified by T-staging and subgroup analyses by baseline T-category were performed for recurrence-free survival (RFS), as presented in Section B.2.7 of Document B of the Company submission. Subgroup analyses by T-staging was pre-specified over the American Joint Committee on Cancer (AJCC) staging; T-staging is static, whereas AJCC staging is subject to change and as such T-staging was favoured to allow interpretation to remain consistent when the AJCC is updated. All subgroup analyses on the KEYNOTE-716 trial are not statistically powered to detect differences in efficacy and any additional subgroup analysis by AJCC staging (compared with pre-specified analyses based on T-staging) would be conducted post-hoc. As such, subgroup analyses for RFS, separated by patients with stage 2B and stage 2C disease, have not been provided here but are presented in Table 14.2-12 and Table 14.2-13, and Figure 14.2-11 and Figure 14.2-12 of the study CSR.

As explained in the clarification call of 14 March 2022 OS and DMFS data are not yet available as of the second interim analysis (IA2) data cut-off presented in this submission, due to insufficient events occurring to enable analysis of these endpoints.

Systematic literature review (SLR)

A11. Please clarify how many reviewers were involved in the quality assessment of included studies for the clinical evidence SLR and cost effectiveness SLR, if there were discrepancies in assessments and how they were resolved, if any.

For the clinical evidence SLR, three reviewers were involved in the quality assessments of the included studies. Two reviewers conducted the quality assessments independently and any discrepancies were reconciled by a third reviewer. No discrepancies were identified.

The same approach was taken for the cost-effectiveness SLR. The quality assessments of included studies were conducted by two independent reviewers, with any discrepancies in the decisions of the two reviewers being resolved by a third, independent, senior reviewer by selecting the most appropriate explanation. Minor discrepancies were identified and resolved by this method.

A12. Please provide PDFs for the following excluded studies, listed in Table 7 of Appendix D:

120	Euctr	2018	Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma	CCTR	Article	Outcome
141	Kenneth	2021	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	Northern Light Life Sciences Conference Abstracts	Abstract	Population
142	Gu	2020	Association of Prior Interferon-Alpha Treatment With the Efficacy of Adjuvant Pembrolizumab In Resected Melanoma	Northern Light Life Sciences Conference Abstracts	Abstract	Population

Please also provide more detailed reasons why these studies have been excluded.

Portable document formats (PDFs) of the Kenneth et al. 2021 and Gu et al. 2020 references are included in the reference pack accompanying these responses. Kenneth et al. 2021 was excluded because the trial was conducted in patients with stage 3A/B/C and 4 melanoma, rather

than stage 2B/C and was therefore beyond the scope of this decision problem. Gu et al. 2020 was excluded because no stage 2B/C subgroup results, which are relevant for decision making, are provided and therefore the study cannot be used in any evidence synthesis or model validation.

Euctr 2018 is a clinical trial record from the European Union Clinical Trials Register (EUCTR) of KEYNOTE-716, available at the following webpage: https://www.clinicaltrialsregister.eu/ctr-search/search?query=Adjuvant+Therapy+with+Pembrolizumab+versus+Placebo+in+Resected+High-risk+Stage+II+Melanoma. This record was excluded as the full CSR of KEYNOTE-716 is available to MSD.

Trials and data analysis

A13. Priority Question: Please provide information about planned analyses and approximate dates when these might be performed for the analyses of OS and DMFS in the KEYNOTE-716 trial. Please specify when IA3 is likely to be done and which outcomes will be analysed in IA3; and please specify when DMFS and OS data are likely to be mature and included in a future interim analysis.

CS, Page 24: "DMFS and OS are also being collected in KEYNOTE-716, however these are event-driven outcomes and the number of events required to enable analysis have not yet been reached. Currently, at IA2, reported events have reached [redacted] DMFS events and [redacted] OS events, representing only [redacted] and [redacted] of the final number of events needed for analysis, respectively.[45]"

Since the company submission, the database lock for the IA3 analysis for KEYNOTE-716 has occurred, and DMFS met statistical significance at this IA.[98] These results build on the previously reported significant RFS benefit seen in the trial. These data are not yet available; full results from this analysis of KEYNOTE-716 are currently expected to be available in [redacted]. MSD will ensure to inform NICE about specific dates as soon as further information is available to be shared.

A14. The CS states that patients with "no more than 12 weeks between final surgical resection and randomisation, with complete surgical wound healing" were eligible for enrolment into the KEYNOTE-716 trial (Part 1).

Please clarify if patients in the KEYNOTE-716 trial needed to have achieved No Evidence of Disease (NED) following surgical resection, to be eligible for enrolment.

Patients considered eligible for the KEYNOTE-716 trial required no evidence of disease (NED) following surgical resection. Final surgical resection is defined in the KEYNOTE-716 protocol as complete resection of melanoma and a sentinel lymph node (SLN) biopsy. If the wide excision was followed by the SLN biopsy (i.e. they were not performed at the same time), no more than 12 weeks may have elapsed between the two surgical procedures. If a second wide excision needed to be completed after SLN biopsy, this date was used to calculate the final surgical resection date. Patients also required a pathologically confirmed negative SLN biopsy, or no disease at baseline in order to meet the inclusion criteria. Initial tumour scans at Screening were performed within 28 days prior to the date of randomisation and reviewed by the site study team in order to confirm the participant had no evidence of disease at study entry. Thus, the combination of these prespecified criteria constitute NED for all patients enrolled in the KEYNOTE-716 trial.

A15. The overall incidence of study discontinuation related to study drug was higher on the pembrolizumab arm compared to the placebo arm in the KEYNOTE-716 trial.

a. Please discuss the most frequently reported of these adverse events (AEs) that led to study discontinuation.

As highlighted by the EAG and as shown in Table 21, Document B of the Company submission, the overall incidence of drug-related AEs was higher in the pembrolizumab group compared with the placebo group. The overall incidence of drug-related AEs that led to discontinuation of study intervention was also higher in the pembrolizumab group ([redacted]%) compared with the placebo group ([redacted]%). The most frequently reported of these drug-related AEs were colitis ([redacted] [redacted]%]) and autoimmune hepatitis ([redacted] [redacted]%]) in the pembrolizumab group, and diarrhoea ([redacted] [redacted]%] in each group) and autoimmune hepatitis ([redacted] [redacted]%]) in the placebo group. Colitis and autoimmune hepatitis are known adverse drug reactions for pembrolizumab. The incidence of all drug-related AEs resulting in treatment discontinuation reported in either group are presented in Table 13.

Table 13: Participants with drug-related AEs resulting in treatment discontinuation by decreasing incidence (incidence >0% in one or more treatment groups) (APaT population)

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Autoimmune hepatitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Autoimmune nephritis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Hypopituitarism	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Polyarthritis	[redacted]	[redacted]
Pulmonary sarcoidosis	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Autoimmune colitis	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Chronic gastritis	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Genital erythema	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Immune thrombocytopenia	[redacted]	[redacted]
Immune-mediated arthritis	[redacted]	[redacted]
Immune-mediated enterocolitis	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Lichen planus	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Macular detachment	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]
Myelitis transverse	[redacted]	[redacted]
Myopathy	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Palatal oedema	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Skin fissures	[redacted]	[redacted]
Tendonitis	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Autoimmune myocarditis	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Neuralgic amyotrophy	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Polyneuropathy	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V24.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database cut-off date: 21JUN2021
Abbreviations: AE: Adverse event; APaT: All participants as treated.
Source: KEYNOTE-716 CSR[3]

b. Please tabulate and discuss the overall incidence of Grade 3-5 AEs in the trial, by arm.

In terms of drug-related Grade 3 to 5 AEs, overall incidence was higher in the pembrolizumab group ([redacted] [[redacted]%]) compared with the placebo group ([redacted] [[redacted]%]). Most drug-related Grade 3 to Grade 5 AEs were Grade 3 in severity in both the pembrolizumab group ([redacted] [[redacted]%]) and placebo group ([redacted] [[redacted]%]). There were [redacted] drug related Grade 4 AEs ([redacted]%) in the

pembrolizumab group and [redacted] ([redacted]%) in the placebo group. There were no drug-related Grade 5 AEs.

The most frequently reported drug-related Grade 3 to Grade 5 AEs in the pembrolizumab group (in ≥1.0% of participants) were autoimmune hepatitis, rash, colitis, diarrhoea, and increased lipase. Autoimmune hepatitis, rash, colitis, increased lipase, and diarrhoea are known adverse drug reactions (ADRs), or clinical manifestations of ADRs, for pembrolizumab. There were no drug related Grade 3–5 AEs with incidence ≥5% in one or both treatment arms. The incidence of all drug-related Grade 3–5 AEs reported in either group are presented in Table 14.

Table 14: Participants with drug-related Grade 3–5 AEs by decreasing incidence (incidence >0% in one or more treatment groups) (APaT population)

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Autoimmune hepatitis	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Autoimmune colitis	[redacted]	[redacted]
Autoimmune nephritis	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]
Hypopituitarism	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Asthenia	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood sodium decreased	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Endocrine disorder	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Immune-mediated enterocolitis	[redacted]	[redacted]
Lip dry	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Myelitis transverse	[redacted]	[redacted]
Myopathy	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Palatal oedema	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Polyarthritis	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
Autoimmune myocarditis	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neuralgic amyotrophy	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V24.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database cut-off date: 21JUN2021
Abbreviations: AE: Adverse event; APaT: All participants as treated.
Source: KEYNOTE-716 CSR[3]

A16. The CS states that, “The majority of patients treated with pembrolizumab (95.4%) and placebo (92.0%) took concomitant medications.”

a. Please clarify if non-protocol specified concomitant medications were used in the management of mild/ moderate/ severe adverse events in this trial (protocol violations).

b. Please tabulate and discuss the most frequently reported categories of concomitant medications, by arm.

A list of frequently reported concomitant medications (≥5% in one or more treatment group) by treatment arm is presented in Appendix L.4 of Submission Document B. The most common concomitant medications categories that were reported in >40% of patients in either treatment arm were ophthalmologicals, analgesics, stomatological preparations, corticosteroids for systemic use, antidiarrheals/intestinal anti-inflammatory/anti-infective agents, and corticosteroids for dermatological preparations. Among these categories, the following were reported more frequently in the pembrolizumab group than in the placebo group:

- Corticosteroids for systemic use ([redacted] [redacted] patients in the pembrolizumab arm versus [redacted] [redacted] patients in the placebo arm)
- Antidiarrheals/intestinal anti-inflammatory/anti-infective agents ([redacted] [redacted] patients in the pembrolizumab versus [redacted] [redacted] patients in the placebo arm)
- Corticosteroids for dermatological preparations ([redacted] [redacted] patients in the pembrolizumab arm versus [redacted] [redacted] patients in the placebo arm)

A17. Please explain how COVID-19 may have affected the KEYNOTE-716 trial in terms of:

a) Patient recruitment

In March 2020, the countries with recruitment sites for KN-716 reported a high-level impact on recruitment due to COVID-19. It was reported that there was a high probability that the last patient in (LPI) planned for 30 June 2020 would be delayed due to the impact of COVID-19. Six out of the sixteen countries stopped or limited recruitment at this time, including the United Kingdom, Italy, France, Germany, Spain and Chile. Japan was added as a new country for recruitment in March 2020 at which time, any impact on recruitment due to COVID-19 was

unforeseen. However, in June 2020, Japan requested an extension to continue enrolment until November 2020 due to the pandemic surge.

b) Treatment administration

c) Follow-up

d) Other

Standard operating procedures for study conduct, monitoring and oversight were adhered to during the COVID-19 pandemic and a risk-based approach, consistent with Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance, was used to assess and mitigate impact on study conduct. There were no changes in the planned analyses due to the COVID-19 pandemic. All protocol deviations in Part 1 of the KEYNOTE-716 study that were associated with the COVID-19 pandemic were similar across treatment groups. Most were visit deviations (e.g. missed, delayed or early) or dose deviations (e.g. missed or delayed). No patient's data were excluded from analyses due to a protocol deviation associated with the COVID-19 pandemic, and no protocol deviations that occurred due to the COVID-19 pandemic were considered important by patients or study sites. A summary of protocol deviations reported as associated with COVID-19 that were deemed to have the potential to impact interpretation of study results is provided in Table 15.

Table 15: Accounting of selected protocol deviations associated with COVID-19 (ITT population)

	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Subjects with ≥1 visit deviation, n (%)	[redacted]	[redacted]	[redacted]
≥1 visit missed	[redacted]	[redacted]	[redacted]
≥1 visit where dosing was scheduled	[redacted]	[redacted]	[redacted]
≥1 visit delayed	[redacted]	[redacted]	[redacted]
≥1 visit where dosing was scheduled	[redacted]	[redacted]	[redacted]
Subjects with ≥1 visit deviation, n (%)	[redacted]	[redacted]	[redacted]
≥1 dose missed	[redacted]	[redacted]	[redacted]
≥1 dose delayed	[redacted]	[redacted]	[redacted]
Subjects with ≥1 imaging scan deviation	[redacted]	[redacted]	[redacted]
≥1 imaging scan missed	[redacted]	[redacted]	[redacted]
≥1 imaging scan delayed	[redacted]	[redacted]	[redacted]
≥1 imaging scan early	[redacted]	[redacted]	[redacted]
≥1 imaging scan other	[redacted]	[redacted]	[redacted]
Subjects with ≥1 survival assessment deviation	[redacted]	[redacted]	[redacted]
≥1 survival assessment missed	[redacted]	[redacted]	[redacted]

	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Subjects with ≥1 safety assessment deviation	[redacted]	[redacted]	[redacted]
≥1 imaging scan missed	[redacted]	[redacted]	[redacted]
≥1 imaging scan delayed	[redacted]	[redacted]	[redacted]
≥1 imaging scan early	[redacted]	[redacted]	[redacted]
≥1 imaging scan other	[redacted]	[redacted]	[redacted]

Abbreviations: ITT: Intention to treat.

As indicated in Table 10, Document B of the company submission, a total of [redacted] deaths associated with COVID-19 were recorded in the KEYNOTE-716 trial. In addition, [redacted] patients discontinued study medication due to AEs associated with COVID-19, a further [redacted] patients discontinued due to a physician decision associated with COVID-19, [redacted] patient discontinued due to relapse/recurrence associated with COVID-19, and [redacted] patients chose to withdraw for reasons associated with COVID-19.

A18. In the company submission (CS, page 37) it is stated that: "Reported events at IA2 have reached [redacted] DMFS events and [redacted] OS events". Please provide numbers by treatment arm.

MSD are unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm, as these data are not available. As described in response to question A13, the database lock for the IA3 analysis of KEYNOTE-716 has now occurred. Full results from this analysis, which will include DMFS events by arm, are expected to be available in [redacted].[9] MSD will ensure to inform NICE about specific dates as soon as further information is available to be shared.

As explained in the clarification call on 14 March 2022 OS and DMFS data are not yet available as of the second interim analysis (IA2) data cut-off presented in this submission, due to insufficient events occurring to enable analysis of these endpoints.

Section B: Clarification on cost-effectiveness data

Model structure

B1. The model consisted of four mutually exclusive health states designed to reflect the natural history of melanoma: recurrence-free (RF), locoregional recurrence

(LRR), distant metastases (DM), and death. The DM state incorporated two sub-states (pre-progression and post-progression).

Please give the exact definition and justification of the two substates in the DM state.

a) Please clarify and justify how patients are divided over the two substates.

b) Please clarify and justify which model input parameters are different for patients in the two substates.

c) Please provide an updated economic model and scenario analysis in which it is assumed that patients who enter the DM state cannot progress further within that state (i.e. with the DM post-progression state removed).

The DM state consists of 2 sub-states: pre-progression DM and post-progression DM. This structure enables the costs and HRQoL implications of metastatic melanoma to be more accurately captured and is reflective of the health states that would typically be included in metastatic oncology modelling. This approach is also consistent with the methods used in the recent appraisal of pembrolizumab for the adjuvant treatment of stage 3 melanoma (TA766).[10]

The pre-progression DM state represents patients who have a confirmed DM recurrence; all patients who transition to the DM health state enter the pre-progression sub-state and are assumed to receive first-line systemic therapy for metastatic melanoma. The post-progression DM state represents patients who have progressed on first-line therapy; a proportion of these patients are assumed to receive second-line systemic therapy for metastatic melanoma. Therefore, by definition:

1. *Time spent in the pre-progression DM sub-state* = PFS, as measured from the time of initiating first-line treatment for advanced melanoma; and

2. *Time spent in the post-progression DM sub-state* = Overall survival (OS) minus PFS, where both OS and PFS are measured from the time of initiating first-line treatment for advanced melanoma.

3. *Total time spent in the DM state* = Sum of #1 and #2 = PFS + (OS - PFS) = OS

The ratio of PFS:OS therefore represents the proportion of time within the DM state that a patient spends in the pre-progression DM sub-state, while 1 - (PFS/OS) represents the remaining proportion of time spent in the post-progression DM sub-state.

Within the model, mean PFS (in weeks) and mean OS (in weeks) are estimated for each first-line subsequent treatment option that patients may receive in the DM state, based on published trial data in the advanced melanoma setting. (Note: These inputs and related calculations are presented on the "Effectiveness" tab of the Excel model under the section "Efficacy of advanced treatment regimens".) Mean OS following DM was then calculated for each model arm as a market share-weighted average of expected OS under different first-line treatment options. Mean PFS following DM was similarly calculated for each model arm. (These weighted average calculations are shown in the "Market Shares" tab of the Excel model under the heading "Weighted average OS and PFS in the distant metastases state".) The ratio of mean PFS:OS was then calculated for each model arm. (These weighted average calculations are shown in the "Market Shares" tab of the Excel model under the heading "Weighted average OS and PFS in the distant metastases state".) The ratio of mean PFS:OS was then calculated for each model arm, and this ratio used to determine the relative weight given to the pre-progression DM versus post-progression DM values for the following model input parameters (i.e. those that differ between the two substates):

- Subsequent treatment costs (drug acquisition and administration costs) – pre-progression DM: first line therapies; post-progression DM: second-line therapies (see CS section B.3.5.2)

- Disease management costs (see CS Table 62, section B.3.5.2)

- Utility values (see CS section B.3.4.5)

There were both conceptual and practical reasons for considering time spent pre- vs. post-progression when calculating overall DM-related utility and disease management costs:

- Upon entering the DM state, patients are expected to initiate a first-line treatment for advanced melanoma, and their subsequent health outcomes are expected to depend largely upon the efficacy of the specific treatment received. In clinical trials of treatments for advanced melanoma, efficacy is measured by the dual endpoints of PFS and OS. Although life-years in the DM state is determined solely by OS, QALYs and costs in this state depend on both PFS and OS, as prior evidence indicates meaningful differences in utility[11, 12] and disease management costs[13] before vs. after progression. To more accurately capture HRQoL and costs during the period of time from distant recurrence until death, both pre- and post-progression utility and disease management cost inputs are considered within the DM state.

- Prior NICE appraisals in advanced melanoma settings have conventionally used three-state partitioned survival models that extrapolate PFS and OS to estimate time spent in

the pre- and post-progression DM states. By considering the proportion of time spent pre- vs. post-progression within the DM state, the present model captures downstream costs and health outcomes of stage IIB-IIC melanoma in a way that aligns with HTA precedence from advanced melanoma indications.

- Relatedly, because past NICE appraisals in advanced melanoma have distinguished between pre- and post-progression DM, relevant input values were more readily available for these sub-states than for the overall DM state. For example, healthcare resource use frequencies from TA319 were leveraged to compute disease management costs in the pre- and post-progression DM states.[13]

In row 75 of the Specifications tab of the Excel model, a new dropdown menu has been added for "Assume no progression in the distant metastases state?" (set to "No" under the base case). Under an exploratory scenario assuming no progression in the DM state, utility and per-cycle disease management costs in the post-progression DM sub-state are assumed to equal that of the pre-progression DM sub-state, and no costs of second-line treatment for advanced melanoma are included. This scenario is assumed to have no impact on the duration of the first-line treatment for advanced melanoma; this is a conservative assumption, as first-line therapy for advanced melanoma is expected to continue until progression and use of adjuvant pembrolizumab for resected stage 2B-2C melanoma reduces the probability that a patient will develop advanced melanoma. This scenario generates an ICER of £3,843 per QALY.

Population, intervention and comparator

B2. Priority question. The dosage used in the economic model is 400mg administered every 6 weeks.

a) Referring to question A8, please further justify this dosage in terms of likely use in the NHS in England.

b) Please conduct sensitivity analyses, one using 200 mg every 3 weeks (Q3W), and the other using a mixture of dosing regimens according to likely use in the NHS in England. Please also provide an updated economic model including these analyses.

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 400 mg every

6 weeks (Q6W) in addition to the already approved dose of 200 mg every 3 weeks (Q3W), across all monotherapy indications. As discussed in question A8, modelling and simulation exercises demonstrated that there are no clinically significant differences in efficacy or safety between 400 mg Q6W dosing and 200 mg Q3W dosing.[4]

Compared with the Q3W dosing regimen, clinical experts have 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 with no increase in toxicity.[8, 14] Consequently, Q6W dosing has been particularly crucial in assisting with capacity and social distancing measures during the COVID-19 pandemic. Clinicians have indicated that they expect this dosing schedule to remain standard practice after the pandemic and its use is now mandated in some centres.[8, 14] Given the capacity constraints currently faced by the NHS, it is anticipated that pembrolizumab will be given Q6W in most practices as familiarity with the Q6W dosing schedule increases and as centres seek to increase efficiency in service delivery.

However, MSD acknowledge that there may be some regional variation in the use of the Q6W dosing regimen, therefore a scenario was presented to explore the impact of using Q3W pembrolizumab dosing instead (please see CS Table 70, p132 – Scenario 18). This scenario can be replicated in the economic model by editing as necessary the percentages in cells L102:L104 on the 'Specifications' tab. Market research conducted by MSD (in May to September 2021) suggests that [redacted]% of patients receiving adjuvant pembrolizumab for stage 3 melanoma and [redacted]% of patients receiving pembrolizumab in the metastatic setting are on a 400 mg Q6W dosing schedule, either from the point of initiation or switched from Q3W shortly thereafter.[15] The latest Ipsos Oncology Monitor market research suggests that [redacted]% and [redacted]% of patients on pembrolizumab in the adjuvant and metastatic settings, respectively, were on a Q6W dosing schedule.[16] However, the Ipsos data do not account for patients who initiated Q3W and then switched to Q6W regimens shortly after, therefore the total proportion of the incident recipients who get Q6W for most of their time on treatment may be underestimated. Scenarios using these the values from these sources are presented in Table 16, and can be replicated by editing as necessary the percentages in cells L102:L104 on the 'Specifications' tab. Given prior experience in the stage 3 setting and the capacity constraints in the NHS, MSD anticipates the adoption of Q6W will be closest to the MSD market research estimates.

Table 16: Scenario analyses – Alternative pembrolizumab dosing regimens

Scenario	% on Q6W regimen (Adjuvant / Metastatic)	ICER (£/QALY)
All on Q3W (see CS Table 70, p132 – Scenario 18)	0% / 0%	£5,300
MSD market research	[redacted]	£4,824
Ipsos Oncology Monitor	[redacted]	£4,940

† The Ipsos data do not account for patients who initiate pembrolizumab on a Q3W dosing schedule, and then switch to Q6W shortly thereafter, therefore the total proportion of incident pembrolizumab recipients who receive Q6W regimens for most of their time on treatment may be underestimated.

B3. Based on the results of analyses requested in question A10, please perform subgroup analyses with patients with stage 2B and patients with stage 2C disease. Please also provide an updated economic model including these analyses.

As discussed in response to question A10, subgroup analyses by T-staging were pre-specified over the American Joint Committee on Cancer (AJCC) staging. T-staging is static, whereas AJCC staging is subject to change and as such T-staging was favoured to allow interpretation to remain possible when the AJCC is updated. All subgroup analyses on the KEYNOTE-716 trial are not statistically powered to detect any differences in efficacy between treatment arms, and additional subgroup analysis by AJCC staging (compared with pre-specified analyses based on T-staging) would be conducted post-hoc. As such, subgroup analyses for RFS, separated by patients with stage 2B and stage 2C disease, have not been presented here – however, these post-hoc analyses are provided in the KEYNOTE-716 CSR. The marketing authorisation for pembrolizumab is expected to apply to the intention to treat population from KEYNOTE-716, therefore it is considered most relevant to assess the cost-effectiveness of pembrolizumab for the entire eligible population.

Effectiveness

B4. Priority question. Although CS section B3.3 contains an extensive description of the estimation of the transition probabilities in the economic model, consideration of the separate parametric survival curves is limited. Please provide separately for all individual parametric survival curves that were estimated (i.e. all parametric curves for 1) RF→LRR; 2) RF→DM; 3) RF→Death; 4) LRR→DM and; 5) LRR→Death) separately for the intervention and comparator:

a) **Kaplan-Meier curve with the estimated parametric survival models (ensuring that the curves on the Figures can be visually distinguished)**

One important clarification is that the 6 individual parametric distributions fitted to the cause-specific hazards of a given transition (e.g., RF→LRR) cannot be visually inspected separately from the distributions fitted to other transitions (e.g., RF→DM). Each unique combination of distributions for RF→LRR / RF→DM / RF→Death yields a distinct extrapolation not only of the composite endpoint RFS, but also of the cumulative incidences of each transition starting from the RF state. In total, 54 unique combinations of distributions were available for consideration, as summarized in Table 17.

Table 17: Summary of unique combinations of distributions considered for base case

Overall approach	**Distributions fitted to the cause-specific hazards of each transition:**			**# of potential combinations of distributions**
	RF→LRR	***RF→DM***	***RF→Death***	
Approach #1: Parametric models separately fitted to each treatment arm	Exponential Weibull Gompertz Log-normal Log-logistic Generalized gamma	Exponential Weibull Gompertz Log-normal Log-logistic Generalized gamma	Exponential*	36 (=6*6*1)
Approach #2: Proportional hazards parametric models jointly fitted to both arms with a time-constant HR	Exponential Weibull Gompertz	Exponential Weibull Gompertz	Exponential*	9 (=3*3*1)
Approach #3: Proportional hazards parametric models jointly fitted to both arms with a time-varying HR – *allows for different treatment effect before vs. after 1 year, based on the maximum duration of adjuvant treatment*	Exponential Weibull Gompertz	Exponential Weibull Gompertz	Exponential* **(due to the small number of direct RF to death transitions)*	9 (=3*3*1)
			Total:	54

It is also important to state that LRR→DM and LRR→Death transitions could not be modelled using KEYNOTE-716 IA2 data and were instead assumed to depend on the treatment that patients received in the LRR state (i.e., whether or not they received one of the adjuvant treatments approved for resected stage 3 melanoma, and which of these stage 3 adjuvant treatments was received, if any). For patients who receive no adjuvant treatment in the LR state, exponential models of LR→DM and LRR→Death were fitted as part of a real-world study using US Oncology Network (USON) electronic health records (see CS section B.3.3.2). Competing risk-adjusted cumulative incidence curves for LRR→DM and LRR→Death based on USON data were not produced due to data privacy rules for this data source.

A series of graphs provided below present the predictions generated by different combinations of parametric functions against observed data, using the approach recommended by Williams et al.

(2017).[17, 18] In lieu of competing risk-adjusted cumulative incidence curves based on the USON data, the following figures are included:

- Predicted vs. observed cumulative incidence of RF→LRR (Figure 1), RF→DM (Figure 2), and RF→Death (Figure 3) in each arm
    - Note: The observed curves in these graphs are competing risk-adjusted cumulative incidence curves generated using the *cuminc*() function from the R package *cmprsk*. (In the presence of competing risks, it would have been incorrect to compute cumulative incidence curves using the Kaplan-Meier method.)
- Predicted vs. observed RFS in each arm (Figure 4)
- Predicted vs. observed time from LRR to DM or death among patients in the US Oncology Network (USON) cohort who received no subsequent adjuvant therapy for LRR (Figure 5)
- External validation of predicted DMFS in the observation arm vs. observed DMFS in the real-world stage 2B-2C melanoma cohort from the USON study (Figure 6)
    - *Note:* Predicted DMFS depends upon the combination of distributions used for RF→LRR, RF→DM, RF→Death, LRR→DM, and LRR→Death. Because exponential distributions are used for transitions starting from LRR, there are 54 different combinations of distributions that yield different extrapolations of DMFS.

Apart from the figure presenting time from LRR→DM or LRR→Death (Figure 6), the graphs below present different extrapolations based on all 54 possible combinations of parametric functions. Solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1). Dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2). Dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3). In the figures for RF→LRR, each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→LRR, while the different shades within a colour family represent different distributions fitted to the cause-specific hazards of RF→DM. In the figures for RF→DM, RF→Death, RFS, and DMFS, each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→DM, while the different shades within a colour family represent different distributions fitted to the cause-specific hazards of RF→LRR.

Key takeaways from each graph are summarized in Table 18.

Table 18: Key takeaways from validation figures

Figure	Interpretation
Error! Reference source not found.**: Predicted vs. observed cumulative incidence of RF→LRR in each arm**	All combinations of parametric functions produced a close visual fit to the observed cumulative incidence of RF→LRR.
Figure 2: Predicted vs. observed cumulative incidence of RF→DM in each arm	The 12 combinations using exponential for the cause-specific hazards of RF→DM demonstrated worse visual fit to the cumulative incidence of RF→DM, and were excluded from base-case consideration.
Figure 3: Predicted vs. observed cumulative incidence of RF→Death in each arm	During the trial period, fit was indistinguishable between different combinations of parametric functions due to the very small number of observed RF→Death events in KEYNOTE-716. The large divergence seen in the long-term is due to the interplay between competing risks and background mortality: Under combinations of distributions that yield low risks of LRR and DM, more patients are estimated to die directly from RF (rather than from LRR or DM) once patients reach ages at which background mortality is high.
Figure 4: Predicted vs. observed RFS in each arm	Combinations using exponential for the cause-specific hazards of RF→DM demonstrated worse visual fit to observed RFS.
Figure 5: Predicted vs. observed time from LRR to DM or death among patients in the US Oncology Network cohort who received no subsequent adjuvant therapy for LRR	Using exponential distributions for the cause-specific hazards of LRR→DM and LRR→Death produced a suitably close fit with time from LRR to DM or death among patients who receive no adjuvant treatment following LRR.
Figure 6: External validation of predicted DMFS in the observation arm vs. observed DMFS in the real-world stage 2B-2C melanoma cohort from the USON study	Results from this external validation strongly supported the selected base-case combination of distributions. Combinations using log-normal for the cause-specific hazards of RF→DM yielded the closest visual fit to observed real-world DMFS over a 10-year time horizon.

Figure 1. Predicted vs. observed cumulative incidence of RF→LRR in each arm

Figure 2. Predicted vs. observed cumulative incidence of RF→DM in each arm

Figure 3. Predicted vs. observed cumulative incidence of RF→Death in each arm

Figure 4. Predicted vs. observed RFS in each arm

Figure 5. Predicted vs. observed time from LRR to DM or death among patients in the USON cohort who received no subsequent adjuvant therapy for LRR

Figure 6. External validation of predicted DMFS in the observation arm vs. observed DMFS in the real-world stage IIB-IIC melanoma cohort from the USON study

Solid lines: Approach #1; dashed lines: Approach #2; dotted lines: Approach #3.

b) Tables with the numbers of patients at risk, per 3 months.

Table 19 summarizes the number at risk for RFS failure at 3-month intervals in each arm of KEYNOTE-716. (Number at risk for RFS failure is also summarized at weekly intervals within the Excel model; see columns M and P in the tab “Observed survival curves”. The number at risk at each weekly interval was used in the calculation of mean squared error [MSE] for predicted vs. observed RFS, as described in response to question B10.) Table 20 summarizes the number at risk for DM or death from LRR among patients in the US Oncology Network study who were included in the survival analyses of LRR→DM and LRR→Death. The included patients (N=[redacted]) had undergone surgical resection of stage 2B or IIC melanoma, were subsequently identified as having LRR, and received no adjuvant treatment for LRR. Due to data privacy rules for this data source, numbers at risk are reported at 9-month intervals only.

Table 19: Number at risk for RFS failure in KEYNOTE-716

Months	N at risk for RFS failure in KEYNOTE-716	
	Pembrolizumab	Placebo
0	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
9	[redacted]	[redacted]
12	[redacted]	[redacted]
15	[redacted]	[redacted]
18	[redacted]	[redacted]
21	[redacted]	[redacted]
24	[redacted]	[redacted]
27	[redacted]	[redacted]
30	[redacted]	[redacted]

Table 20: Number at risk for DM or death from LRR among patients in the USON who received no adjuvant treatment following LRR

Months	N at risk
0	[redacted]
9	[redacted]
18	[redacted]
27	[redacted]

c) Tables with Goodness of fit statistics (AIC and BIC).

An explanation of why AIC and BIC are not suitable measures of statistical fit in the presence of competing risks is provided in response to question B10. As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, assessing model fit is more challenging in the context of multistate models than partitioned survival models (PSMs), as the target outcomes of interest are determined by a combination of survival models rather than by a single survival model.[19] This is true not only for composite endpoints such as RFS, but also for the cumulative incidences of specific transitions such as RF→LRR, RF→DM, and RF→Death. As illustrated by the long-term figures provided in response to B4.a, the 54 unique combinations of parametric functions each yielded different cumulative incidence curves for these three transitions. Consequently, the selection process required a measure of statistical fit that would allow all possible combinations of distributions for the cause-specific hazards of RF→LRR, RF→DM, and RF→Death to be ranked.

Mean squared error (MSE) was therefore used in place of the AIC/BIC statistics that would normally be presented for PSMs, in which parametric distributions are fitted to composite endpoints such as RFS. MSD believe that this MSE-based approach aligns with best practice recommendations from NICE DSU TSD 14, while making necessary adjustments to accommodate the differences between multistate models vs. PSMs. As described in response to B10, the calculation of MSE accounted for the number of patients at risk at each weekly interval along the observed RFS curve.

As shown in CS Table 26 and Table 27, MSE statistics supported the exclusion from consideration for the base case of all 12 combinations of distributions that used exponential distributions for the cause-specific hazards of RF→DM, consistent with the exclusions made based on visual inspection (see response to B4.a above).

d) To examine the proportional hazard assumption:

i. Plot the scaled Schoenfeld residuals versus time (all survival curves)

ii. Plot the log cumulative hazard versus log time

Schoenfeld residual plots are provided in Figure 7. Log-cumulative hazard plots are presented in Figure 8.

Figure 7: Schoenfeld residual plots for KEYNOTE-716 RFS and cause-specific hazards

Figure 8: Log-cumulative hazard plots for KEYNOTE-716 RFS and cause-specific hazards

Schoenfeld residual plots are used to check the independence between time and the scaled Schoenfeld residuals from a Cox proportional hazards (PH) model with a time-constant treatment covariate. In principle, a random pattern of Schoenfeld residuals against time shows support of the PH assumption. The 'curvy' lines in the Schoenfeld plots provided in Figure 7 indicate a random pattern of Schoenfeld residuals and provide support for the PH assumption in KEYNOTE-716. The log-cumulative hazard plots in Figure 8 show generally parallel lines between treatment arms, providing further support for the PH assumption.

This reinforces the suitability of applying Approach #2 and Approach #3 (described in CS section B.3.3.1) to estimate the transition probabilities from RF state. However, as elaborated in CS section B.3.3.1 and here in response to question B4.g, models using Approaches #2 and #3 generally performed less well in terms of statistical fit and external validation compared to individually fitted parametric distributions (Approach #1; independent fitting given the availability of PLD from KN-716) which were also preferred based on guidance provided in NICE DSU TSD 14.[20]

e) To examine the heuristics of the hazard function over time:

i. Plot the smoothed hazards over time

Smoothed hazard plots are used to assess the fit of parametric distributions fitted to KM data for traditional partitioned survival modelling. As explained in response to question B4.a, the parametric distributions fitted to the cause-specific hazards of a given transition (e.g., RF→LRR) cannot be visualised separately from the distributions fitted to other transitions (e.g., RF→DM). Each unique combination of distributions for RF→LRR / RF→DM / RF→Death yields a distinct extrapolation not only of the composite endpoint RFS, but also of the cumulative incidences of each transition starting from the RF state. Thus, assessment of fit and selection of base case distributions produced using a competing risks approach as applied in the current multistate model cannot be handled in the same way as in a partitioned survival model. Given competing risks, it is not appropriate to use smoothed hazard plots to assess the fit of parametric functions to cause-specific transitions or inform selection of the base case parametric models. Furthermore, assessing the fitting of parametric distributions to cause-specific hazards without adjustment for competing risk will overestimate the transition probabilities.

f) To examine diagnostics of parametric survival models (using the observed data):

i. Plot the cumulative hazard versus time

ii. Plot the log smoothed hazard versus time

iii. Plot the standard normal quartiles versus log time

iv. Plot the log survival odds versus log time

As iterated in the response to B8.c, to obtain a complete set of transition probabilities for the present Markov model, it was necessary to select an approach that would yield probabilities of each individual transition from the RF state (i.e., RF→LRR, RF→DM, and RF→Death), rather than just the composite probability of any RFS failure event in each cycle. If parametric functions were fitted directly to RFS KM data, it would require more assumptions to disaggregate the composite probability into separate probabilities of RF→LRR, RF→DM, and RF→Death. This approach would have required stronger assumptions and was thus considered less robust than our selected multistate modelling approach.

Furthermore, the AIC/BIC ranking and diagnostic plots of six standard parametric distributions directly fitted to RFS KM data (for the validation exercise described in CS section B.3.10) are not necessarily consistent across pembrolizumab and routine surveillance arms which may lead to diverging conclusions. After implementing the 95% risk reduction to all six standard parametric distributions directly fitted to RFS KM data in this validation exercise, it was observed that Gompertz and Generalized gamma functions resulted in implausible cross-over of pembrolizumab and routine surveillance arms (see figures provided in question B23). Among the four remaining parametric distributions, exponential and log-logistic are the two directly fitted validation distributions which align closest to model predicted RFS. Therefore, it is not necessary to provide plots requested in B4 (e) and (f) to assess the fit of different parametric distributions to RFS data.

g) To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted.

Extensive external validation of the estimated extrapolations for RFS, DMFS and OS was provided in CS section B.3.3.1, and a summary of the process for selecting the most appropriate base case functions was provided in CS Appendix M, Table 42. To summarise, the plausibility of long-term extrapolations was assessed as follows:

- Initial exclusions based on clinical plausibility: Due to clinical implausibility, combinations of parametric functions that resulted in crossing RFS curves (i.e., higher long-term RFS under routine surveillance compared with pembrolizumab) were excluded from consideration as base case. This exclusion was supported by the available data from KEYNOTE-716, as well as longer-term RFS and DMFS data from the KEYNOTE-054 trial of pembrolizumab as an adjuvant treatment of resected high-risk stage 3 melanoma. Combinations were further excluded if they resulted in lower 4-year RFS and/or DMFS for either pembrolizumab or observation than that reported for the corresponding arms of KEYNOTE-054, given the expectation of better prognosis in the stage 2B-2C population.

- External validation of predicted RFS, DMFS, and OS in the routine surveillance arm: Longer-term extrapolations in the routine surveillance arm were externally validated against observed data from several real-world studies (see CS Table 28). Specifically, survival projections in the routine surveillance arm were validated against long-term RFS, DMFS, and OS observed in a real-world cohort study among patients with resected stage 2B or 2C melanoma using US Oncology Network electronic health records.[21, 22] Additional sources used for external validation included three published studies that reported long-term RFS and/or OS in real-world cohorts of patients diagnosed with AJCC 8th edition stage 2B or 2C melanoma.[23-25] For each of these three published sources, the following steps were performed: (1) RFS and/or OS were extracted separately for the stage 2B and 2C subgroups (using digitized KM data where available); and (2) these subgroup-specific results were then pooled as a weighted average to obtain RFS and/or OS for the combined stage 2B/2C target population, based on the percentages of patients with stage 2B vs. 2C melanoma in KEYNOTE-716.

Findings from these external validity/plausibility assessments are detailed below:

- Initial exclusions based on clinical plausibility: Of the 54 combinations of parametric distributions under consideration, 12 combinations were initially excluded based on these criteria (see CS Appendix M, Table 42).

- External validation of predicted RFS, DMFS, and OS in the routine surveillance arm: Predicted RFS in the observation arm was validated against long-term RFS data from two external studies. Across the Bajaj et al. (2020) study and the US Oncology Network study, RFS for observation ranged narrowly over a 7-year period (e.g., RFS at 7 years ranged from 33.6% to 35.0%; simple average: 34.3%); 10-year RFS for observation was only available from the US Oncology Network study, at 23.2% although there were a very small number at risk at 10 years ([redacted]). Given the close alignment of RFS and the generalisability to the UK of these two studies, and the fact that management of stage

2B/2C patients has not changed since these studies were conducted, further exclusions were applied based on the requirement that predicted RFS for routine surveillance must fall within the range of these studies ±5 percentage points over 7 years. Twelve of the 54 combinations of distributions met this external validity requirement (CS Appendix M, Table 42), and all other combinations were tentatively excluded from further consideration for the base case analysis. Focusing on the 30 combinations of distributions that were not previously excluded due to suboptimal visual/statistical fit or based on initial plausibility assessments, Table 21 uses color-coding to illustrate which combinations met this external validity requirement in each year from years 1-7.

Table 21: External validation among the 30 combinations of distributions not previously excluded based on visual inspection, statistical fit, or initial plausibility assessments

RFS (%) by year:	1 yrs	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	10 yrs
Real-world cohort, observed RFS (Bajaj et al. 2020)	87.4	64.6	56.7	48.7	44.2	41.4	33.6	--
Real-world cohort, observed rwRFS (USON)	85.6	70.9	58.0	50.1	43.2	37.5	35.0	23.2
Pooled, Bajaj et al. (2020) and USON study (simple average)	**86.5**	**67.8**	**57.4**	**49.4**	**43.7**	**39.5**	**34.3**	**--**

Rank by MSE	Approach #	Parametric functions		MSE vs. observed RFS	Predicted RFS							
		RF → LR	RF → DM		1 yrs	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	10 yrs
1	**#1**	**Weibull**	**Generalized gamma**	**0.0000812**								
2	#1	Log-logistic	Generalized gamma	0.0000828								
3	**#1**	**Gompertz**	**Generalized gamma**	**0.0000834**								
4	#1	Exponential	Generalized gamma	0.0000846								
5	#1	Generalized gamma	Generalized gamma	0.0000858								
6	**#1**	**Log-normal**	**Log-normal**	**0.0000987**								
7	#1	Log-normal	Generalized gamma	0.0000989								
8	**#1**	**Generalized gamma**	**Log-normal**	**0.0001078**								
9	**#1**	**Log-logistic**	**Log-normal**	**0.0001129**								
10	#1	Exponential	Log-normal	0.0001137								
11	#1	Gompertz	Log-normal	0.0001151								
12	#1	Weibull	Log-normal	0.0001168								
13	#1	Log-normal	Log-logistic	0.0001182								
14	#1	Log-normal	Weibull	0.0001248								
15	#1	Generalized gamma	Log-logistic	0.0001306								
16	#1	Log-logistic	Log-logistic	0.0001372								
17	#1	Generalized gamma	Weibull	0.0001390								
18	#1	Exponential	Log-logistic	0.0001395								
19	#1	Gompertz	Log-logistic	0.0001411								
20	#1	Weibull	Log-logistic	0.0001426								
21	#1	Log-logistic	Weibull	0.0001462								
22	#1	Exponential	Weibull	0.0001487								
23	#1	Gompertz	Weibull	0.0001506								
25	#1	Weibull	Weibull	0.0001522								
24	#2	Gompertz	Weibull	0.0001509								
29	#2	Weibull	Weibull	0.0001581								
31	#2	Exponential	Weibull	0.0001609								
26	#3	Gompertz	Weibull	0.0001536								
33	#3	Weibull	Weibull	0.0001638								
34	#3	Exponential	Weibull	0.0001668								

Cells highlighted in green show predicted RFS is within ±5 percentage points of observed RFS averaged across Bajaj et al. (2020) and USON.

- Of the 30 combinations of distributions that were not already excluded, 5 combinations of distributions met this external validity requirement; 3 combinations (in bold below) were also within +/- 5 percentage points of the USON study at 10 years. These five combinations were therefore prioritised and further assessed for appropriateness for the base case model:
    - Weibull/Generalized gamma under Approach #1 (separately fitted)
    - Gompertz/Generalized gamma under Approach #1 (separately fitted)
    - **Log-normal/log-normal under Approach #1 (separately fitted)**
    - **Generalized gamma/log-normal under Approach #1 (separately fitted)**
    - **Log-logistic/ log-normal under Approach #1 (separately fitted)**

- (Note that seven additional combinations which used exponential for the RF→DM transition also met this requirement but had higher MSE and had therefore been excluded based on statistical fit. Given the close fit to external data, these were considered for scenario analyses.)

- RFS, DMFS and OS predictions for these five combinations of functions compared with the observed data from external sources over 10 years are presented in Figures 8–11 in section B.3.3.1 of the CS. A full discussion of each of these figures is also provided in the CS. Note that all studies (and in particular the study by Bleicher et al, 2020[24]) enrolled patients diagnosed before recent advances in treatment for stage 3 and metastatic melanoma were available. These advances have resulted in significantly improved survival rates therefore the OS estimates in these sources may be underestimated relative to current clinical practice.

h) Please justify the selection of the parametric survival curve, taking into account the responses to the preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.

The base-case combination of parametric distributions was selected based on statistical fit and visual assessment in conjunction with external validity / clinical plausibility of the long-term extrapolations, as described in CS section B.3.3.1 and in response to parts a–g of this question. The selection criteria are aligned with best practice recommendations from the NICE DSU TSD 14,[20] with some necessary modifications based on the differences between multistate models vs. PSMs. (Namely, as described in response to B4.c, statistical fit was assessed using MSE instead

of AIC/BIC, and the selection process compares different combinations of survival models rather than single survival models.)

The Lognormal-Lognormal combination for RF→LRR and RF→DM, respectively, was the most consistent with external sources for routine surveillance RFS over 10 years and provided a middle-ground estimate in terms of the treatment benefit of pembrolizumab versus routine surveillance. There was less scope to differentiate between the plausible curves for DMFS and OS, therefore RFS fit was prioritised in the selection process – however, DMFS and OS estimates were also aligned with the external sources available. The exponential function was used to model the transition from RF→Death due to the small number of death events that had occurred in the RFS analysis at IA2.

An overview of this selection process is provided in Table 22.

Table 22: Summary of selection process for base-case parametric distributions of RF→LRR and RF→DM

Step #	Description of criterion applied at each step	# combinations of distributions that meet criterion
0	**All candidate combinations of parametric functions** Included total of 54 combinations, including 36 under Approach #1 (separately fitted), 9 under Approach #2 (jointly fitted, time-constant HR), and 9 under Approach #3 (jointly fitted, time-varying HR)	54
1	**Initial exclusions based on clinical plausibility** 12 out of 54 combinations of parametric distributions were excluded when using 4-year RFS and DMFS in KEYNOTE-054 (adjuvant stage III melanoma setting) as lower bounds 6 of these 12 combinations also resulted in implausible crossing of the survival curves for pembrolizumab and observation	42
2	**Statistical fit based on MSE vs. observed RFS** MSEs vs. observed RFS were ranked for all 54 combinations of distributions in each arm In both treatment arms, and across Approaches 1 – 3, the 12 combinations that used exponential for RF → DM had larger MSEs relative to other options, and were therefore excluded from consideration as base case	30
3	**Visual assessment of fit** Visual assessment aligned with MSE statistics: the 12 combinations of distributions that used exponential for RF → DM yielded slightly worse visual fit to this transition, particularly during the first 6 months, and were excluded from consideration as base case	30
4	**External validity / clinical plausibility of long-term RFS, DMFS, and OS in the observation arm** Predicted RFS in the observation arm up to 7 years was required to fall within ±5 percentage points of external RFS data averaged across two real-world cohort studies.	5 **Base case:** Approach 1 / log-normal / log-normal

	Among the 30 combinations not excluded at the previous step, 5 combinations were retained for further consideration based on this external validity assessment. Three of these 5 combinations used log-normal for RF→DM, and all 5 combinations were based on Approach #1. The selected base case yielded RFS predictions that were closest to the two external studies at 5-7 years and remained within ±5 percentage points at 10 years. External validations of the base case against digitized external RFS and DMFS data were very encouraging and provided strong empirical support for the model's long-term survival projections in the observation arm. Predicted OS followed the trends observed in the external data although was slightly above real-world OS data; however recent advances in the treatment of stage 3 and metastatic melanoma have resulted in significantly improved survival rates therefore the OS estimates in these sources may be underestimated relative to current clinical practice.	

B5. Priority question. For the patients in the RF health state, the risk (relative to the parametric function) was assumed to linearly decrease from 7 years until a 95% risk reduction is reached at 10 years.

a) **Please provide supporting empirical evidence (other than referring to NICE TAs) clearly supporting this assumption, including the assumed time points and percentages.**

b) **Please provide an updated economic model and results for a scenario without assuming that for the patients in the RF health state, the risk (relative to the parametric function) begins to linearly decrease from 7 years until a 95% risk reduction is reached at 10 years, i.e. assuming no decrease in risk over time.**

Active treatment strategies for stage 2 melanoma are a relatively recent development in melanoma research, and therefore there is limited long-term published evidence reporting on the risk of recurrence over time in the stage 2 setting. Accordingly, MSD are not aware of a published study that explicitly evaluates the change in recurrence risk over time. However, a retrospective analysis by Lee et al, 2017 of 738 patients with resected stage 2 melanoma (226 stage 2B, 112 stage 2C) treated between 1993 and 2013 demonstrated that, among patients who had a relapse, half of all relapses occurred in the first 2 years after resection (23 months for stage 2B and 15 months for stage 2C).[26] As illustrated in Table 23, 114/125 (91.2%) of relapses occurred in the first 5 years and are skewed towards earlier relapses, while the cumulative incidence figures presented in the study publication illustrate that few relapses were detected

after 5 years and that the rate at which the cumulative incidence increases slows as time progresses.[26] Two further retrospective studies in stage 1-2 and stage 1-3 melanoma reported that 73% to 90.7% of recurrences were recorded in the first 5 years of follow-up.[27, 28]

Table 23: Number of relapses over time, by substage

Substage (Patients in study)	Absolute number of recurrences				
	≤3 years	3-4 years	4-5 years	>5 years	Total
Stage 2B (N=226)	56	7	4	6	73
Stage 2C (N=112)	41	4	2	5	52

Table recreated from Lee et al, 2017[26]

In addition, there are now long-term 7-year data from the EORTC-18071 trial in resected stage 3 melanoma demonstrating a distinctive plateau in the RFS curves from 3 years and showing that very few recurrences occur after 5 years (and virtually none after 7 years).[29] While this is in the stage 3 setting and may not be directly generalisable to stage 2B/2C melanoma, it is likely that the general trends remain applicable.

In the stage 2 setting resection surgery is performed with 'curative intent' and a proportion of patients will have no further recurrences. A recent study by Eriksson et al, 2021 estimated that 62% and 42% of patients with resected stage 2B and 2C melanoma, respectively, would be cured by surgery (weighted average: 53.9%).[30] Clinical experts were highly supportive of the assumption that any patients who reached 10 years without recurrence were very unlikely to subsequently have a recurrence. They also stated that the risk decreases with time, and therefore the risk at 5 years is much less than at baseline and by 10 years the risk is extremely small. Accordingly, they felt that the RFS curves estimated by the model without applying a risk reduction were pessimistic and underestimated long-term RFS. These curves also appear implausible in the context of the estimated cure proportions reported by Eriksson et al. Given the body of published evidence demonstrating that few recurrences occur after 5 years, and expert clinical opinion, it is a conservative assumption to apply the risk reduction starting from 7 years until the maximum reduction is reached at 10 years. This assumption was supported by UK clinical experts.[8, 14]

Since parametric functions cannot provide an absolute constant estimate of recurrence risk that is meaningful between different patient cohorts, there is no empirical evidence on the appropriate risk reduction percentage to apply to the parametric model. Instead, the 95% risk reduction was selected based on prior precedent in HTA appraisals and clinical expert opinion that recurrence after 10 years is highly unlikely but never zero. If the risk of recurrence was zero after 10 years, the risk reduction would be 100%; a 95% risk reduction reflects that the risk after this point is expected to be very low, but not zero. The impact of decreasing the risk reduction percentage to 80% was explored in a scenario analysis (please see CS Table 70, p132 – Scenario 6).

A scenario in which the risk reduction assumption is not applied yields an ICER of £12,626 per QALY. This can be implemented in the model by selecting 'No' from the dropdown in cell K46 on the 'Specifications' tab. However, MSD wish to reiterate that this scenario should be considered to estimate unrealistically pessimistic RFS outcomes in light of the available evidence and expert clinical opinion based on the conducted model validations.

B6. Priority question. In the CS base-case no treatment waning was assumed (according to CS Table 25), i.e. transition probabilities from the LR health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon.

a) **Please justify the assumption of no treatment waning, i.e. that there is a lifetime difference in transition probabilities from the LR health state based on the initial treatment.**

b) **Please provide an updated economic model and scenario analyses while assuming treatment waning (at different time points).**

Firstly, MSD would like to clarify that the model assumes that the transition probabilities **from the RF state** are assumed to be different for pembrolizumab and routine surveillance for the duration of the time horizon, not those from the LRR state. Therefore it is **conservatively assumed that there is no ongoing treatment benefit of adjuvant pembrolizumab after recurrence**, therefore baseline transition probabilities from the LRR and DM health states are the same in both treatment arms. These transition probabilities from the LRR and DM states are then adjusted based on the relative efficacy of subsequent therapies received in each state, therefore the transitions from these states differ based only the market shares of subsequent therapies applied in each treatment arm. As a result, the transition probabilities from LRR→Death actually favour routine surveillance.

Secondly, there are two approaches through which pembrolizumab is anticipated to provide a lasting treatment effect:

1. **'Immune surveillance' mechanism of action of pembrolizumab**
   Immunotherapies activate and enhance the ability of the patient's immune system to recognise and destroy tumour cells and micro-metastases.[31] The potential for immune memory enables the activated immune system to continue to identify and remove residual disease after stopping therapy, and therefore this 'immune surveillance' effect of pembrolizumab is expected to be maintained after stopping adjuvant therapy.

2. **Removal of residual micro-metastases**
   Given the setting in which adjuvant therapy is given (i.e. following curative intent surgery), it is expected that a proportion of patients in both arms will never have a melanoma recurrence. Adjuvant therapy is intended to supplement surgery by removing any residual micro-metastatic disease to further reduce the risk of recurrence and progression to metastatic disease.[8, 10] It is therefore expected that adjuvant pembrolizumab will increase the proportion of patients who have no residual micro-metastatic disease and who will therefore never have disease recurrence. For these patients, it is illogical to consider that the treatment effect (i.e. the removal of residual micro-metastases) would be reversed.

The maintenance of the pembrolizumab treatment effect after stopping therapy is supported by evidence from several large clinical studies:

- KEYNOTE-716: After 20.5 months follow-up, there is no evidence of the RFS curves converging and therefore no evidence of an increasing relative hazard of recurrence for pembrolizumab over time

- In the stage 3 adjuvant treatment setting, KEYNOTE-054 provides RFS data for adjuvant pembrolizumab vs placebo that demonstrates a durable separation of RFS curves from month 3 which is sustained for the duration of follow-up (median 45.5 months).[32] This effect has also been observed in other adjuvant immunotherapy trials in melanoma: over 4 years with nivolumab in CheckMate238[33] and over 7 years with ipilimumab in EORTC-18071.[29]

- In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years. In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation.[34] The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule.[35] The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials (Figure 9 and Figure 10). This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma patients.

- Studies in metastatic melanoma have demonstrated that immunotherapies are associated with prolonged survival over time in a subset of patients with metastatic disease across several tumours. In melanoma specifically, the ‘immune-therapeutic’

effect has been characterised in multiple studies of which all demonstrate a prolonged and durable survival benefit, supporting an enduring treatment effect.[34, 36-38]

Figure 9: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001 and KEYNOTE-006

A) Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001

B) Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006

Figure 10: Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in advanced melanoma

Further, evidence reported in Lee et al, 2017 indicates that most recurrences in stage 2 melanoma occur in the first two years post-surgery, and that the risk of recurrence decreases with time spent recurrence-free.[26] Therefore, for the treatment benefit of pembrolizumab relative to routine surveillance to be lost over time, the hazard of recurrence with pembrolizumab would have to either increase over time, or decrease significantly less versus routine surveillance, such that the risk of recurrence with pembrolizumab is higher at later timepoints compared with routine surveillance. Both of these scenarios appear to be highly unlikely based the mechanism of action of pembrolizumab and the expectation of complete removal of residual disease in additional patients in the pembrolizumab arm. This would effectively penalise patients who remain recurrence-free for longer, which is contrary to published evidence.

Consequently, given the mechanism of action of pembrolizumab, the aim of adjuvant therapy, and the published data on the use of adjuvant immunotherapies in the stage 3 setting, MSD do not believe it is appropriate to implement treatment waning in the economic model.

B7. Priority question. In CS Table 36, the subsequent treatment proportions are provided for both treatments (based on estimated market shares).

a) **Please justify assuming no systemic therapy after pembrolizumab.**

b) **Please provide an updated economic model and results for a scenario analysis wherein no systemic therapy is assumed for routine surveillance as well.**

c) **Please provide an updated economic model and results for a scenario analysis wherein for pembrolizumab the same distribution is assumed as for routine surveillance (as reported in CS Table 36).**

To clarify, CS Table 36 refers to subsequent **adjuvant** systemic treatments used **in the LRR health state**. Clinical experts advised that patients with stage 2B/2C melanoma who had a LRR would typically be considered to have stage 3 melanoma, and in current practice would therefore be eligible to receive systemic adjuvant therapy with one of the three treatments recommended by NICE in the adjuvant setting: pembrolizumab, nivolumab, or dabrafenib + trametinib.[8, 14, 39] The market shares for adjuvant treatments in the LRR state for the routine surveillance arm were sourced from Ipsos Oncology Monitor market research,[16] and confirmed by clinical experts to be reflective of current clinical practice.

However, in the pembrolizumab arm all patients entering the LRR health state have previously received adjuvant therapy with pembrolizumab. As discussed in CS B.3.3.2, clinical experts advised that they would not consider patients to be eligible for further adjuvant therapy, as there is currently no evidence on the efficacy of a second treatment course in the adjuvant setting and they were uncertain whether funding would be available. It was therefore deemed unlikely that patients who had adjuvant treatment at stage 2B/2C would receive further adjuvant treatment after LRR, and consequently this assumption was applied in the economic model. Given the high risk of recurrence in the stage 2B/2C setting, the experts highlighted the advantage of treating patients at the earliest eligible stage to reduce the risk of recurrence and thus the need for further systemic therapy.

Based on the rationale provided above, the requested scenarios were deemed to be implausible based on clinical expert opinion and are highly unlikely to reflect clinical practice. As such, MSD do not feel it appropriate or meaningful to conduct these scenario analyses. An alternative scenario in which patients with BRAF mutation positive melanoma were eligible for targeted adjuvant therapy in the LRR state was provided in CS Table 70. Given the feedback from clinical experts, this should still be considered a highly conservative scenario.

B8. In CS section B.3.3.1, section details regarding the estimation of transition probabilities are provided.

a) Please justify the approach “When analysing time to each specific type of RFS failure, the two competing failure types were treated as censoring events and patients who experienced a censoring event were therefore treated as lost to follow-up at the time of the earlier competing event”. Specifically, why this potentially informative censoring would not bias the estimated transition probabilities.

b) Please justify the approach described in “Calculation of transition probabilities based on cause-specific hazards” and elaborate on the potential limitations.

c) Please clarify why hRFS was not estimated using a separate parametric survival model considering LRR, DM and death as an event (instead of calculating hRFS based on the sum of the average cause-specific hazard for all three causes within that cycle).

d) Please provide an updated economic model and results for a scenario analysis wherein hRFS was estimated using a separate parametric survival model considering LRR, DM and death as an event.

The cost-effectiveness model accounted for competing risks using the approach described in Section 4.2.1 (Implementation of state transition models) of the NICE DSU Technical Support Document 19.[19] "The handling of competing risks in the model is also consistent with the parametric multistate modeling approach" described by Williams et al. (2017a & 2017b).[17, 18]

Broadly, two modifications to standard survival analysis methods were required to appropriately account for competing risks when computing transition probabilities between individual health states. In short, the first modification does not constitute informative censoring because it is done in conjunction with the second modification:

1. The first modification was made when fitting parametric models to the cause-specific hazards of each transition (i.e., RF→LRR, RF→DM, and RF→Death). Namely, when analysing time to each specific type of RFS failure, the two competing failure types were treated as censoring events.[19, 40] This step is covered in Section 4.2.1 of the NICE DSU Technical Support Document 19.[19] After these additional censoring criteria were applied to the patient-level time-to-event data for each transition, parametric curve fitting was performed using the survival analysis package flexsurvreg in R software,[41] similar to the process for fitting parametric functions for a partitioned survival model.

2. The second modification was implemented within the cost-effectiveness model. Specifically, in each weekly cycle, the probability of each transition starting from the recurrence-free state depended upon all three cause-specific hazards functions. For example, the transition probability for RF→LRR depended on not only the cause-specific hazards function for RF→LRR, but also the cause-specific hazards functions for RF→Death and RF→DM. This accounted for the fact that patients who experience one type of RFS failure in a given cycle have zero risks of experiencing the other two types of RFS failure. Without this adjustment for competing risks, the probabilities of each individual transition would be overestimated, and the first modification described above would represent informative censoring.

To further elaborate on the second modification, the specific calculation steps performed were described in CS section B.3.3.1 (p60-61).

Figure 11 below demonstrates the close fit between the resulting RFS predictions and the observed Kaplan-Meier curve for RFS in each arm of the KEYNOTE-716 trial. Additionally, Figure 12 shows the close fit between the predicted vs. observed cumulative incidences of each individual transition starting from the recurrence-free state. (Of note, the observed curves in Figure 12 represent the competing risks-adjusted cumulative incidences of each specific type of RFS failure. The plot points for these curves were generated using the *cuminc*() function from the R package *cmprsk*. It would have been incorrect to estimate these cumulative incidence curves using the Kaplan-Meier method in the presence of competing risks.)

As with any parametric survival modelling approach, there is inherent uncertainty associated with extrapolating long-term survival based on short-term data observed in trials. However, the parametric multistate modelling approach used for the present model is no more subject to this limitation than the traditional approach of fitting parametric models directly to the composite endpoint RFS (as per a partitioned survival approach). The present approach also has the advantage of yielding a larger number of different RFS extrapolations to consider, as each unique combination of distributions for RF→LRR, RF→DM, and RF→Death results in a distinct extrapolation of RFS.

Figure 11. Validation of predicted vs. observed RFS within the trial period under the base-case parametric distributions

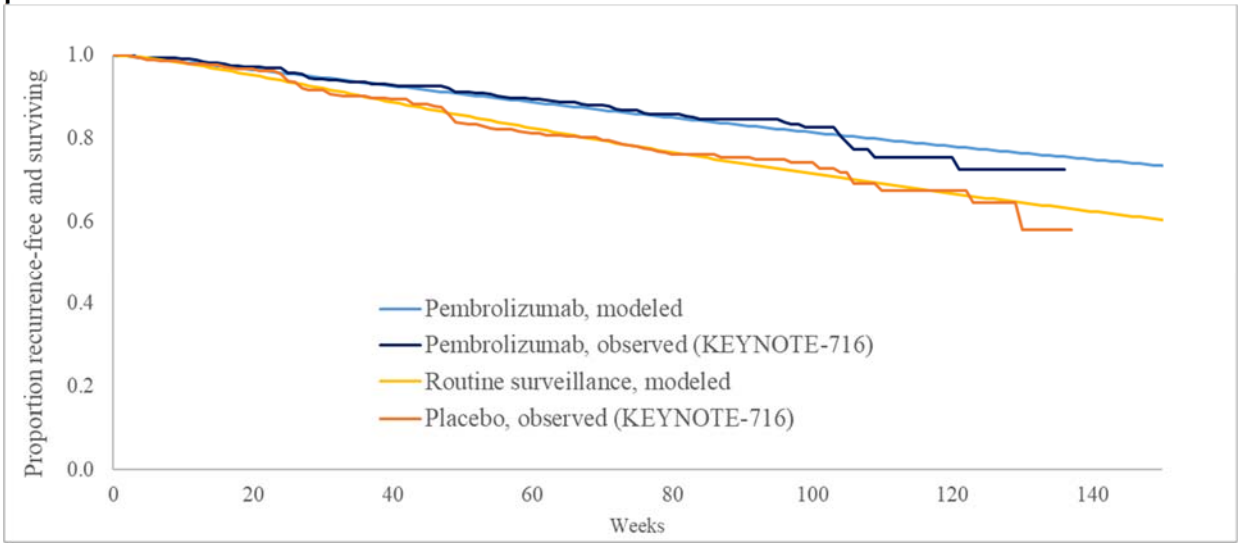

Figure 12. Validation of predicted vs. observed cumulative incidences of transitions starting from the RF state under the base-case parametric distributions

To obtain a complete set of transition probabilities for the present Markov model, it was necessary to select an approach that would yield probabilities of each individual transition from the RF state (i.e., RF→LRR, RF→DM, and RF→Death), rather than just the composite probability of any RFS failure event in each cycle. As implied by the question, a parametric model fitted directly to RFS would enable us to estimate $\overline{h}_{RFS}(\mathrm{t})$ in each cycle, which could be directly converted to a probability of RFS failure in each cycle by the formula $1 - e^{-\overline{h}_{RFS}(\mathrm{t})}$; however, we would have been left with the task of disaggregating this composite probability into separate probabilities of RF→LRR, RF→DM, and RF→Death. In some prior NICE submissions for adjuvant oncology indications (e.g., NICE TA569 for pertuzumab in breast cancer), the manufacturer disaggregated this composite probability using fixed proportions in each cycle, based on the percentage breakdown of all failure events observed in the trial thus far.[42] This approach would have required stronger assumptions and was thus considered less robust than our selected multistate modelling approach.

B9. For approach 3 described in CS section B.3.3.1 (Parametric proportional hazards models with a time-varying treatment effect (before and after year 1))

a) Please clarify what is meant with "a time-varying binary indicator equal to 1 in the pembrolizumab arm during the portion of follow-up after 1 year and 0 otherwise".

b) Please justify that year 1 was used as a cut-off point for this approach and elaborate on the implications.

Table 24 provides the general formulas for computing the hazard ratio for pembrolizumab vs. routine surveillance before and after 1 year from the parameter estimates for Approach #3 (located in the "Raw_Param Estimates" tab of the model). In this table, the *trtpn_new* covariate refers to the time-constant binary indicator equal to 1 in the pembrolizumab arm and 0 in the placebo arm. The *trtpn_new:g1yr* covariate is the time-varying binary indicator equal to 1 in the pembrolizumab arm during the portion of follow-up after 1 year and 0 otherwise. In other words, for patients in the pembrolizumab arm, this covariate was equal to: 0 during the portion of time from randomization until the earliest of 1 year, censoring, or the event of interest; and 1 during the remainder of the patient's follow-up (for patients who were still in the risk set beyond the 1-year mark). For patients in the placebo arm, the *trtpn_new:g1yr* covariate was always set equal to 0.

Table 24: Computation of HRs of RFS failure with pembrolizumab vs. observation (i.e., placebo) using parameter estimates under Approach 3

Distribution	HR before 1 year	HR after 1 year
Exponential or Gompertz	= EXP(trtpn_new)	= EXP(trtpn_new + trtpn_new:g1yr)
Weibull	= EXP(-trtpn_new)^shape	= EXP(-trtpn_new - trtpn_new:g1yr)^shape

The 1-year cut-off point was selected to provide structural flexibility for a change in the hazard ratio after the protocol-defined maximum adjuvant treatment duration of 1 year, although no such treatment effect waning was expected (see response to question B6). Ultimately, neither of the jointly fitted modelling approaches (Approach #2 or #3) were used in the base-case analysis, as the combinations of distributions under these approaches were outperformed by several combinations of distributions under Approach #1 based on statistical fit, visual assessment and external validations.

B10. In CS section B.3.3.1 considering statistical fit, it is stated that AIC is not suitable when modelling competing risks and the mean squared error (MSE) is used instead.

a) Please justify that AIC/BIC are not appropriate to consider individual parametric survival models, as a first step.

AIC and BIC, fit statistics commonly used in partitioned survival models, are not suitable measures of fit with observed data when modelling competing risks.[17] This is because, in the context of competing risks, transition probabilities are determined by the cause-specific hazards of all competing events, not solely by the cause-specific hazards of one particular event. Therefore, the AICs associated with different parametric distributions for the cause-specific hazards of a particular event do not provide sufficient information to assess fit.

To elaborate further on this point, our response to question B8 above describes the two modifications to usual survival analyses that are required to correctly account for competing risks, and notes that modification #1 (i.e., censoring patients at competing events) would constitute informative censoring unless modification #2 (i.e., using all three cause-specific hazards to calculate each transition probability) is also performed. AIC/BIC statistics would be produced at the time of modification #1, before modification #2 is performed. Any assessments of statistical fit with observed cumulative incidences of RF→LRR, RF→DM, and/or RF→Death would need to occur after modification #2, which accounts for the fact that patients who experience a given type of RFS failure have zero risk of subsequently experiencing a competing RFS failure type.

As such, MSE is used to assess statistical fit for each of the 54 distinct combinations of parametric functions, which produce different predictions of RFS and cumulative incidences of RF→LR, RF→DM, and/or RF→Death (as shown in response to question B4). MSE was calculated based on the average of the squared difference in predicted versus observed RFS at weekly intervals across the within-trial period, with weighting by number of patients at risk in each weekly interval. The ranking of combinations according to MSE aligned well with the conclusions drawn from visual inspection, as would normally be the case with AIC/BIC statistics.

b) What would be the implications of considering the AIC/BIC of the individual parametric survival models, for the approach adopted for the CS base-case?

AIC/BIC should not be used as a measure of statistical fit for the reasons described above. Moreover, the choice of an alternative measure for statistical fit is unlikely to have impacted the selected base-case combination of distributions: As demonstrated by the figures included in response to B4, most combinations of distributions yielded indistinguishably close visual fits to all transitions from the RF state (as of the current data cut-off date). Visual inspection led to the elimination of only 12 combinations (i.e., those using exponential for the cause-specific hazards of RF→DM), and statistical fit according to MSE led to the same eliminations. Because the predicted curves widely diverged beyond the available trial period, external validations against real-world cohort studies were more important to the selection of base-case distributions. Only a small number of distributions met our external validity requirement, most of which used the log-normal distribution for the cause-specific hazards of RF→DM.

Quality of life

B11. Priority question. Health state utility values in the economic model were informed by EQ-5D data from KEYNOTE-716.

a) Please provide, per measurement timepoint, separately for pembrolizumab and routine surveillance:

i. the total number of EQ-5D responses

ii. the estimated mean utility values and standard error

iii. a breakdown of how many patients were recurrence-free and had LRR and DM and the respective utility scores

iv. a breakdown of how many patients were on and off treatment and the respective utility scores

v. the extent of missing data observed

The utilities in the cost-effectiveness model are not applied as a change from baseline over time but instead as absolute values by health state and AE status. Thus, the utilities applied in the model are intended to represent the average HRQoL over the complete duration of time in health state and therefore there is no requirement to investigate utilities per measurement timepoint. To obtain utilities for use in the model, it would also be necessary to further split the data into health state (i.e. RF, LRR and DM) which would reduce the sample size and increase the variance of each utility estimate. Furthermore, it is not possible to determine from the available utility dataset which patients are missing at which scheduled visits. Consequently, utility estimates per measurement timepoint would be associated with significant limitations and provide no further value to the model.

Testing of treatment effect via mixed effects linear regression analyses was conducted, and demonstrated no statistically significant difference in utility between the pembrolizumab and placebo arms in the KEYNOTE-716 trial (p=[redacted] by AE status; p=[redacted] by health state) when the utilities were mapped from 5L to 3L. Analogous results were observed when the 5L utilities were assessed directly (p=[redacted] by AE status; p=[redacted] by health state). In addition, the numerical difference in utility between the pembrolizumab and placebo arms (e.g. [redacted] by AE status; [redacted] by health state [mapped utilities]) was not clinically meaningful based on the minimally important difference (MID) in EQ-5D scores for cancers, considered to be 0.08 for UK-based scores.[43] Similar results were observed for the direct 5L utilities. As such, the model uses utilities calculated based on pooled data across treatment arms, and responses to this question are provided based on the pooled analysis set. (The impact of AEs while on adjuvant treatment was captured by applying a disutility to the RF health state, weighted to account for the difference in AE incidence between treatment arms.)

- In KEYNOTE-716, the total number of EQ-5D-5L measurements for pembrolizumab and placebo arms in the FAS (full analysis set) population was [redacted].
- The estimated mean utility values and standard errors were provided in CS Table 42.
- The number of patients (and number of associated records) used to inform the utility estimates for the RF, LRR and DM health states is provided in Table 25. The corresponding estimated utility values were provided in CS Table 42.

Table 25: Sample size and number of records by health state (FAS Population)

Health state	Number of patients	Number of records
RF and during grade 3+ AEs	[redacted]	[redacted]
RF and without AEs (toxicity free)	[redacted]	[redacted]
LRR	[redacted]	[redacted]
DM	[redacted]	[redacted]

- On and off treatment is highly correlated with disease recurrence and AEs. The impact of recurrence on utility is already captured by the model health states and the impact of AEs on utility has been captured through the AE disutility. Thus, adding on- and off-treatment as covariates in the utility regression analyses will overfit the data and tend to double count the effect. Thus, it is not recommended to add on- and off-treatment as covariates in utility regression analyses.

- A summary of the EQ-5D-5L completion and compliance rates at scheduled visits was provided in CS Appendix Q, Table 62. As expected, a trend of decreasing completion rates over time was seen, particularly after year 1 (i.e. after completion of adjuvant treatment period), however this was comparable between treatment arms. However, the compliance rate remained above >80% at all time points in both treatment arms. These findings are common, and widely considered acceptable, in clinical trials.[44, 45] There were no missing covariates including recurrence status and AE status in the utility dataset.

b) Please explain, with appropriate justifications, how missing data were handled and the implications of this approach.

The utility regression analyses were focused on the full analysis set (FAS; patients with at least one EQ-5D measurement). There was no missing covariate including recurrence status and AE status in the utility dataset. Although there were patients who missed scheduled visits to complete the EQ-5D-5L questionnaire and patients who didn't complete the questionnaire as expected, overall compliance was high (CS Appendix Q, Table 62) and the reasons of missingness didn't demonstrate that they were correlated with patients' response to the treatment or QoL. As explained above, there is no information available in the utility dataset regarding which patients have missing EQ-5D-5L measurements at which scheduled visits, so it is not possible to assess the impact of EQ-5D-5L measurement missingness on utility estimates. For utility regression analyses, complete data analysis based on observed data was conducted.

c) Please clarify what the likely causes of missing data were and what the potential impact of these missing data on the estimation of the utility

scores would be, separately for patients who had completely and partially missing utility data.

Most frequent reasons for patients not completing the EQ-5D-5L questionnaire were: not completed due to site staff error; subject refused for other reasons; other with visit and no record. Reasons for non-completion that may affect utility (subject in hospital or hospice, due to side effects, due to disease under study, physically unable to complete) were uncommon (0–2 patients at each measurement timepoint) and therefore are not expected to affect the validity of the utility results. The reasons for missing by design include: discontinuation; completed study treatment; translation not available in subjects' language; subjects died; visit not reached; visit not scheduled.

The most common reasons/mechanisms for missing data on patients' EQ-5D measurements at scheduled visits relate to trial discontinuation and are not correlated with patients' QoL, and therefore the missingness can be deemed as 'missing at random'.[46]

Furthermore, there is no information available in in the utility dataset regarding which patients have missing EQ-5D-5L measurements at which scheduled visits, so it is not possible to analyse the impact of EQ-5D-5L measurement missingness on utility estimates.

d) Please recalculate the utility estimates while imputing missing values (for the patients with completely missing utility data and patients with partially missing utility data) using multiple imputation (incorporating potential explanatory variables and using at least 10 imputations).

i. Please provide in detail, the methods used to impute and pool the utility data

ii. Please elaborate on the plausibility of the imputed utility values

iii. Please provide an updated economic model as well as scenario analysis incorporating these newly calculated utility values

As explained in parts a–c, missing data on patients' EQ-5D measurements at scheduled visits were excluded from the utility dataset and not considered in the analysis. Given the current structure of the utility dataset, it is not feasible to conduct analyses to assess the impact of EQ-5D-5L measurement missingness on utility estimates. For utility regression analyses, complete data analysis based on observed data was conducted.

Multiple imputation methods replace missing values by a random sample of plausible value imputations from complete datasets generated via some chosen imputation model. Then complete data analysis is performed separately for each compete dataset and the results are combined into a single multiple-imputation result. There are some inherent limitations with imputation methods: the imputation model must be compatible with the analysis model and the imputation model needs to be more general than the analysis model.[47] Considering the complexity and uncertainty associated with conducting multiple imputations and the structure of the utility dataset (no information is available about which patients have missing EQ-5D-5L measurements at which visits), it is neither feasible nor meaningful to conduct such analyses.

Furthermore, given the reasons/mechanisms of outcome missingness, the missingness can be deemed as missing at random and won't cause significant bias to the results.[46] Also, considering that previous TAs for pembrolizumab have never conducted imputations for utility values, as well as the uncertainty on accuracy of imputed utility values, this approach is not recommended.

e) Please compare patient characteristics of patients with complete utility measurements and patients with missing utility measurements for both treatment groups separately and for the whole trial population combined (independent of treatment groups) and comment on potential differences.

Given the extent of missingness in outcomes and the reason/mechanism of missingness, it is not necessary to compare the patient characteristics between patients with complete utility measurements and patients with missing utility measurements. Furthermore, as explained in the previous responses, the existing utility dataset doesn't allow us to analyse the patient characteristics for those who have missing utility measurements vs. those who have complete utility measurements.

f) Please rerun the analyses performed to obtain the utility values (i.e. original approach from the CS) for pembrolizumab and routine surveillance separately.

As explained in the response to part a, treatment effect was added as a covariate in the mixed linear regression analyses and its impact was found not to be statistically significant, indicating that there was no significant difference in utility between pembrolizumab and placebo. In addition, since the model is not set up to apply different utility values by treatment arm, results of this analysis would not be accommodated by the economic model.

g) Please provide an updated economic model as well as a scenario analysis incorporating the estimated utility values in response to sub-questions e and f.

The analyses requested in parts e–f could not be conducted based on the rationale provided above. As such, an updated economic model is not provided. To test the sensitivity of the model to utility estimates, a range of alternative sources to inform utilities for health states have been explored (see CS Table 70) – these demonstrated that the utility values have a negligible impact on the cost-effective of adjuvant pembrolizumab.

B12. In the CS, the post-progression DM utility (0.59) was informed by a study of Beusterien et al., in which a standard gamble approach was used to derive health state utilities. The post-progression DM utility was substantially lower than the other health state utilities in the economic model.

a) Please justify why the post-progression DM utility was informed by the study of Beusterien et al. and elaborate on the potential implications of the standard gamble approach that was used in this study.

b) Please provide an updated economic model and scenario analysis using TA766 and other relevant TAs to inform the post-progression DM utility and elaborate on how this value compares to the one currently used in the economic model

As discussed in CS section B.3.4.1, it was not possible to generate separate utility values for the pre- and post-progression DM health states from KEYNOTE-716 as the available follow-up data from the trial to date was too limited to capture the average utility over the entire post-progression disease course until death. Specifically, at the data cut-off, only [redacted] patients had had a DM recurrence and had an available EQ-5D record after their DM recurrence. Across these [redacted] patients, there were [redacted] individual EQ-5D records collected in the DM health state. The estimated utility value for the DM state is therefore already based on relatively few patients, and the utility for the post-progression DM state would consider a small proportion of this sample. In addition, given the duration of follow-up, EQ-5D data for post-progression would not capture the decrease in patients' HRQoL associated with toxic subsequent therapies and further disease progression. As such, the estimated utility for post-progression DM from KEYNOTE-716 would be highly unreliable and would likely overestimate the true utility for patients with progressed, metastatic melanoma.

Consequently, to ensure the HRQoL implications of progressed, metastatic melanoma were robustly captured, it was necessary to source the utility value for the post-progression health state from alternative sources. As explained in CS section B.3.4.3, the limitations precluding calculation of a post-progression DM utility from KEYNOTE-716 also apply to KEYNOTE-054, therefore a suitable utility for this sub-state was also unavailable from KEYNOTE-054 (TA766).[10] A progressed disease utility of 0.7 was available from KEYNOTE-006 (TA366; pembrolizumab for treatment of metastatic melanoma not previously treated with ipilimumab).[48] However this was not considered appropriate for use in the base case model as utility values in KEYNOTE-006 were collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit (i.e. immediately after progression), but no further. As a result, the utility does not capture the decrease in HRQoL associated with toxic subsequent therapies and further progression and is therefore likely to be overestimated.

Instead, two non-trial-based studies (Beusterien et al, 2009 and Middleton et al, 2017) were identified that reported utilities for advanced melanoma valued by the UK general population.[11, 12] The post-progression utility in Beusterien et al, 2009 was higher compared with the corresponding utility reported by Middleton et al, 2017, and is therefore a more conservative choice. It has also been used in previous NICE TAs for melanoma, including TA384 and TA766,[10, 49] and was considered to be the best source in the absence of suitable data from KEYNOTE-716.

Scenarios exploring the impact of using utilities sourced from KEYNOTE-054 (TA766) for the LRR and pre-progression DM states, and using utilities from Middleton et al, 2017 for the DM state, were presented in CS Table 70 (scenarios 15 and 16, respectively). The impact of these scenarios on the ICER was negligible. In response to question B12b, a highly conservative scenario using the utility for progressed disease (0.7) sourced from KEYNOTE-006 (TA366) was performed,[48] which produced an ICER of £4,764 per QALY. Consistent with the scenarios presented in the CS, the effect on the ICER was negligible. This scenario can be replicated by selecting ‘User-specified utility’ from the dropdown in row 19 on the ‘Utility’ tab and entering ‘0.7’ in cell I30.

B13. The company stated for patients in the DM state in the CS that “the ratio of mean PFS to mean OS was estimated for each arm. In each model arm, this ratio was used to calculate utility values and weekly disease management costs”. From this, it appears that utility values and disease management costs in the DM state are treatment dependent. Please justify the plausibility of treatment dependent utility

values and provide an updated economic model and scenario analyses assuming treatment independent health state utility values.

To clarify, the model does not use treatment dependent utility values. The utility inputs (including pre-progression DM utility and post-progression DM utility) are determined only by model health state and are therefore independent of adjuvant treatment arm. The ratio of mean PFS to mean OS relates to the proportion of total time in the DM state that a patient spends in the pre-progression DM state versus the post-progression DM state. The average utility for the DM health state is then calculated as a weighted average of the pre-progression DM utility and post-progression DM utility, based on the PFS:OS ratio.

As described in CS section B.3.3.3, the PFS:OS ratio is determined based on the market shares of first-line treatments received for advanced melanoma in the DM health state and the relative efficacy (in terms of PFS and OS) of each first-line treatment option. This enables the model to provide a more accurate estimation of outcomes by accounting for the actual usage of systemic treatments used in UK clinical practice. In addition, it also allows the potential impact of adjuvant pembrolizumab on the treatment pathway to be captured, by permitting the market shares to differ between the two treatment arms considered in the model (i.e. adjuvant pembrolizumab and routine surveillance). As a result of applying different market shares between treatment arms, the PFS:OS ratio will differ between arms and consequently the weighted average DM utility for each treatment arm will also be slightly different. This should be considered a strength of the model, as it enables more accurate estimation of overall health outcomes. However, note that in practice the weighted average DM utility is actually very similar between treatment arms (pembrolizumab: [redacted]; routine surveillance, [redacted]) – this can be observed in the model in I42:45 on the 'Utility' tab. The only way to explore identical DM utilities between arms is to assume the same market shares of first-line treatments in each treatment arm, which is not deemed realistic based on clinical expert feedback.[14]

Costs and resource use

B14. In the base case analysis, market shares of subsequent treatment regimens for the routine surveillance arm in the LRR health state were sourced from Ipsos Oncology Monitor and MSD market research. The company stated that data from KEYNOTE-716 on the use of subsequent treatments for patients who developed LRR were incomplete with respect to the use of combination regimens and were based on a small number of patients (n=[redacted]). Therefore, according to the company, these were not suitable for informing the economic model. The company also presented alternative market shares from Wilmington Specialist Share Data and

MSD market search alone. The mean duration of each subsequent treatment in the stage 3 setting was estimated using observed time on treatment statistics reported from the corresponding clinical trial in this setting, which were used to calculate the exponential rate of discontinuation.

a) Please comment on the generalisability of the different sources for market shares of subsequent treatment regimens in the LRR health state (i.e. Ipsos Oncology Monitor, MSD market research, trial data from KEYNOTE-716, Wilmington Specialist Share Data) to the NHS in England.

b) Despite the mentioned limitations, please provide an updated model and scenario analysis using data from KEYNOTE-716 as source for market shares of subsequent treatment regimens for the routine surveillance arm in the LRR health state.

c) Please provide an updated model and scenario analyses using data from Wilmington Specialist Share Data and MSD market search alone as source for market shares of subsequent treatment regimens for the routine surveillance arm in the LRR health state (as reported in CS Table 37).

d) Please elaborate on the effectiveness of the individual subsequent treatment options after LRR and justify whether this is correctly reflected in the market share.

e) Please provide a detailed description of how treatment duration of each subsequent treatment was applied to the economic model.

Ipsos Oncology Monitor, Wilmington Specialist Share Data (SSD) and MSD Market research are different sources of market research data specific to the UK NHS, and therefore are directly relevant to current treatment practice in the NHS. Ipsos Oncology Monitor provides regularly updated industry-wide, market-specific insights; the melanoma dataset used in this submission was based on [redacted] UK physicians surveyed who were treating [redacted] patients with systemic adjuvant therapy in the stage 3 setting.[16] The SSD dataset is compiled via a survey of Trusts across the UK that treat melanoma, designed to gather data on treatment volumes and market shares. In the latest wave, [redacted] Trusts treating melanoma patients provided data separately for the adjuvant versus metastatic setting and are therefore included in the exploratory market share proportions for the LRR health state – this dataset is therefore based on [redacted] patients in

the adjuvant setting. However, [redacted]% of patients in the SSD adjuvant dataset were categorised as 'Other' which is not defined, and there is some uncertainty around the accuracy with which the research questions were interpreted and completed.[50]

The MSD market research collected data on current treatment practices from [redacted] clinicians corresponding to [redacted] patient records via an online survey. There was representation from General and University hospitals across all four key regions in the UK, and market share data for the adjuvant setting were based on [redacted] patients.[15] As discussed in CS section B.2.3.2, the KEYNOTE-716 trial population is considered generalisable to the UK setting. However, it is a global trial and there is variability in terms of available treatment options for recurrent melanoma between countries. As such, market share data from KEYNOTE-716 may not be reflective of UK practice. The Ipsos dataset was selected as the source for base case market shares in the LRR state as it is an industry-recognised source, comprised a large sample, and contained less ambiguity in the research methods than the SSD dataset.

The available data on subsequent treatments after LRR from KEYNOTE-716 were presented in CS Appendix P (Table 58). As shown in that table, there were 14 therapies recorded after LRR in the trial of which only four (pembrolizumab, nivolumab, dabrafenib and trametinib) are relevant to the UK setting, and combination regimens are not defined. Further, as the data related to only [redacted] patients, the findings are unlikely to be reliable. It is therefore not possible to determine the actual use of subsequent treatment regimens from the KEYNOTE-716 trial data and attempts to do so would not provide meaningful results.

Scenario analyses conducted using the SSD data and the MSD market research data (as presented in CS Table 37) in the routine surveillance arm are presented in Table 26. These can be replicated by selecting 'User-specified' from the dropdown in row 120 on the 'Specifications' tab and entering the relevant market shares in D5:D11 on the 'Raw – Market Shares' tab.

Table 26: Scenario analyses – Alternative market share sources for the LRR state

Data source for routine surveillance arm	ICER (£ per QALY)
Wilmington Specialist Share Data (SSD)[50]	£4,449
MSD Market Research[15]	£4,578

With regards to the effectiveness of the individual subsequent adjuvant treatment options used in the LRR state, baseline transitions from the LRR state were estimated using real-world data from the USON database for patients diagnosed with stage 2B/2C melanoma who had a LRR and received no adjuvant therapy.[21] This population is directly relevant to the current indication. The baseline transition rate from the LRR state was then adjusted to reflect the relative efficacy of the individual subsequent treatments using data from the pivotal clinical trial for each regimen (KEYNOTE-054, COMBI-AD) – HRs for each treatment versus no adjuvant therapy were

presented in CS Table 34. Note that KEYNOTE-054 permitted enrolment of patients with stage 3 disease following recurrence from earlier stages (subject to criteria ensuring no prior systemic therapy beyond surgery [prior treatment with interferon was allowed in some instances]), which should offer reassurance that the findings of the stage 3 trials are applicable to the current setting. The transitions used in the model therefore represent the best available data to reflect the effectiveness of each subsequent treatment option. An alternative scenario was presented in CS Table 70 which used real-world data from the USON database from the subset of patients who received *any* adjuvant therapy after LRR instead of trial data for the individual treatment options. The impact on the ICER in this scenario was negligible; combined with the scenarios presented in Table 26, this indicates that the method used to model subsequent therapies in the LRR state is not a key model driver.

The treatment duration for each adjuvant therapy in the LRR state was estimated using the observed time on treatment statistics reported from the corresponding clinical trial in the stage 3 setting, which were used to calculate the exponential rate of discontinuation.[32, 51, 52] These exponential rates are presented in CS Table 54. All adjuvant therapies were capped at 52 weeks in line with the label-recommended maximum duration of each treatment. Drug acquisition and administration costs for adjuvant therapies were then applied as lump-sum costs upon entry into the LRR state.

B15. For the pembrolizumab arm, it was deemed unlikely that patients treated with adjuvant pembrolizumab in the stage 2B/2C setting would receive further subsequent therapy after LRR as there is currently no evidence on the efficacy of repeat treatment with adjuvant therapy, and clinical advisors were not sure funding for further subsequent therapy would be available. Consequently, all patients in the pembrolizumab arm who had a LRR recurrence were assumed to have no further systemic subsequent therapy.

a) Please provide further justification regarding the assumption that patients in the pembrolizumab arm who had a LRR recurrence did not receive further subsequent treatment. Cross validate this assumption with other TAs, provide evidence from clinical guidelines and compare with real-world data (preferably UK).

b) Please provide an updated economic model and scenario analysis assuming that the same proportion of patients in the pembrolizumab arm who had a

LRR recurrence would receive subsequent treatment as was given in the routine surveillance arm.

MSD have engaged with several clinical experts with extensive experience treating melanoma in both adjuvant and metastatic settings, via an advisory board and through individual engagements. With regards to this question, experts advised that they currently consider patients to have 'one shot' at adjuvant therapy. Upon recurrence, they typically send patients for resective surgery but further systemic therapy would not be given unless they had a metastatic recurrence. This is due to the absence of trial data to demonstrate the efficacy of a second course of adjuvant therapy, and therefore clinicians were highly doubtful that a second course would ever be funded.[8, 14]

There are no agents currently approved in the UK for adjuvant treatment of stage 2B/2C melanoma therefore it is not possible to compare this assumption with other directly relevant TAs and there are no guidelines to advise on the appropriate course of action in this scenario. However, the recent NICE appraisal of pembrolizumab for the adjuvant treatment of stage 3 melanoma (TA766)[10] also assumed that patients with a LRR would be treated with surgery only. In TA684 (nivolumab for the adjuvant treatment of stage 3 melanoma), subsequent treatment data from the CheckMate238 trial appear to have been used, but the market shares are redacted and therefore it is not possible to assess the number of patients in each arm who received systemic therapy. It is also relevant to note that many of the systemic agents reportedly used after a LRR in CheckMate238 are not approved for use in this setting in the UK.[53] In TA544 (adjuvant dabrafenib + trametinib in stage 3 melanoma), only the 10% of patients who were unresectable after LRR were assumed to receive systemic therapy.[54]

As discussed in response to questions B7, a scenario in which patients in the pembrolizumab arm received the same mix of adjuvant therapies as in the routine surveillance arm was deemed to be implausible based on clinical expert opinion and is highly unlikely to reflect clinical practice. As such, MSD do not feel it appropriate or meaningful to conduct this scenario analyses. An alternative scenario in which patients with BRAF mutation positive melanoma were eligible for targeted adjuvant therapy in the LRR state was provided in CS Table 70. Given the feedback from clinical experts, this should still be considered a highly conservative scenario.

B16. The proportions of patients in the DM first-line setting who received subsequent therapy were sourced from the Systemic Anti-Cancer Treatment (SACT) report developed based on real-world use of adjuvant pembrolizumab in the stage 3 setting. The company stated that data from KEYNOTE-716 on the use of subsequent treatments for patients who developed DM were incomplete with respect to the use

of combination regimens and were based on a small number of patients (n=[redacted]). The distribution of DM second-line subsequent regimens was sourced from Ipsos Oncology Monitor. The company further stated minimal use of IO monotherapy was observed in the SACT data, suggesting that, based on the 2-year follow-up reported by the SACT dataset, IO rechallenge for patients having a DM recurrence within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice in the absence of mature evidence on the efficacy of a rechallenge strategy. This was also assumed in the second-line setting.

a) Please comment on the generalisability of the different sources for proportion of patients receiving subsequent treatment regimens in the DM first-line setting (i.e. SACT, Ipsos Oncology Monitor, trial data from KEYNOTE-716) to the NHS in England.

b) Despite the mentioned limitations, please provide an updated model and scenario analysis using data from KEYNOTE-716 as source for the proportions of patients in the DM first-line setting (and if possible also the second-line setting) receiving subsequent therapy.

c) Please provide further justification regarding the assumption that patients in the pembrolizumab arm having a DM recurrence were, both in the first and second-line setting, not retreated with pembrolizumab within two years post-adjuvant treatment initiation. Cross validate this assumption with other TAs and provide evidence from clinical guidelines.

d) It was assumed that 5% of patients who entered the DM state more than 2 years after adjuvant pembrolizumab initiation would receive rechallenge with pembrolizumab monotherapy in the first-line setting. This was 10% for the second-line setting. Please provide further details and justify where these percentages (5% and [redacted]) were based on.

Ipsos Oncology Monitor provides regularly updated industry-wide, market-specific insights, and the shares presented in the CS reflect Ipsos market research specific to the UK. For the first-line metastatic melanoma setting, the Ipsos dataset was based on [redacted] UK physicians treating [redacted] patients, and therefore represents a large, representative sample of patients currently receiving first-line treatment on the NHS.[16] The SACT dataset represents 153 patients who had a

recurrence after being treated with adjuvant pembrolizumab in the NHS, and is therefore directly applicable to the NHS in England as well as to the patient population in the current appraisal (albeit after recurrence from stage 3 melanoma).[55] As discussed in CS section B.2.3.2, the KEYNOTE-716 trial population is considered generalisable to the UK setting. However, it is a global trial and there is variability in terms of available treatment options for recurrent melanoma between countries. As such, data on subsequent treatment use from KEYNOTE-716 may not be reflective of UK practice.

The available data on subsequent treatments after DM from KEYNOTE-716 were presented in CS Appendix P (Table 59). As shown in that table, there were 15 therapies recorded after DM in the trial of which five are not used in the UK setting and combination regimens are not defined. Further, the data related to only [redacted] patients distributed thinly across the 15 agents and two treatment arms, so the findings are likely to be unreliable. It is therefore not possible to determine the actual use of subsequent treatment regimens from the KEYNOTE-716 trial data and attempts to do so would not provide meaningful results.

With regards to retreatment with pembrolizumab, the SACT dataset (which covers a period of approximately 2 years) reports that a very small proportion of patients treated for recurrent melanoma were rechallenged with IO monotherapy (4/153 [2.6%]). The SACT report also states that the “median time from a patient’s last pembrolizumab cycle in SACT to their next treatment was 49 days” and the “median time from a patient’s first pembrolizumab cycle in SACT to their next treatment was 218 days.”[55] This indicates that patients receiving systemic treatment within 2 years of adjuvant treatment initiation are not receiving IO monotherapy. In addition, MSD have engaged with several clinical experts with extensive experience treating melanoma in both adjuvant and metastatic settings, via an advisory board and through individual engagements. The clinicians confirmed that this assumption was consistent with clinical practice, as most patients who recurred during or shortly after (usually within 6 months of) adjuvant treatment would preferentially be given combination therapy with nivolumab + ipilimumab, provided they were deemed fit enough, or targeted therapy with dabrafenib + trametinib (if they were BRAF mutant). However, they advised that IO monotherapy would be considered for some patients who recurred >18 months after adjuvant treatment initiation particularly if they were deemed unfit for combination therapy. Consequently, this assumption was incorporated into the model with the threshold for IO monotherapy rechallenge conservatively set at 2 years. This was consistent with the approach used in TA684.[53]

Although clinical experts were confident that some patients with a DM recurrence 2 years after adjuvant treatment initiation would receive rechallenge with IO monotherapy, the exact proportion is unknown as there is no data with sufficient follow-up to directly address this question. Instead, these proportions were set to 5% and [redacted] for first- and second-line settings, respectively, to

reflect a small proportion of patients in each setting based on clinical expert opinion. A scenario in which no rechallenge was assumed was presented in CS Table 70 – this can be replicated by selecting, in the 'Specifications' tab, 'SACT from TA553' from the dropdown in row 136, and 'Ipsos Oncology Monitor, no anti-PD-1/PD-L1 permitted' from the dropdown in row 140. Additional scenarios in which the pembrolizumab rechallenge percentages were varied are presented in Table 27. These can be replicated by editing cells H20 and H37 on the 'Raw – Market Shares' tab for first- and second-line rechallenge, respectively.

Table 27: Scenario analyses – Alternative rechallenge assumptions

	Pembrolizumab rechallenge market share		ICER (£/QALY)
	First line	Second line	
Increased rechallenge first line	10%	[redacted]	£3,332
No rechallenge first line	0%	[redacted]	£5,893
Decreased rechallenge second line	5%	[redacted]	£5,524
Increased rechallenge second line	5%	[redacted]	£3,707
Increased rechallenge for first **and** second line	10%	[redacted]	£2,421

B17. The company stated that a small percentage of patients in the pembrolizumab arm of KEYNOTE-716 remained on adjuvant therapy beyond 1 year, as the protocol allowed patients to complete all scheduled doses past the 1-year point if there had been earlier delays in treatment. Within the economic evaluation, the costs of adjuvant pembrolizumab treatment were modelled based on a fixed interval of Q6W, and so the costs of the final dose were applied at t=48 weeks from baseline for the percentage of patients still on adjuvant treatment at this time point. Therefore, the model did not use the portion of the Kaplan-Meier curve beyond the scheduled 1-year treatment period. Please provide an updated economic model and scenario analysis incorporating the treatment costs of patients still on treatment beyond the 1-year time point.

This summary of the CS is correct. The ToT Kaplan-Meier illustrates the proportion of patients still receiving treatment at each time point, and thus also the proportion of patients who had discontinued (i.e. received no further doses of pembrolizumab). The portion of the ToT Kaplan-Meier beyond 1-year represents patients who had a delay in treatment during the first year, and therefore the final dose(s) of their scheduled treatment were completed early in year 2 instead of at the end of year 1. However, the model assumes that there were no delays in treatment and therefore the treatment costs of the small proportion of patients who completed their scheduled treatment in year 2 in the trial are already incorporated into the year 1 treatment costs in the model calculations. This is in effect a conservative approach that biases against pembrolizumab,

as discounting of costs incurred after year 1 would reduce the overall treatment cost of adjuvant pembrolizumab. Increasing the maximum ToT above the default value would results in the application of more than the maximum number of dosages for some patients, which is inconsistent with the observed dosages received by patients in KEYNOTE-716.

B18. Resource use frequencies in the DM health state were based on TA319 and were reported in Table 62 of the CS. Please elaborate on the plausibility of the frequencies reported in Table 62 by cross validation with other relevant TAs, and justification based on expert opinion, clinical guidelines and real-world data.

The resource use frequencies in the DM health state were sourced from TA319, which used resource use data collected from the MELODY study.[13, 56] MELODY was a longitudinal survey of patients with unresectable stage 3–4 melanoma and included 220 patients across 10 UK sites.

The MELODY study has been used to inform health state resource use in six previous NICE TAs of treatments for advanced melanoma (TA319, TA357, TA366, TA384, TA396, TA400) and the values have been deemed appropriate in these appraisals. In addition, the recent appraisal of pembrolizumab for the adjuvant treatment of stage 3 melanoma (TA766) also used resource use data from MELODY to inform the DM health state. In other appraisals in the adjuvant melanoma setting, TA684 used data from the CheckMate238 trial (values redacted) and TA544 applied one-off costs sourced from estimates reported in prior NICE appraisals and thus individual resource use values are not available. The only appraisal to use an alternative source was TA562 (encorafenib + binimetinib in metastatic melanoma), which utilised resource use data from a study on healthcare resource use for melanoma conducted in Australia and five countries in Europe, including the UK (McKendrick et al, 2016).[57] Whilst this is a more recent study than MELODY, the resource use values reported are comparable between the two studies indicating that disease management practices have not changed significantly over the intervening period.

Consequently, the use of resource use inputs from TA319 (based on the MELODY study) is aligned with substantial prior precedent and the plausibility of the inputs is supported by data from a more recent study. In addition, it is worth noting that the impact of disease management costs on the ICER is minimal and the source of resource use inputs is unlikely to affect the results of the analysis.

B19. Section B.3.5.2 of the CS reported the health state unit costs and resource use.

a) Please clarify whether these health state unit costs and resource use were treatment dependent, and if so, justify this.

b) If applicable, please provide an updated model and scenario analysis assuming treatment independent health state unit costs and resource use.

In all health states, unit costs and resource use were treatment independent, as there are not anticipated to be differences in the frequency or cost of surveillance activities for patients on adjuvant pembrolizumab versus routine surveillance. This was confirmed with UK clinical experts based on their experience using adjuvant pembrolizumab in the stage 3 resected melanoma setting,[8] and is aligned with the methods applied in previous adjuvant melanoma appraisals, including TA684 and TA766.[10, 53] Further details on the calculation of the methods used to calculate health state unit costs and resource use in the DM state are provided in response to question B20.

B20. The company stated for patients in the DM state in the CS that "the ratio of mean PFS to mean OS was estimated for each arm. In each model arm, this ratio was used to calculate utility values and weekly disease management costs". From this, it appears that utility values and disease management costs in the DM state are treatment dependent. Please justify the plausibility of treatment dependent disease management costs provide an updated economic model and scenario analyses assuming treatment independent disease management costs.

To clarify, the model does not use treatment dependent resource use (and consequently disease management costs). The resource use inputs (including for the pre-progression DM state and post-progression DM state) are determined only by model health state and are therefore independent of adjuvant treatment arm. The ratio of mean PFS to mean OS relates to the proportion of total time in the DM state that a patient spends in the pre-progression DM state versus the post-progression DM state. The average resource use for the DM health state is then calculated as a weighted average of the pre-progression DM resource use and post-progression DM resource use, based on the PFS:OS ratio.

As described in CS section B.3.3.3, the PFS:OS ratio is determined based on the market shares of first-line treatments received for advanced melanoma in the DM health state and the relative efficacy (in terms of PFS and OS) of each first-line treatment option. This enables the model to provide a more accurate estimation of outcomes and costs by accounting for the actual usage of systemic treatments used in UK clinical practice. In addition, it also allows the potential impact of adjuvant pembrolizumab on the treatment pathway to be captured, by permitting the market shares to differ between the two treatment arms considered in the model (i.e. adjuvant pembrolizumab and routine surveillance). As a result of applying different market shares between treatment arms, the PFS:OS ratio will differ between arms and consequently the weighted

average DM resource use for each treatment arm will also be slightly different. This should be considered a strength of the model, as it enables more accurate estimation of overall health outcomes and costs. However, note that in practice the weighted average DM resource use, and therefore disease management cost, is actually very similar between treatment arms (pembrolizumab: £113.70 and £113.71 per week before rechallenge permitted and after rechallenge permitted, respectively; routine surveillance, £113.74 per week) – this can be observed in the model in J125:K128 on the 'HCRU' tab. The only way to explore identical DM state resource use between arms is to assume the same market shares of first-line treatments in each treatment arm. This is not deemed realistic based on clinical expert feedback,[14] or based on the understanding of NICE appraisal committees that adjuvant therapies would affect subsequent treatment pathways.[10, 53]

Results and uncertainty analyses

B21. Priority question. Considering the CS base-case results.

a) **Please provide a comparison of the observed survival as well as progression free survival (e.g. using restricted mean survival time; RMST) and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model by combing the LRR and DM health states) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.**

b) **Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:**

   i. **Pembrolizumab**

   ii. **Routine surveillance**

   iii. **the increment**

Note: During our clarification call with the EAG, we understood that 'progression-free survival' was a typographic error and the EAG referred to RFS.

The table shell below, provided by the EAG, (Table 28) has been populated with RMST and lifetime undiscounted LYs during RFS (i.e., time spent in the RF state). Lifetime undiscounted total LYs (i.e., overall survival) has also been included in the table; however, OS was not

included as part of the pre-specified analyses for the second interim analysis of KEYNOTE-716 and RMST for OS thus could not be included in the table.

Table 28: RMST estimates

	Observed	Modelled	
	Restricted mean survival time (RMST)	**Estimated (lifetime time horizon)**	**Proportion beyond observed data**
OS			
Pembrolizumab	Not available	[redacted]	Not available
Routine surveillance	Not available	[redacted]	Not available
Increment	Not available	[redacted]	Not available
RFS - RMST period / truncation point: 136 weeks (selected based on end of Kaplan-Meier RFS curve in KEYNOTE-716 as of June 21, 2021 data cutoff)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
RFS - RMST period / truncation point: 89 weeks (selected based on median follow-up in KEYNOTE-716 as of June 21, 2021 data cutoff)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; RFS, recurrence-free survival; RMST, restricted mean survival time.

For both pembrolizumab and routine surveillance, the percentages of LYs during RFS that accumulate after the 89- and 136-week truncation points are plausible based on the disease stage of patients in the target population and the use of a lifetime horizon. To elaborate on these points:

- The target population includes patients with completely resected stage IIB-IIC melanoma. Although a large proportion of patients develop recurrence in the years following surgical resection when managed by routine surveillance alone, stage IIB-IIC is nevertheless a stage at which cure is achievable for many patients, even under the routine surveillance strategy. As observed in a retrospective study by Lee et al. (2017), the cumulative incidence of image-detected and physician-detected relapses levelled off at three years for stage IIB and two years for stage IIC.[26] The NICE clinical guideline NG14 implies that patients with stage II melanoma are discharged beyond 5 years.[58] Furthermore, two retrospective care series studies indicate that 71%-90.7% of recurrences were recorded in the first 5 years of follow up for stage I/II and stage I/II+III melanoma patients.[27, 28] UK clinicians noted that very few recurrences occur beyond 10 years for patients with stage II melanoma who have remained recurrence-free.[8, 14] It is therefore plausible that ~80%

of recurrence-free LYs would accrue after the end of the observed Kaplan-Meier curve in each arm.

- In a general population cohort with the same starting age and gender distribution as the model cohort, undiscounted life expectancy from cycle 0 is 24.77 years overall and 1.70 and 2.59 years up to the 89- and 136-week truncation points, respectively.[59] (These calculations have been added to the model tab named “Mortality by Cycle”.) The corresponding percentage of LYs that accrue beyond the 89- and 136-week truncation points is 93.1% and 89.6%, respectively, in a general population cohort. Relative to these percentages, the proportion of recurrence-free LYs that accrue in the modelled treatment arms after these truncation points ([redacted], respectively) are smaller than proportional and therefore plausible.

The proportion of incremental recurrence-free LYs that accrue beyond the observed trial period is also plausible based on the following considerations:

- Time is needed for the RFS curves in the two treatment arms to separate, and incremental recurrence-free LYs will therefore be particularly small towards the beginning of the modelled time horizon. Note that when increasing the truncation point from 89 weeks to 136 weeks (which is only a 53% increase in the number of weeks), the RMST of recurrence-free LYs increases by [redacted] from [redacted].

- In the KEYNOTE-054 trial (stage 3 melanoma setting), which had a maximum follow-up of over 4 years as of the last data cut-off date, the observed increment in recurrence-free LYs when increasing the truncation point similarly increased more than proportionally to the increase in weeks. For example, when increasing the truncation point from 89 weeks to 221 weeks (a 148% increase in number of weeks), the observed increment in recurrence-free LYs increased from [redacted] to [redacted], an increase of [redacted]% (Table 29). The percentage increase in the observed recurrence-free LYs when increasing the truncation point in KEYNOTE-716 is likely to be even larger due to the earlier disease stage, which may increase the amount of time needed for the RFS Kaplan-Meier curves in the pembrolizumab and placebo arms to fully separate.

Table 29: RMST increment in KEYNOTE-054

Truncation point along the KEYNOTE-054 RFS Kaplan-Meier curves	RMST for RFS in KEYNOTE-054 (stage III melanoma setting), by arm		Increment	% increase in incremental recurrence-free LYs relative to the 89-week truncation point
	Pembrolizumab	Placebo		
89 weeks	[redacted]	[redacted]	[redacted]	-
136 weeks	[redacted]	[redacted]	[redacted]	[redacted]
221 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Note: 221 weeks is the last week available on the observed RFS Kaplan-Meier curve for both arms of KEYNOTE-054 (stage III melanoma setting).

c) Regarding the model estimated differences between the intervention and the comparator (in terms of PFS, LYs and quality-adjusted life years (QALYs)); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence.

The key transition probabilities driving the incremental LY and QALY results are the three transitions starting from the recurrence-free state (i.e., recurrence-free to locoregional recurrence, recurrence-free to distant metastases, and recurrence-free to death). These transition probabilities were modelled directly using randomized controlled trial data from KEYNOTE-716 for the pembrolizumab and observation arms. The improvement in total LYs and total QALYs with pembrolizumab relative to observation follows from the reduction in recurrence risk, as patients experience higher risks of death upon transitioning in the LR or DM states. There is strong published evidence supporting that an improvement in RFS, such as that observed in KEYNOTE-716, will translate into an OS benefit.[29, 60-62] In particular:

- 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).[29]

- In a recent meta-analysis of 13 clinical studies (n>5,000 patients) involving adjuvant interferon for the treatment of resected stage II-III melanoma, RFS was shown to be a good predictor and valid surrogate endpoint for OS.[62] The findings of this meta-analysis 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.[60]

Of note, the model conservatively assumes that, once patients experience a recurrence event (LRR or DM), there are no ongoing benefits from the initial adjuvant pembrolizumab course within these health states. (In other words, the original course of adjuvant pembrolizumab that a patient receives following resection of stage 2B or 2C melanoma was assumed to confer no increase in survival within the LRR or DM states.) Base-case transition probabilities starting from the LRR and DM states differed between the pembrolizumab and observation arms only to the extent that the mix of subsequent treatments were expected to differ between these two arms.

B22. CS Appendix Table 35 provides an overview of the estimated costs by cost category. Please elaborate on the plausibility of the differences in costs regarding

a) Subsequent treatment costs (LRR state)

b) Subsequent treatment costs (DM state)

c) Please provide a disaggregated overview of LYs, QALYs and costs for the DM sub-states (pre-progression and post-progression)

Pembrolizumab is expected to reduce the cost of salvage surgery for LRR relative to the observation arm due to the reduction in the risk of transitioning into LRR. Based on consultations with UK clinicians, patients who develop LRR after having received adjuvant pembrolizumab for resected stage 2B-2C were not expected to receive a subsequent adjuvant treatment for stage 3 melanoma, while most patients who develop LRR in the routine surveillance arm were expected to receive subsequent adjuvant treatment for stage 3 melanoma. Consequently, the costs of subsequent adjuvant treatment in the LRR state are zero in the pembrolizumab arm and non-zero in the routine surveillance arm. (Note: The receipt of subsequent adjuvant treatment in the LRR state leads to lower transition probabilities from LRR to DM and LR to death in the routine surveillance arm than in the pembrolizumab arm.)

Pembrolizumab is expected to reduce the cost of first-line treatments for advanced melanoma in the DM state relative to the observation arm due to the reduction in the risk of transitioning into DM. As shown in the Disaggregated Base-Case Results tab (which now disaggregates first-line vs. second-line treatment costs in the DM state), the cost of second-line treatments for advanced melanoma in the DM state are estimated to be slightly higher in the pembrolizumab arm than the observation arm, despite the reduction in risk of DM with pembrolizumab. This result is due to the expectation that patients in the pembrolizumab arm will on average receive costlier second-line treatment options than in the observation arm, based on the expected second-line market shares in each arm.

The ‘Disaggregated Base-Case Results’ tab of the model has been updated to separately report costs, QALYs, and LYs for the pre- and post-progression DM sub-states. In addition to disaggregating disease management costs for these sub-states, subsequent treatment costs in the DM state have also been disaggregated by allocating the costs of first-line treatment for advanced melanoma to the pre-progression DM sub-state and the costs of second-line treatment to the post-progression DM sub-state. This is summarised in Table 30.

Table 30: Disaggregated summary of predicted costs by cost category (update to CS Appendix J, Table 35)

Cost category	Pembrolizumab	Routine surveillance	Absolute increment	% absolute increment
Subsequent treatment costs (pre-progression DM state)	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (pre-progression DM state)	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]
RF state	[redacted]	[redacted]	[redacted]	[redacted]
LR state	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression DM state	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression DM state	[redacted]	[redacted]	[redacted]	[redacted]

Validation and transparency

B23. Priority question. In CS section B.3.10, Figure 17 and the associated description is very helpful to validate the approach used by the company. CS Figure 17 is based on the best fitted survival model distribution for RFS (log-logistic) and not the survival model distributions used for RFS in the CS base-case (log-normal distribution and exponential distribution according to CS Table 66).

a) **Please provide, in addition to CS Figure 17 a Table with the estimated RFS per year (for all curves), as well the estimated area under the curve i.e. mean RFS (for all curves). Please include data for all six standard parametric models (exponential, Weibull, Gompertz, lognormal, log-logistic, and Generalised gamma), as well as AIC/BIC in this Table (for both treatments).**

b) **Please provide a revised version of CS Figure 17 as well as the requested Table (previous sub-question) using the following outcomes**

   i. **DMFS**

   ii. **OS**

iii. PFS (combining the LRR and DM health states)

c) Please provide a new version of CS Figure 17 as well as the requested Figures (previous sub-question), focusing on the observed data period (excluding the survival curve extrapolations)

The RFS curves estimated based on parametric survival analysis using the six standard parametric functions are illustrated over the complete time horizon in Figure 13, and over the observed data period in Figure 14. For each of these parametric functions, the AIC/BIC statistics, the estimated RFS by year, and the area under the curve (mean RFS) are presented in Table 31. Note that all figures and values incorporate the 95% risk reduction assumption used in the base case analysis.

As shown here and discussed in CS section B.3.10, the log-logistic curve provided the best balance of goodness-of-fit in the pembrolizumab arm and goodness-of-fit in the routine surveillance arm. There was considerable variability between the different parametric functions, particularly in the pembrolizumab arm, however the base case model was closely aligned with the log-logistic curve and with the exponential curve. Of note, the undiscounted mean RFS in the base case model ([redacted] years in the routine surveillance arm and [redacted] years in the pembrolizumab arm) was highly comparable with the estimated mean RFS produced by the log-logistic function (9.14 years and 13.00 years, respectively).

With respect to question B23 part b, as DMFS and OS data are not yet available from KEYNOTE-716 it is not possible to conduct survival analyses on these endpoints or generate analogous validation results for these model outcomes. In addition, PFS is not a relevant endpoint in the adjuvant melanoma setting and therefore is not an outcome of the model. PFS outcomes are predominantly relevant in the advanced disease setting, and accordingly PFS data are used in the current model to model survival and progression and survival outcomes for patients in the DM health state only. As the LRR state represents resectable stage 3 melanoma, these patients are typically considered ‘disease-free’, and the next transition would therefore be either recurrence (to the DM state) or death. Consequently, it is not appropriate or meaningful to combine the LRR state with the DM state to generate an estimate of PFS.

Figure 13: Validation of modelled RFS versus directly fitted parametric models

A) Routine surveillance

B) Pembrolizumab

Figures include 95% risk reduction, as applied in the base case model.

Figure 14: Validation of modelled RFS versus directly fitted parametric models – observed period

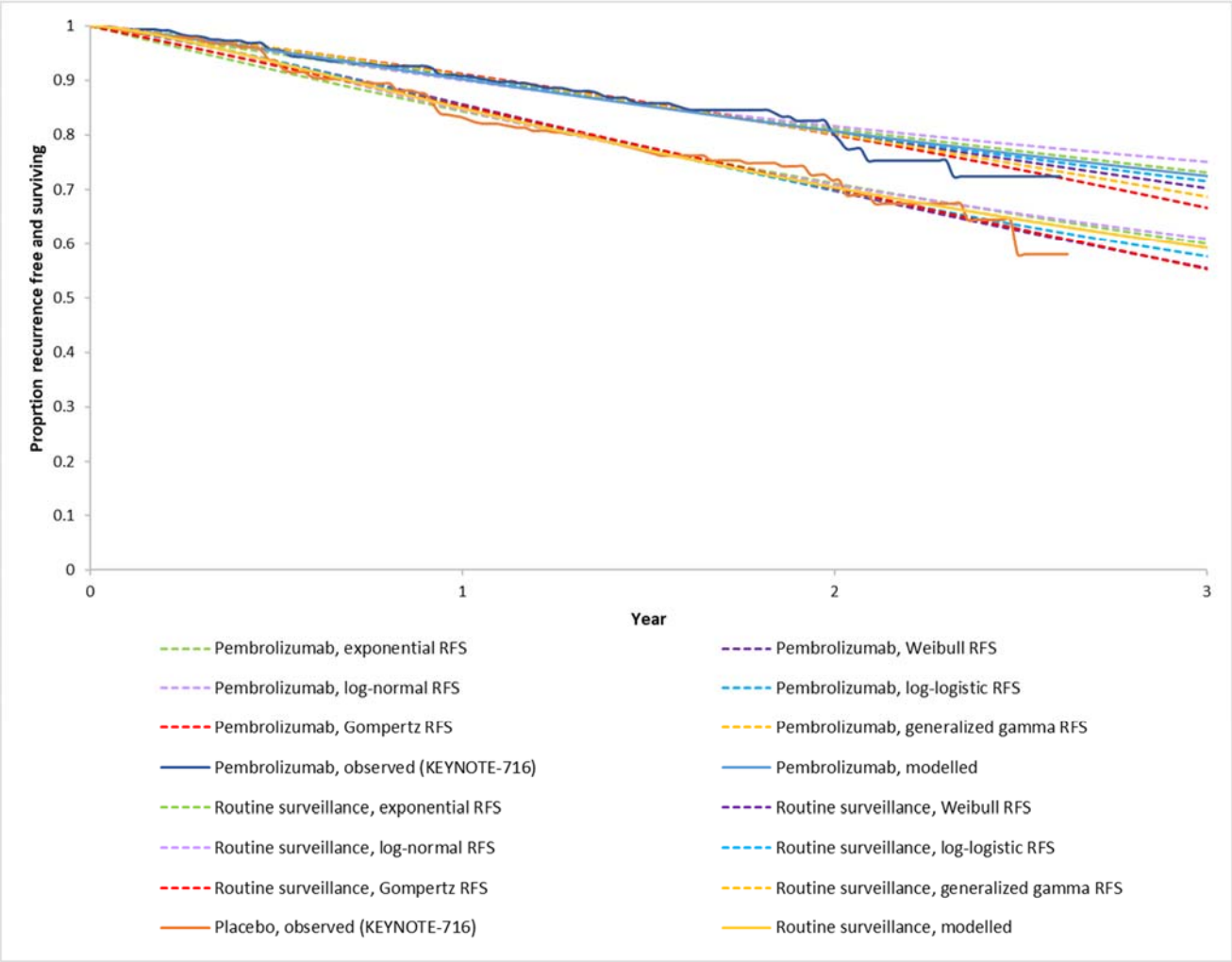

Table 31: Validation of RFS using externally fitted parametric functions – fit statistics and output

Parametric function	AIC	BIC	RFS, %							Mean RFS (AUC),† years
			1 year	5 years	10 years	15 years	20 years	25 years	30 years	
Routine surveillance										
Base case	***N/A***	***N/A***	***84.9%***	***43.8%***	***27.3%***	***24.4%***	***20.6%***	***15.5%***	***9.2%***	[redacted]
Exponential	1548.77351	1552.96588	84.4%	42.8%	23.3%	21.3%	18.3%	13.9%	8.4%	8.77
Weibull	1545.95067	1554.33539	85.7%	33.6%	12.1%	11.1%	9.5%	7.3%	4.4%	6.20
Log-normal	1544.19948	1552.58421	84.6%	47.4%	33.4%	30.6%	26.2%	20.0%	12.1%	10.95
Log-logistic	1544.54214	1552.92687	85.3%	41.1%	25.5%	23.4%	20.1%	15.3%	9.3%	9.14
Gompertz	1549.29474	1557.67946	85.3%	29.1%	3.5%	2.2%	0.7%	0.0%	0.0%	3.97
Generalised gamma	1545.66026	1558.23735	85.0%	43.7%	27.6%	25.3%	21.7%	16.6%	10.0%	9.66
Pembrolizumab										
Base case	***N/A***	***N/A***	***90.3%***	***59.6%***	***42.9%***	***38.7%***	***32.8%***	***24.7%***	***14.8%***	[redacted]
Exponential	1040.95099	1045.13925	90.1%	59.5%	40.9%	37.4%	32.1%	24.5%	14.8%	13.13
Weibull	1040.69657	1049.07310	90.9%	52.5%	29.4%	26.9%	23.1%	17.6%	10.6%	10.59
Log-normal	1047.55027	1055.92680	90.1%	65.4%	53.7%	49.2%	42.2%	32.2%	19.5%	15.89
Log-logistic	1041.12446	1049.50099	90.8%	57.3%	40.7%	37.3%	32.0%	24.4%	14.8%	13.00
Gompertz	1040.32003	1048.69656	91.2%	36.1%	1.5%	0.3%	0.0%	0.0%	0.0%	4.22
Generalised gamma	1042.37672	1054.94151	91.0%	44.9%	8.1%	4.4%	1.6%	1.2%	0.7%	5.36

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; BIC, Bayesian information criterion; N/A, not applicable; RFS, recurrence-free survival.
† Undiscounted.
All values include the 95% risk reduction, as in the base case model.

B24. The results of the validity assessments are not described nor are detailed validation exercises (i.e. specific black-box tests) described (in CS section B.3.10).

a) Please provide a detailed description of the validity assessment performed as well as the results.

b) Please provide complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

Throughout model development extensive validation procedures were conducted to ensure the model met MSD's quality control standards. This included completion of MSD's internal model review checklist which involved ensuring clear and transparent calculation flows, minimising formulae complexity, cell-by-cell auditing, and logic checks. In addition, the model was reviewed by an independent, external agency to ensure the model was fit for purpose, logical, and that calculations were correctly implemented.

The completed TECH-VER checklist has been provided accompanying this response.

B25. In CS section B.3.10 it is stated that "A targeted search for HTA submissions in adjuvant oncology settings did not identify any prior submissions for adjuvant treatments for high-risk stage 2 melanoma. Consequently, it was not possible to cross-validate the current model results against other, independently developed economic evaluations in the same indication. However, prior HTAs and published cost-effectiveness studies in other adjuvant oncology indications provided support and precedence for the assumptions used in the current model". Despite differences in the decision problem/scope it is informative to provide cross validations with other relevant NICE TAs including those mentioned in the final scope. Please provide cross validations, i.e. comparisons with other relevant NICE TAs (including TA553, TA357 and TA366 mentioned in the scope) as well as TA766 and elaborate on the identified differences regarding:

a) Model structure and assumptions

b) Input parameters related to:

    i. Clinical effectiveness

    ii. Health state utility values

iii. Resource use and costs

c) Estimated (disaggregated) outcomes per comparator/ intervention

i. Life years

ii. QALYs

iii. Costs

NICE TA357 and TA366 assessed treatments for advanced melanoma and therefore it is not appropriate to make comparisons relating to model structure and outcomes between these analyses and the current model. With respect to inputs, they can only be informative regarding modelling of the DM state in the current model. In both these appraisals, healthcare resource use inputs were sourced from the MELODY study (see response to question B18) and utilities were implemented based on time to death, ranging from 0.82 for patients with ≤360 days to death to 0.33 for patients with <30 days to death.[48, 63] This suggests that the inputs used in the current analysis are appropriate.

The model employed in TA766 (pembrolizumab for adjuvant treatment of stage 3 melanoma) was highly comparable to the current model. A four state Markov cohort state transition model was used with health states similarly defined, and this was deemed appropriate for decision making by the ERG and the appraisal committee.[10] In all previous NICE TAs of adjuvant therapies for melanoma (TA766, TA684, TA544), clinical effectiveness has been predominantly informed by the pivotal clinical trial for the treatment under assessment and supplemented by published data where necessary. Health state utilities were also sourced mainly from the relevant clinical trials, with the DM states typically informed by published data as there was insufficient evidence available within the trial follow-ups to provide robust estimates. Healthcare resource use inputs were informed by a mixture of trial data where available and published sources, but comparable approaches were used across appraisals. Of note, TA544 employed a 'pay-off' approach to model the DM state in which costs and QALYs associated with the DM health state were sourced from previous NICE appraisals and applied as one-off gains on entry to the DM state. However, this approach precludes generation of an OS curve which limits the ability to fully assess model validity.

Estimated outcomes across the previous adjuvant TAs are mostly redacted, therefore it is not possible to conduct a robust comparison. However, comparison of the LYs and QALYs for the routine surveillance arm between TA544, TA766 and the current analysis shows that estimates are of a similar magnitude. Further, estimates from the current analysis are slightly higher

compared with the stage 3 models which is expected given the earlier disease stage being modelled here (e.g. LYs: TA766, 9.02; current analysis, 9.97; QALYs: TA766, [redacted]; current analysis, [redacted]).

B26. In CS section B.3.10 it is stated that "Clinical experts were consulted via an advisory board and through additional individual engagements to validate the efficacy inputs (e.g. the plausibility of long-term RFS, DMFS, and OS) and other key model decisions (e.g. assumptions about post-recurrence treatments) from a clinical perspective, to ensure that the model was reflective of the UK setting."

a) Please provide supporting documents for the advisory board meeting(s), i.e. the minutes/ input obtained from this meeting and how the expert opinion was exactly gathered.

b) Please clarify why the experts were considered to qualify as experts to address these questions.

An advisory board was held on 10th December 2021 and was attended by eight clinicians with extensive experience in treating melanoma from a surgical, oncological and dermatological perspective. The panel included representation from across England, including major centres in Cambridge, London, Leeds and Bristol. Most of these centres have been involved in clinical trials of treatments for melanoma, in both metastatic and adjuvant settings, and several individuals on the panel have been principal investigators on clinical trials of immunotherapy in melanoma. The clinicians therefore were highly familiar in the current management of stage 2B/2C melanoma and with strategies for managing patients who have recurrence.

An anonymised version of the summary report documenting this advisory board has been provided accompanying this response. This report was developed independently by an external agency and provides a top-line summary of the discussions. Please note that the report does not include a detailed summary of any discussions, and content relating to topics other than the health economic modelling has been redacted as it is not relevant for this appraisal.

B27. In CS section B.3.10 it is stated that "In the current model, the expected survival ranged from [redacted] years, based on the first line market shares applied in each arm; this is highly comparable to the 5.08 life years in the TA366 model. This provides reassurance that the current modelling of this health state is reasonable, and thus the predicted OS is likely to be plausible."

a) Please clarify how the [redacted] years are calculated.

b) Please justify why the 5.08 life years in the TA366 model were considered to be an appropriate benchmark to state that the "predicted OS is likely to be plausible".

c) Please elaborate on the maturity of the data used for the TA366 model and whether updating the TA366 model using more mature data would substantially alter the estimated life years.

The expected survival range of [redacted] years cited here refers to the mean number of years a patient who enters the DM health state is expected to remain in that health state (i.e. the expected survival in the DM state), based on the market share distribution in each arm. For the pembrolizumab arm, expected survival is calculated separately for the 'rechallenge-ineligible' and 'rechallenge-eligible' groups, to reflect the impact of eligibility for pembrolizumab rechallenge in the DM state after 2 years. Expected survival for each treatment arm can be estimated in the model by dividing the OS estimates (in weeks) in H244:H246 on the 'Effectiveness' tab by the number of weeks per year. Using 52 weeks as an approximation of the number of weeks per year gives the expected survival range cited above.

TA366 evaluated pembrolizumab monotherapy for patients with advanced melanoma not previously treated with ipilimumab, and thus reflects patients receiving first-line treatment.[48] The DM state in the current model also reflects patients receiving first-line treatment for advanced melanoma, therefore the survival estimates from the TA366 model provide a benchmark for the expected survival for patients in the DM state. The ERG for the TA766 appraisal of pembrolizumab for adjuvant treatment of stage 3 melanoma considered life year estimates from TA366 to be an appropriate benchmark for assessing the validity of the survival estimates from the DM health state.[10] Confirmation that the survival estimates from this health state are comparable to those estimated in a model designed specifically to model the advanced setting provides reassurance that the approach to modelling the DM state is appropriate and reasonable. Given that most deaths in the first half of the model occur from the DM state, this suggests that the OS predictions are also plausible.

The TA366 model used OS data from interim analysis 2 (IA2; data cut-off 3 March 2015) of KEYNOTE-006 which had a minimum follow-up duration of 12 months. The most recent data cut of KEYNOTE-006 (data cut-off 19 April 2021) reports a median follow-up of 85.3 months.[64] It is not possible to determine whether updating the TA366 model with the more mature OS data would substantially alter the estimated life years. However, in TA366 the NICE committee were satisfied that the modelling was appropriate and sufficiently robust to conclude that pembrolizumab was a cost-effective use of resources. Consequently, whilst comparison versus

the TA366 estimate is not proof that the current model is accurate, combined with the extensive validation versus other external sources presented in the CS, it provides additional support for the validity of the predicted model outcomes.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

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

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

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

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**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, sponsorship and grants 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**

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.)	To reduce the risk of cancer recurrence and death following a diagnosis of stage 2 melanoma.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A reduction in risk of 3-5% or more of death is felt to be clinically meaningful.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – currently these patients are offered no adjuvant therapy
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Clinical observation only
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – NICE – but don't include latest data relating to this technology for stage 2
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	yes

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Patients would be offered to see melanoma specific oncology service to discuss adjuvant therapy – which would then need to be supervised and delivered.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	n/a -as not currently used for stage 2 melanoma. The drug is used for stage 3 and 4 and many other cancers.
• How does healthcare resource use differ between the technology and current care?	n/a -as not currently used for stage 2 melanoma. The drug is used for stage 3 and 4 and many other cancers.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Melanoma specific tertiary services
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Drug costs, administration costs, costs of managing side effects, clinic visits and extra scans.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
• Do you expect the technology to increase length of life more than current care?	yes
• Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per the clinical trials – greater than stage 2a
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As above -the drug is widely used but this is a new cohort of patients to be treated
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	One year of therapy -as per the trial leading to approval and licencing
15. Do you consider that the use of the technology will result in any substantial health-	no

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes -these patients are at risk of relapse that is currently not being met

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?	Side effects can occasionally be severe and long lasting -as per SPC for the drug.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Recurrence rates
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	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) for relevant NICE technology appraisal guidance?	no
21. How do data on real-world experience compare with the trial data?	Yet to be used in real world for stage 2
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.

- Stage 2 melanoma has a risk of relapse and death
- Pembrolizumab given for one year significantly reduces this risk
-
-
-

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

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].

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Melanoma UK
3. Job title or position	[redacted]
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. The organisation started off as Factor 50 and officially became Melanoma UK in 2013. At Melanoma UK it is our challenge and desire to give patients and their families much needed support during the very difficult times faced upon diagnosis. We aim to get patients 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 manufacturers are listed in the appraisal matrix.]	No

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?	For this submission we asked our patients via a survey through our various social media platforms and during our weekly patient calls via Zoom.
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?	**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 side effects such as lymphedema and scarring, along with stress, depression, and anxiety. The whole experience can be so confusing for some patients. It can also depend on where they are in their diagnosis – an early-stage melanoma patient can sometimes feel more lost because the only option for them is surgery, what do they do if surgery doesn't work? What other options are there? It is also clear that the treatment options are a bit of a 'postcode lottery' and where a patient lives has a lot

	to do with options available. Our patients talk openly with each other via several private Facebook groups and the general feeling is, if you don't live close to a melanoma centre of excellence, then a patient has another battle on their hands getting access to treatment. Patients are also not fully aware of what treatments or clinical trials are available to them, they don't know where to look or even the questions they should be asking - they rely heavily on having a good specialist/oncologist and/or clinical nurse specialist to explain options. **Personal (as a Carer)** I acted as a carer for 18 months and 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. The uncertainty of what could happen to her was unbearable and knowing that my niece faced physical and emotional challenges bought on a wide range of feelings including, fear, shock, desperation, and isolation. 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. Although we have an increasing proportion of patients who are highly sophisticated in their research and understanding of melanoma, that is not the majority. We need to keep things simple and arm them with relevant information. Signpost patients to the support of a patient organisation/s who can help equip both the patient/carer with the type of questions they should be asking of their medical team.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The treatment landscape for melanoma is moving now at such a pace that it is sometimes very confusing for a patient (and carers) to keep abreast of the options available to them. A lot of patients are not fully aware of what treatments or clinical trials are available to them – we don't make it easy for them and more work needs to continue in this area. There is a need for better sign posting for patients to help them understand the treatment pathway (depending on their stage) available especially the support the 3rd sector/patient organisations can offer.

8. Is there an unmet need for patients with this condition?	Yes, there is a definite need for stage 2 patients with a high risk of recurrence to have more options made available to them. Regardless of the stage, as soon as a melanoma diagnosis is given, that person feels their life is over. A patient needs hope, honesty, and a better understanding of what their quality of life will look like. 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? An early-stage melanoma patient needs reassurance that they are not going to be forgotten and that if surgery doesn't work, that they have options available to them – this treatment gives them that.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	They live in hope that adjuvant treatment may reduce the risk of melanoma recurring following surgery. That it could improve their overall condition and ultimately extend their life.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Side effects will always be an issue, but a patient would prefer to have the choice and weigh up all the options. We know that every patient is different and regardless of stage, they are fighting for their life and will do what is necessary. Injection rather than tablet Hospital visit required
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.	This appraisal may specifically be for stage 2 melanoma patients with a high risk of recurrence, however, by simply having this treatment option available, gives the whole melanoma community so much hope. Regardless of the stage of their melanoma, patients need options. Offering a treatment that has only ever been used in advanced stage melanoma is a huge breakthrough. The feedback from the melanoma community is clear…..There is no downside to offering this treatment option!
Equality	
12. Are there any potential equality issues that should be taken into account when	No Melanoma is a disease that affects young, old, black, white, sex, gender – it does not discriminate so neither should the treatment options.

considering this condition and the technology?	
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 – we 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	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Potential to reduce the risk of melanoma returning • A major breakthrough for the melanoma community as current treatment options seem to focus on advanced stage melanoma	

- This treatment could potentially save/improve a patient's life
- This treatment is vital for our patients - It gives them hope and confidence for their future

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox acted as health economist on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Susan O'Meara and Mark Perry acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Charlotte Ahmadu and Nigel Armstrong acted as systematic reviewer and health economist, critiqued the clinical effectiveness methods, the company's economic evaluation and contributed to writing the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

1L	First-line
AACR	American Association for Cancer Research
ADR	Adverse drug reaction
AE	Adverse events
AEOSI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ApaT	All-patients-as-treated
ASCO	American Society of Clinical Oncology
BCG	Bacillus Calmette-Guérin
BIC	Bayesian information criterion
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CS	Company submission
CSF	Colony stimulating factor
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DM	Distant metastases
DMFS	Distant metastasis-free survival
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
EBM	Evidence-based medicine
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EHR	Electronic health record
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EuroQol-5 Dimension
EQ-5D-5L	EuroQol-5 Dimension-5 level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE	Fixing errors
FV	Fixing violations
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HSUV	Health State Utility Value
HUI	Health Utilities Index

IA2	Second interim analysis
IA3	Third interim analysis
ICER	Incremental cost-effectiveness ratio
IFNα-2b	Interferon-alpha 2b
ITT	Intention-to-treat
KM	Kaplan–Meier
KN-716	KEYNOTE-716 (trial)
KPS	Karnofsky performance status
KSR	Kleijnen Systematic Reviews Ltd
LPI	Last patient in
LPS	Lansky performance status
LRR	Locoregional recurrence
LS	Least squares
LY	Life year
M0	Metastases not present
M1C	Metastases present in a non-central nervous system location
M1D	Metastases present in a central nervous system location
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities (MIMS
MJ	Matters of judgement
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme
N	Number of patients
N/A	Not available
N0	(Lymph) node has no cancer
N1C	(Lymph) node has presence of in-transit, satellite and/or microsatellite metastases
NCI	National Cancer Institute
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Heath and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reached
NX	(Lymph) node cannot be evaluated
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD-1	Programmed (cell) death protein 1
PD-L 1/2	Programmed (cell) death ligand ½
PEG-IFNα-2b	Pegylated interferon-alpha 2b
Pembro	Pembrolizumab
PFS	Progression-free survival
PHE	Public Health England
PICOTS	Population, interventions, comparators, outcomes, timeframe, study design
PK	Pharmacokinetic(s)
POL-103A	Polyvalent melanoma vaccine 103A
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRFS	Progression/recurrence-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services

PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
QxW	Every x weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RF	Recurrence-free
RFS	Recurrence-free survival
rhGM-CSF	Recombinant human granulocyte macrophage-colony stimulating factor
RoB	Risk of bias
RoB2	Cochrane risk of bias tool version 2
SAE	Serious adverse event
SD	Standard deviation
SF-6D	Short-form-6 dimension
SIGN	Scottish Intercollegiate Guidelines Network
SITC	Society for Immunotherapy of Cancer
SLN	Sentinel lymph node
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Society for Melanoma Research
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TNM	Tumour, nodes, metastases
TRAE	Treatment-related adverse event
TSD	Technical Support Document
T-Stage	Tumour stage
UK	United Kingdom
UMC	University Medical Centre
US	United States
USON	United States Oncology Network
UV	Ultraviolet
VAS	Visual analogue scale

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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. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues, Section 1.2 presents the key model outcomes, Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problems), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view and not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	The results described in the CS are not generalisable to adolescent patients (aged 12 to 17 years) because only one patient in this age category was allocated to each treatment arm of the included RCT (2 patients in total).	1.3 and 2.1
2	The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W. No clinical data are available to demonstrate the comparability of efficacy and safety outcomes between the two dosing regimens therefore the relative effects are uncertain.	1.3 and 2.2
3	There is a larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in UK clinical practice. This may result in an overestimation of the therapeutic benefits of the product for the overall population with stage 2B or 2C melanoma in the UK.	1.4, 3.2.3 and 3.2.5.2
4	No data were provided for OS or DMFS and this hinders a full evaluation of effectiveness and cost effectiveness of the product.	1.4, 3.2.5.1 and 3.2.5.3
5	The use of separate regression models for the estimation of RF utility and AE disutility (regression model 1) and LRR and DM utilities (regression model 2) may have had an effect on the ICER of unclear magnitude and direction.	1.5 and 4.2.8
6	The assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs may not be plausible. The ICER may increase or decrease depending on the specific assumptions made.	1.5, 4.2.9 and 5.1

AE = adverse event; CS = company submission; DM = distant metastases; DMFS = distant metastasis-free survival; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; OS = overall

ID1457	Summary of issue	Report Sections
survival; Q3W = every 3 weeks; Q6W = every 6 weeks; RCT = randomised controlled trial; RF = recurrence free; UK = United Kingdom		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the incidence of recurrences (i.e., transition from the recurrence free (RF) health state to the locoregional recurrence (LRR) and distant metastases (DM) health states)

Overall, the technology is modelled to affect costs by:

- Adjuvant treatment costs in the RF health state
- Subsequent treatment costs in the LRR and DM states
- Disease management costs in the DM state

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on adolescent patients (Table 1.2) and uncertainty about the comparability of the two recommended dosing regimens of pembrolizumab (Table 1.3).

Table 1.2: Key issue 1. The results are not generalisable to adolescent patients

Report Section	2.1
Description of issue and why the ERG has identified it as important	The results presented in the submission are not generalisable to adolescent patients (aged 12 to 17 years). The KEYNOTE-716 RCT recruited one patient aged 12 to 17 years to each treatment arm (two such patients in total). This means that the clinical effectiveness results cannot be reliably generalised to this population subgroup.
What alternative approach has the ERG suggested?	Conduct further RCTs that focus on the recruitment of people aged from 12 to 17 years.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further RCTs that focus on the recruitment of people aged from 12 to 17 years.
ERG = Evidence Review Group; RCT = randomised controlled trials	

Table 1.3: Key issue 2. Uncertainty about the comparability of the two recommended doses of pembrolizumab

Report Section	2.2
Description of issue and why the ERG has identified it as important	The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W, administered as an intravenous infusion over 30 minutes. There is uncertainty about the

Report Section	2.2
	comparability of the efficacy and safety profiles of the two recommended doses of pembrolizumab. In the KEYNOTE-716 RCT, only the 200 mg Q3W dose was evaluated. The ERG could not identify any relevant clinical outcomes in order to make a comparison between the two dosing regimens. Therefore, the relative clinical impact of the two dosing regimens is uncertain.
What alternative approach has the ERG suggested?	The two dosing regimens for pembrolizumab need to be assessed with respect to clinical outcomes.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Availability of data on clinical outcomes in relation to the two dosing regimens for pembrolizumab.
ERG = Evidence Review Group; Q3W = every 3 weeks; Q6W = every 6 weeks; RCT = randomised controlled trial	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Regarding the clinical effectiveness evidence, the ERG identified two key issues, namely:

1. A larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in United Kingdom (UK) clinical practice (see Table 1.4), and:
2. No available data for overall survival (OS) or distant metastasis-free survival (DMFS (see Table 1.5).

Table 1.4: Key issue 3. The trial population does not reflect UK clinical practice

Report Section	3.2.3, 3.2.5.2
Description of issue and why the ERG has identified it as important	The trial population for the KEYNOTE-716 RCT may not be a good reflection of that seen in UK clinical practice in terms of the distribution of different stages of melanoma. Among the overall population recruited to KEYNOTE-716, 64.0% of patients had stage 2B and 34.8% had stage 2C melanoma. Data published by PHE suggested that the respective proportions for the UK 57.0% and 43.0%. Therefore, a larger proportion of patients in KEYNOTE-716 had less severe disease compared with people seen in UK clinical practice. Patients with stage 2B melanoma not only have a better prognosis than those with stage 2C, but subgroup analyses appear to show a better outcome for stage 2B.
What alternative approach has the ERG suggested?	Further RCTs with recruitment of participants that are a better representation of people seen in UK clinical practice; or adjustment for the difference between the trial and UK populations.
What is the expected effect on the cost effectiveness estimates?	It is possible that the higher prevalence of people with stage 2B melanoma in the KEYNOTE-716 RCT compared with the UK population may result in an overestimation of the therapeutic

Report Section	3.2.3, 3.2.5.2
	benefits in relation to the overall population with stage 2B or 2C melanoma in the UK and thus an underestimation of the ICER.
What additional evidence or analyses might help to resolve this key issue?	Further RCTs with recruitment of participants that are a better representation of people seen in UK clinical practice; or adjustment for the difference between the trial and UK populations.
ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; PHE = Public Health England; RCT = randomised controlled trial; UK = United Kingdom	

Table 1.5: Key issue 4. No data reported for overall survival or distant metastasis-free survival

Report Section	3.2.5.1 and 3.2.5.3
Description of issue and why the ERG has identified it as important	No data were provided for OS or DMFS. The analyses for OS and DMFS are event driven, with the final analyses anticipated to take place when [redacted] and [redacted] events have occurred respectively. These data are not yet available from the KEYNOTE-716 RCT. Absence of data on these outcomes hinders a full evaluation of pembrolizumab for adjuvant treatment of people with resected stage 2 melanoma with high risk of recurrence.
What alternative approach has the ERG suggested?	An interim analysis of available data would have been very useful for both outcomes (data from the next interim analysis are expected to be available in June 2022). This said, the ERG appreciates that the relatively low number of events for each outcome would have required caution in the interpretation of results.
What is the expected effect on the cost effectiveness estimates?	The impact of the absence of data on OS and DMFS on clinical and cost effectiveness estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	Provision of the results of interim analyses for both outcomes would be helpful.
ERG = Evidence Review Group; DMFS = distant metastasis-free survival; OS = overall survival; RCT = randomised controlled trial	

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

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are summarised in Tables 1.6 and 1.7 below.

Table 1.6: Key issue 5. The use of separate regression models for the estimation of RF utility and AE disutility (regression model 1), and LRR and DM utilities (regression model 2).

Report Section	4.2.8
Description of issue and why the ERG has identified it as important	The company used two separate regression models to estimate the utility values of the RF state and the LRR and DM states.

Report Section	4.2.8
What alternative approach has the ERG suggested?	The ERG would have preferred that the company conducted one regression model for the estimation of utility values in the RF, LRR and DM states, and the estimation of grade 3+ AEs disutility.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	A single regression model including binary indicators for being in the LRR state, being in the DM state and grade 3+ AEs.
AE = adverse event; DM = distant metastases; ERG = Evidence Review Group; LRR = locoregional recurrence; RF = recurrence free	

Table 1.7: Key issue 6. Plausibility of assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs.

Report Section	4.2.9 and 5.1
Description of issue and why the ERG has identified it as important	1. The company made assumptions regarding the proportions of patients in the pembrolizumab arm receiving subsequent treatments in the LRR and DM health states that were not in line with evidence from KEYNOTE-716 subsequent treatment data. 2. It is unclear whether assumptions regarding subsequent treatment duration in the DM state are clinically plausible. 3. Terminal care costs were only applied to patients who transitioned to the death state from the DM state.
What alternative approach has the ERG suggested?	1. Analyses assuming equal proportions of patients receiving subsequent treatment after LRR and DM in the pembrolizumab and routine surveillance arm. 2. Extreme scenario analysis excluding subsequent treatment acquisition costs in the DM state. 3. Analysis assuming terminal care costs for all patients that transitioned to the death state.
What is the expected effect on the cost effectiveness estimates?	1. Equal subsequent treatment after LRR increased the ICER, whereas equal subsequent treatment after LRR and DM decreased the ICER. 2. Excluding subsequent treatment acquisition costs in the DM state increased the ICER. 3. Terminal care costs for all dying patients slightly increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	1. N/A 2. Further evidence to justify the plausibility of the relatively long subsequent treatment duration in the DM states which resulted in high subsequent treatment costs in the DM state. 3. N/A
DM = distant metastases; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; N/A = not applicable	

1.6 Other key issues: summary of the ERG's view

No other key issues were identified.

1.7 Summary of the ERG's view

The company's cost effectiveness model was consistent with the NICE reference case. The most prominent issues highlighted by the ERG were: 1) handling of subsequent treatments after recurrence (both in terms of cost and effectiveness); 2) estimation of transition probabilities from the recurrence free health state; 3) estimation of health state utility values (HSUVs); 4) implementation of terminal care costs and 5) the proportion of recurrence-free survival (RFS) benefit (i.e., increment) accrued beyond the observed data period.

The CS base case probabilistic and deterministic ICERs were £6,761 and £4,616 per QALY gained, respectively. In addition to the above mentioned issues, in the clinical effectiveness sections, it was highlighted that there is uncertainty about the comparability of the efficacy and safety profiles of the two recommended doses of pembrolizumab, i.e., 200 mg every three weeks (Q3W) and 400 mg every six weeks (Q6W). A scenario analysis, conducted by the company, assuming that only the treatment costs would differ between the two recommended doses of pembrolizumab (i.e., assuming equal efficacy and safety), changed the ICER from £4,616 per QALY gained (for 400 mg Q6W) to £5,300 per QALY gained (for 200 mg Q3W).

The ERG base case probabilistic and deterministic ICERs were, based on the ERG preferred assumptions highlighted in Section 6.1, £11,107 and £13,550 per QALY gained, respectively. The most influential adjustment was assuming alternative subsequent treatment proportions/market share in the LRR health state. The ICER increased most in the scenario analysis with alternative assumptions regarding transition probabilities from the RF health state and assuming no subsequent treatment costs in the DM health state.

Table 1.8: Deterministic ERG base case

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	4,616
Company base case + 1 Alternative utility estimate for RF							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	4,790
Company base case + 2 Alternative utility estimate for DM post progression							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	4,764
Company base case + 3 Alternative subsequent treatment proportions/market share in LRR health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	10,045
Company base case + 4 Alternative implementation of end of life costs							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	5,047
ERG base case (1-4)							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	11,107

DM = distant metastases; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; LY = life year; QALY = quality-adjusted life year; RF = recurrence free

Table 1.9: Deterministic scenario analyses (conditional on ERG base case)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ERG base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	11,107
ERG base case + 1 Weilbull-Generalised gamma distributions for transition probabilities from the RF health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	10.721	[redacted]	[redacted]	[redacted]	[redacted]	22,537
ERG base case + 2 Gompertz-Generalised gamma distributions for transition probabilities from the RF health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	10.719	[redacted]	[redacted]	[redacted]	[redacted]	4,231
ERG base case + 3 Alternative transition probabilities in the LRR health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.921	[redacted]	[redacted]	[redacted]	[redacted]	11,075
ERG base case + 4 No subsequent treatment costs in the DM health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	19,035
ERG base case + 5 Alternative subsequent treatment proportions/market share in DM health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	729
ERG base case + 6 Alternative model structure for DM health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	10,708

DM = distant metastases; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; LY = life year; QALY = quality-adjusted life year; RF = recurrence free

Table 1.10: Probabilistic CS base case and ERG base case

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.980	[redacted]	[redacted]	[redacted]	[redacted]	6,761
ERG base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.980	[redacted]	[redacted]	[redacted]	[redacted]	13,550

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
Population	People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection (at high risk of recurrence).	People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection.	By definition, patients with 2B and 2C melanoma are at high risk of recurrence.	The population is in line with the NICE scope. However, only one adolescent (12 to 17 years) was recruited to each arm.
Intervention	Pembrolizumab	Pembrolizumab	N/A	The intervention is in line with the NICE scope.
Comparator(s)	Routine surveillance	Routine surveillance	N/A	The comparators are in line with the NICE scope.
Outcomes	• OS • RFS • DMFS • Adverse effects of treatment • HRQoL	• RFS • Adverse effects of treatment • HRQoL	As the analyses of OS and DMFS are event driven (final analyses expected to take place when [redacted] events and [redacted] events have occurred, respectively), these data are not yet available from KEYNOTE-716.	The outcomes reported are not in line with the NICE scope because OS and DMFS data are not yet available from the KEYNOTE-716 trial.

Based on: Table 1, page 10 of the CS[1]

CS = company submission; DMFS = distant metastasis-free survival; ERG = Evidence Review Group; HRQoL = health-related quality of life; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; RFS = recurrence-free survival

2.1 Population

The population defined in the scope is: *'People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection (at high risk of recurrence)'*.[2] The population in the company submission (CS)[1] is in line with the scope. However, the KEYNOTE-716 study included small numbers of patients who are aged 12 to 17 with one adolescent recruited to each arm.[1] Therefore, results may not be representative for adolescent patients. The Evidence Review Group (ERG) has noted this as a key issue.

The marketing authorisation for pembrolizumab in this indication is expected to be granted by the European Commission in [redacted], and subsequently adopted by the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted]. Pembrolizumab is anticipated to be indicated for use [redacted]

Contraindications include hypersensitivity to the active substance or to any of the excipients (L-histidine; L-histidine hydrochloride monohydrate; Sucrose; Polysorbate 80 (E433); Water for injections).

2.2 Intervention

The intervention (pembrolizumab) is in line with the NICE final scope.[2]

Pembrolizumab is administered via intravenous infusion, initiated and supervised by specialist physicians experienced in the treatment of cancer. The anticipated posology of pembrolizumab, for this indication, is as follows:

- The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W), administered as an intravenous infusion over 30 minutes.

Pembrolizumab should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

It should be noted that there are two recommended doses: 200 mg Q3W and 400 mg Q6W. However, in the KEYNOTE-716 study, patients only received the 200 mg Q3W dose. In the clarification letter (question A.8), the ERG asked the company to discuss the implications on effectiveness and safety of the difference in dosing regimen, supported by evidence where available. The company responded that: *"Pembrolizumab doses of 2 mg/kg every 3 weeks (Q3W), 10 mg/kg Q3W, and 10 mg/kg every 2 weeks (Q2W) were evaluated in melanoma or previously treated non-small cell lung cancer (NSCLC) clinical trials. Based on the pharmacokinetic modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg Q3W, 2 mg/kg Q3W, and 400 mg Q6W as monotherapy."* They also stated that: *"regulatory authority was satisfied that this was the case when the posology changes were approved."*[3]

According to the company, no additional tests or investigations are required before initiating pembrolizumab treatment in this indication (CS, page 12).[1]

ERG comment: Section 4.2 of the summary of product characteristics (SmPC) states that: *"The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes"*.[4] The update of this Section with the amendment allowing for a 400 mg Q6W regimen was issued after authorisation by the European

Medicines Agency (EMA) (application II/0062 with the commission decision issued on 28.03.2019). The underpinning evidence was described as "*modelling and simulation of dose/exposure relationships for the efficacy and safety of pembrolizumab*" and it was also stated that no new clinical or pre-clinical studies were submitted as part of the application.[5] A subsequent application to the EMA in relation to allowing for a 400 mg Q6W regimen of pembrolizumab (application II/0102, commission decision issued on 21.05.2021) was stated to have been based on interim efficacy and safety results from Cohort B in the open-label KEYNOTE-555 trial.[5] No references to this trial were provided by the company and so the ERG performed a quick web-based search to find any publication of the results. No full papers could be located, but the most complete publication was an abstract published in 2021.[6] This abstract reported that the study had enrolled 101 treatment-naïve unresectable stage 3 or 4 melanoma patients with advanced disease and the study concluded that: *"1L treatment with pembro 400 mg Q6W yielded a clinically meaningful ORR in pts with advanced melanoma. PK, efficacy and safety results from KEYNOTE-555 Cohort B support prior findings from the model-based assessment and indicate that the benefit-risk profile for the more practical pembro 400 mg Q6W regimen is consistent with that of 200 mg or 2 mg/kg Q3W regimens"*.[6] None of the efficacy outcomes listed in the NICE final scope for this appraisal (overall survival (OS), recurrence-free survival (RFS), distant metastasis-free survival (DMFS) or health-related quality of life (HRQoL)) were reported. Instead, the following were reported:

- The overall response rate (ORR) was 50.5% (95% confidence interval (CI) 40.4 to 60.6); 12.9% of patients had a complete response (CR) and 37.6% had a partial response (PR).
- Median progression-free survival (PFS) was 13.8 months (95% CI 3.0 to upper limit not reached); estimated PFS rates were 56.5% at 6 months and 54.3% at 12 months.
- Treatment-related adverse events (TRAEs) of any grade occurred in 79.2% of patients (grade 3 to 4 in 6.9% of patients; no deaths occurred due to a TRAE). The most common immune-mediated adverse events (AEs) were hyperthyroidism (6.9%) and hypothyroidism (6.9%).

Following their approval of this new dosing regimen, the United States (US) Food and Drug Administration (FDA) stated that: *"This new dosing regimen is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)."*[7]

In their response to clarification question A.8, the company stated that: "*Based on the pharmacokinetic modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg Q3W, 2 mg/kg Q3W, and 400 mg Q6W as monotherapy.*"[3] However, it is unclear how this judgement was made. The concluding statement from the above publication of KEYNOTE-555 suggested that the benefit-risk profile for the pembrolizumab 400 mg Q6W regimen is consistent with that of the 200 mg or 2 mg/kg Q3W regimens but no comparative efficacy data were reported to support this notion.[6] Furthermore, the data from the KEYNOTE-555 trial is in a different population to the decision problem i.e., stage 3 or 4 unresectable melanoma as opposed to stage 2 resected melanoma. EMA approval does not imply that there are no differences between the 400 mg Q6W and 200 mg Q3W dosing regimens or that such differences might not be clinically relevant or affect the incremental cost-effectiveness ratio (ICER) in such a way as to have implications for reimbursement decision making. Therefore, this remains a key issue.

2.3 Comparators

The description of the comparators in the NICE scope is 'Routine surveillance'.[2]

According to Section B.2.13.2 of the CS:[1] "*the efficacy and safety of adjuvant pembrolizumab was directly compared with that of placebo.*" Furthermore, the company goes on to say that in the KEYNOTE-716 randomised controlled trial (RCT): "*...placebo was in line with routine surveillance which represents the current recommended management of patients with surgically resected stage 2B and 2C melanoma.*"[8, 9] As such, the comparison of adjuvant pembrolizumab to placebo in KEYNOTE-716 directly addresses the decision problem specified by the NICE scope" (CS page 49).[1]

ERG comment: The NICE scope requested that the comparator be routine surveillance, as that is the established current management strategy after surgical resection in stage 2 patients. Because both arms had routine surveillance in the KEYNOTE-716 trial, the actual comparator was placebo + surveillance. The overall comparison was therefore pembrolizumab + surveillance versus placebo + surveillance. Although not strictly in line with the NICE scope this study design makes sense clinically, as well as being the only ethical option, because all patients must have surveillance. Since the placebo is medically inert, the placebo participants will effectively only have surveillance (as per the NICE scope) as an 'active' treatment, but at the same time the use of placebo medication will be an effective way to maintain blinding and avoid bias from placebo effects.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- OS
- RFS
- DMFS
- AEs of treatment
- HRQoL

As outlined in the decision problem (Table 2.1 of this report), the analyses of OS and DMFS are 'event driven', with final analyses anticipated when [redacted] events and [redacted] events have occurred, respectively. The data are not yet available from the KEYNOTE-716 RCT (Table 2.1). However, RFS, AEs and HRQoL were assessed in KEYNOTE-716.

The company states that the absence of OS and DMFS data 'should not be a barrier to effective decision-making given the significant benefit demonstrated in the RFS data from the KEYNOTE-716 trial, and the success of adjuvant therapies in the stage 3 setting'. The company goes on to say that '*In prior NICE appraisals for adjuvant treatments in stage 3 melanoma (TA544, TA684, TA766) mature OS and DMFS data were not available, and improvements in RFS were considered by the committee to be associated with a DMFS and OS benefit.*[10-12]' (CS page 50).[1]

In light of the numbers of OS and DMFS events only being reported for the total population, and not per treatment arm, the ERG asked the company to provide numbers by treatment arm (clarification letter, question A8). The company responded that: "*MSD are unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm, as these data are not available*" and "*Full results from this analysis* [IA3]*, which will include DMFS events by arm, are expected to be available in* [redacted]".[1]

2.5 Other relevant factors

According to the company: "*pembrolizumab has the potential to introduce an important step-change in the management of stage 2B and 2C melanoma in clinical practice in England*" (CS Section B.2.12).[1]

A Patient Access Scheme (PAS) is in place which makes pembrolizumab available to the National Health Service (NHS) for a discount. The details of the discount are described in Table 2 of the CS (page 12).[1]

According to the company, pembrolizumab does not meet the NICE end of life criteria in this indication (CS Section B.2.13.3, page 50).[1]

Regarding equality considerations, the company states that "*it is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities*" (CS Section B.1.4).[1]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the CS.[1] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[13, 14] The ERG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS detailed the systematic literature review (SLR) undertaken to identify relevant literature relating to adjuvant therapies in adult and paediatric (≥12 years) patients with surgically resected stage 2B and 2C melanoma.[15] The searches were conducted in September 2021. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE	Ovid	2011-current	16/9/21
Embase	Ovid	2011-current	16/9/21
CENTRAL CDSR	EBM (Ovid)	2011-current	16/9/21
Conferences			
AACR	Via Northern Light Life Sciences Conference database	2018–2021	16/9/21
ASCO		2018–2021	
ESMO		2018–2021	
SITC		2018–2021	
SMR	https://www.societymelanomaresearch.org/*	2018-2019	28/9/21
ESMO 2021	https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021*	2021	28/9/21
Additional searches			
Clinicaltrials.gov			21.12.21
Handsearching	The bibliographies of selected SLRs and meta-analyses published in the recent three years were reviewed before exclusion		

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; ESMO = European Society of Medical Oncology Targeted Anticancer Therapies; SITC = Society for Immunotherapy of Cancer; SMR = Society for Melanoma Research
*Searched manually as not yet available on Northern Light at time of searching

ERG comment:

- The CS[1] and response to clarification[3] provided sufficient details for the ERG to appraise the literature searches.

- A good range of databases, clinical trials registers and additional grey literature resources were searched. Searches of named conference proceedings were undertaken via Northern Light and supplemented with manual searches where proceedings were not yet available via the database.
- At clarification the ERG queried the outcome of a reported ClinicalTrials.gov search for which no results were reported. The company reported that the search which had been limited to active/recruiting trials, retrieved 70 results, none of which were relevant to the decision problem.
- For the original SLR, the company searched Embase and MEDLINE simultaneously using a single database provider (Ovid) and search strategy. The strategy combined the Scottish Intercollegiate Guidelines Network (SIGN) filters of study types for both MEDLINE and Embase.[16]
- Results were limited by publication date from 2011 onwards, with a limit of 2018 to 2021 for conference abstracts. No language limits were applied. When queried regarding the rationale behind the 10-year date limit the company justified its appropriateness by stating that prior to 2011 *"treatment options for patients with metastatic melanoma or high-risk stage 2 disease were limited and no significant impact on survival was observed. Since 2011, there have been marked changes in the management of metastatic melanoma or high-risk stage 2 disease including adjuvant treatment options"*.[3] The ERG does not find this argument plausible as at least some relevant interventions (e.g., comparator regimens such as routine surveillance or observation) were applicable in clinical practice before 2011.
- Unlike the strategies employed by the cost effectiveness SLR, the clinical effectiveness searches contained limited use of free text synonyms and truncation for the condition of interest. Whilst the use of Emtree subject headings for the term 'melanoma' would have mitigated against some loss of recall, the Emtree term for 'adjuvant' was missing and may have affected the overall recall of results.
- The ERG queried the structure of the clinical effectiveness searches: (Melanoma AND (Stage 2 or resected) AND adjuvant) AND (limits: RCTs/Observation studies, No Animals/2011-C). The company responded that the facets were in line with both the anticipated marketing authorisation and the population in KEYNOTE-716 trial. However, given the low number of hits retrieved the ERG feels that a more sensitive approach may have beneficial. Unfortunately, the ERG was unable to undertake independent clinical effectiveness searches and review the results within the single technology appraisal (STA) timeline, as this would be outside of the ERG remit, so are unable to say what impact these limitations may have had on the overall recall of results. However, combined with the other limitations listed above, the ERG is concerned that some relevant papers may have been missed.

3.1.2 Inclusion criteria

The company performed an SLR to evaluate the evidence on the clinical effectiveness (efficacy and safety) of adjuvant therapies (pembrolizumab and relevant comparators) in adult and paediatric (≥12 years) patients with surgically resected stage 2B and 2C melanoma. The SLR was conducted in September 2021 according to the study eligibility criteria summarised in Table 3.2 below.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion Criteria	Exclusion Criteria
Population	Adult and paediatric patients (aged 12 years and older) with surgically resected stage 2B/2C cutaneous melanoma	Patients with diseases other than surgically resected stage 2B/2C cutaneous melanoma[†] Patients aged younger than 12 years old

	Inclusion Criteria	Exclusion Criteria
Interventions/ Comparators	Pharmacologic adjuvant therapies: • Pembrolizumab • Nivolumab • Ipilimumab • Interferon • Dabrafenib + trametinib combination therapy • POL-103A polyvalent melanoma vaccine • CSF-470 vaccine plus BCG and rhGM-CSF • Observation, best supportive care, or placebo • Any other adjuvant therapies	Treatments other than pharmacologic adjuvant therapies
Outcomes	At least one of the following outcomes[‡]: • OS • EFS • DFS • PFS • RFS • DMFS • Time to subsequent treatment/surgery • Grade 3-5 TEAEs • Grade 3-5 TRAEs • SAEs • Treatment discontinuation due to AE Patient-reported outcomes, including: • Health utility values measured with generic preference-based methods, e.g., EQ-5D, HUI, and SF-6D • QoL measured with instruments including EORTC QLQ-C30, FACT-M, and Skindex-17	Studies not reporting any of the outcomes specified
Time	Full text articles: 1 January 2011 to 16 September 2021 Conference abstracts: 1 January 2018 to 28 September 2021	Full text articles that published before 2011[§] Conference abstracts published before 2018
Study design	RCTs Non-randomised clinical trials Observational cohort studies	Case-control studies, cross-Sectional studies, case reports, and case series SLRs and meta-analyses or review articles[¶]
Others	Geographic location: any Subjects: human only	

	Inclusion Criteria	Exclusion Criteria
Based on Table 5 of Appendix D of the CS[15] †Patients with mixed stages of melanoma (e.g., stages 1–3) including stage 2B/C were included if subgroup results of patients with surgically resected stage 2B/C melanoma were reported. ‡EFS and PFS were not commonly used in melanoma studies in the adjuvant treatment setting; however, these two measures were included for completeness. §Search was restricted to identify articles published after 2011 since evidence in the target population is limited before 2011. ¶Bibliographies of selected SLRs and meta-analyses published in recent 3 years were reviewed before exclusion. AE = adverse event; BCG = Bacillus Calmette-Guerin; CS = company submission; CSF = colony stimulating factor; DFS = disease-free survival; DMFS = distant metastasis-free survival; EFS = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACT-M = Functional Assessment of Cancer Therapy – Melanoma; HUI = health utilities index; OS = overall survival; PICOTS = population, interventions, comparisons, outcomes, timeframe, study design; PFS = progression-free survival; QoL = quality of life; RCT = randomised controlled trial; RFS = recurrence-free survival; rhGM-CSF = recombinant human granulocyte macrophage-colony stimulating factor; SAE = serious adverse event; SF-6D = Short-form six-dimension; SLR = systematic literature review; TEAEs = treatment emergent adverse events; TRAEs = treatment related adverse events		

ERG comments:

Comparators

It could be inferred that the comparator defined in the NICE final scope[2] ('*routine surveillance*') has been expressed by the comparators listed in the company's study eligibility criteria in Table 3.2 above ('*Observation, best supportive care, or placebo*').[15] However, the term '*observation*' with no further definition could refer to a less intensive type of follow-up where the regular photography of the skin and active monitoring for recurrence, as would be expected in routine surveillance, may not be recommended. Since people with stage 2B or 2C cutaneous melanoma who have undergone complete resection are at a high risk of recurrence, '*observation*' without further definition may not be an appropriate comparator. The ERG concurs that if observation and routine surveillance are used interchangeably in the literature, relevant evidence may not have been overlooked, however, the ERG is still uncertain about the applicability of this SLR comparator relative to what has been defined in the NICE final scope.[2]

In order to gain clarification, the ERG asked the company (in clarification question A9) to further justify that routine surveillance as observed in the KEYNOTE-716 trial is reflective of routine surveillance in the NHS in England. The company's response[3] was as follows:

"According to the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of cutaneous melanoma, there is no consensus on the frequency of follow-up examinations and the use of imaging techniques and blood tests for patients with resected melanoma. In the KEYNOTE-716 trial, routine surveillance of disease involved tumour imaging for the abdomen, pelvis and brain. The protocol stipulated that the preferred method of imaging for the abdomen and pelvis was by computerised tomography (CT) scan. For the brain, magnetic resonance imaging (MRI) was preferred. This is in line with imaging surveillance guidance published by Melanoma Focus for the follow-up of high risk cutaneous melanoma in the UK, which recommends imaging by CT for the chest, abdomen and pelvis, plus imaging by MRI for the head.

Furthermore, the guidance from Melanoma Focus recommends imaging should occur at baseline and then be repeated 6 monthly to 3 years, then annually to 5 years. Clinical experts confirmed that in UK clinical practice, patients receiving adjuvant treatment undergo general surveillance post-treatment in

line with these current guidelines. This is reflected in the KEYNOTE-716 trial, where tumour scans were prespecified at the following intervals:

- *Initial tumour scans were performed at Screening, within 28 days of randomisation*
- *The first on-study scan time point was performed 6 months (26 weeks ± 7 days) from the date of randomisation*
- *Subsequent tumour scans were then performed every 6 months (26 weeks ± 7 days) while on treatment*
- *A further scan was performed at the end of treatment*
- *Tumour scans were then performed every 6 months (26 weeks ± 14 days) from years 2 to 4 after randomisation*
- *Finally, a scan was performed once in year 5 (365 ± 28 days) from randomisation or until recurrence, whichever occurred first.*

As such, routine surveillance as observed in the KEYNOTE-716 can be considered reflective of routine surveillance in the NHS in England."

In line with Larkin 2013[9], the ERG is satisfied that the comparator in the KEYNOTE-716 trial is reflective of routine surveillance in clinical practice for England/the UK.

Date restrictions

The date restrictions of January 2011 to September 2021 for full-text articles and January 2018 to September 2021 for conference abstracts featured both in the search strategy (Section 3.1.1 above) and in the study eligibility criteria (Table 3.2 above) of the CS.[1] The ERG critique of this restriction is outlined in Section 3.1.1 above and therefore not repeated here.

Study designs

The restrictions placed on study design to identify only RCTs, interventional non-RCTs and observational studies, appears to be appropriate.

Review methods

The company stated that: *"each abstract was assessed for inclusion by two independent reviewers using the eligibility criteria"* and also that *"each full-text article was then assessed for inclusion by two independent reviewers using the eligibility criteria".*[15] They also mention that disagreements were settled through discussion until a consensus was met, or resolved by a third reviewer. This appears to have followed best practice in systematic review methods as recommended by Cochrane (formerly: The Cochrane Collaboration).[17]

3.1.3 Critique of data extraction

Appendix D states the data items were prespecified and that: *"information from included studies were extracted independently by two individuals, with a third individual resolving any discrepancies, where necessary".*[15] The ERG is satisfied that this reflects recommended best practice in systematic review methods.[17]

3.1.4 Quality assessment

The company proposed to conduct quality assessments of included RCTs using the revised Cochrane risk of bias tool version 2 (RoB2)[18] for randomised trials and to make use of the Downs and Black checklist[19] to assess risk of bias for non-randomised clinical trials and observational cohort studies.

ERG comment: In its clarification letter, the ERG asked the company to confirm how many reviewers were involved in the quality assessment of included studies for the clinical evidence SLR; whether there were discrepancies in the quality assessments; and if so, how they were resolved. In its response to clarification, the company stated that: *"For the clinical evidence SLR, three reviewers were involved in the quality assessments of the included studies. Two reviewers conducted the quality assessments independently and any discrepancies were reconciled by a third reviewer. No discrepancies were identified"*.[3] The ERG considers the proposed choice of quality appraisal tools and methods for their application to be appropriate.

Although *"seven publications corresponding to seven unique studies were considered eligible for data extraction"*, the company considered only the publication reporting on the KEYNOTE-716 (NCT03553836)[20] to be of relevance to this appraisal and did not conduct quality assessments on the other six publications.[15] The company's RoB assessment of the KEYNOTE-716 trial has been explored in Section 3.2.4 of this report.

3.1.5 Evidence synthesis

Given that the KEYNOTE-716 RCT provided robust, head-to-head data for pembrolizumab versus routine surveillance, and only this one trial was identified that evaluated the efficacy and safety of pembrolizumab in patients with surgically resected stage 2B and 2C cutaneous melanoma, the company did not perform a meta-analysis.[1]

An SLR and consequent network meta-analysis (NMA) was performed to identify and synthesise RCT evidence evaluating the efficacy of interventions for first-line treatment of advanced melanoma, which informed the cost effectiveness model hazard ratio (HR) inputs for subsequent advanced melanoma treatments.[1, 15] The SLR and its associated NMA were discussed in B.3.3.3 of the CS[1] and are referred to in Section 4.2 of this report. The SLR and NMA are not discussed here because they are not directly applicable to clinical effectiveness relating to the decision problem i.e., stage 2B or 2C cutaneous melanoma.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

In the abstract/title screening phase of the CS SLR, 552 records were excluded and 161 were retained for full text screening.[15] The full text screening yielded seven included records and 154 excluded records. Exclusions were because of irrelevant: populations (n=106); interventions (n=12); outcomes (n=31); study designs (n=3); or because of article duplication (n=2). The included records reported seven unique studies, including five clinical trials and two observational studies, as shown below:

- **EORTC 18081** is an open-label phase III RCT that compared pegylated interferon-alfa2b (PEG-IFNα-2b) with observation.[21]
- **BRIM8** is a triple-blind phase III RCT that compared vemurafenib with placebo.[22]
- **Nordic IFN** is an open-label phase III RCT that compared 1-year treatment with interferon alfa-2b (IFNα-2b) and 2-year treatment with IFNα-2b with observation.[23]
- **Wilson 2021** is an investigator initiated, open-label single-arm trial of nivolumab.[24]
- **KEYNOTE-716** is a double-blind phase III RCT that compared pembrolizumab with placebo.[25]
- **Akman 2015** is a retrospective analysis of medical records from patients treated with IFNα-2b.[26]
- **Bilgin 2012** is a prospective study that investigated the efficacy of chemoimmunotherapy (interferon, dacarbazine, and other treatments based on patients' disease history).[27]

Of the identified studies, only KEYNOTE-716[25] reported on pembrolizumab as the intervention and also included data on the comparator. As such KEYNOTE-716[25] is the only study of relevance to this appraisal.

3.2.1 Details of the included trial: the KEYNOTE-716 trial

The CS[1] identified the KEYNOTE-716 trial as the only RCT evaluating pembrolizumab for resected stage 2 melanoma. The relevant publications cited in the CS[1] are two abstracts[25, 28] and the clinical study report (CSR).[29]

KEYNOTE-716 is a double-blind, randomised, placebo-controlled, multi-centre, phase III trial to determine the efficacy and safety of pembrolizumab for reducing disease recurrence in patients (≥12 years) with surgically resected stage 2B and 2C cutaneous melanoma. There are two parts to the trial: part one is ongoing, and comprises an initial randomised phase of 51 weeks, followed by the unblinded crossover/rechallenge phase of the study (part two) in which eligible patients with disease recurrence, from either the pembrolizumab arm or placebo arm, can receive adjuvant treatment with pembrolizumab. No results have yet been obtained for part two, and therefore the CS[1] only pertains to part one.

Participants in the treatment arm were administered intravenous pembrolizumab (N=487) over 17 cycles at 2 mg/kg (maximum 200 mg) Q3W for paediatric participants (≥12 and <18 years old) and at 200 mg Q3W for adults (≥18 years of age). Treatment started less than 12 weeks after complete surgical resection. Randomisation was achieved with stratification as follows: one stratum for paediatric patients (≥12 years of age and <18 years of age) and three strata for adult patients (≥18 years of age), each based on T-stage tumour thickness and ulceration (T3b, T4a, T4b, respectively). Attempts to ensure allocation concealment were made by use of "*an interactive response technology system*" (as described in Table 6 and Section B.2.13.2 of the CS).[1] The outcomes in the trial were RFS (the primary endpoint), HRQoL assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EuroQol-5 Dimension-5 level (EQ-5D-5L), DMFS, OS and AEs. A summary of the study methodology from KEYNOTE-716 is presented in Table 3.3.

Table 3.3: Study methodology for KEYNOTE-716

Study	KEYNOTE-716 (NCT03553836)[25, 28, 29]
Study design	Phase III, multi-centre, randomised, double-blind, placebo-controlled study (part one), followed by the unblinded crossover/rechallenge phase of the study in which eligible patients with disease recurrence, from either the pembrolizumab arm or placebo arm, can receive adjuvant treatment with pembrolizumab (part two). No results have yet been obtained for part two.
Location	160 centres in 16 countries: Australia, Belgium, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Poland, South Africa, Spain, Switzerland, United Kingdom (four sites; [redacted] patients) and United States.
Inclusion/ exclusion criteria	Inclusion: • Patients aged ≥12 years with recently surgically resected and histologically/pathologically confirmed new diagnosis of stage 2B or 2C cutaneous melanoma • Not previously treated for melanoma beyond complete surgical resection • No more than 12 weeks between final surgical resection and randomisation, with complete surgical wound healing • No evidence of metastatic disease on imaging as determined by investigator assessment; suspicious lesions amenable to biopsy confirmed negative for malignancy • Performance status of 0 or 1 on the ECOG Performance Scale at the time of enrolment, LPS score ≥50 (for patients ≤16 years old), or a KPS score ≥50 (for patients >16 and <18 years old) Exclusion: • Has a known additional malignancy that is progressing or has required active antineoplastic therapy (including hormonal) within the past 5 years • Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment • Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor • Has received prior systemic anticancer therapy for melanoma including investigational agents • Has received a live vaccine within 30 days prior to the first dose of study drug
Intervention(s)	Pembrolizumab (N=487) administered intravenously over 17 cycles at 2 mg/kg (maximum 200 mg) Q3W for paediatric participants (≥12 and <18 years old); 200 mg Q3W for adults (≥18 years of age). Treatment commenced less than 12 weeks after complete surgical resection.
Comparator(s)	Placebo (N=489) administered intravenously over 17 cycles. Treatment commenced less than 12 weeks after complete surgical resection.

Additional treatments	In both groups, patients were given active surveillance, in line with current practice. They were monitored for disease recurrence by imaging including full chest/abdomen/pelvis CT and/or (MRI), neck CT and/or MRI for head and neck primaries, and other CT and/or MRI (as clinically needed) every 6 months during treatment and at the end of treatment. Disease recurrence was confirmed by investigator radiographically and/or by exam/biopsy and, when clinically appropriate, confirmed by the site via pathology. Patients were also monitored for disease recurrence post-treatment (every 6 months from years 2 to 4 from randomisation and then once in year 5 from randomisation or until disease recurrence). Patients who had disease recurrence were then unblinded. The majority of patients treated with pembrolizumab (95.4%), and placebo (92.0%) took concomitant medications. The following are specific restrictions or prohibitions for concomitant therapy or vaccination during the course of the study: • Antineoplastic systemic chemotherapy, immunotherapy or biological therapy not specified in the protocol • Investigational agents other than pembrolizumab • Radiation therapy • Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed • Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI that is suspected to have an immunologic aetiology. Inhaled or topical steroids are allowed, and systemic steroids at doses ≤5 mg/m2/day (maximum allowed 10 mg/day) prednisone or equivalent for paediatric participants (≥12 years old and <18 years old) and ≤10 mg/day prednisone or equivalent are allowed for adults
Reported outcomes specified in the decision problem	RFS (primary endpoint) AEs HRQoL (assessed by EORTC QLQ-C30 and EQ-5D-5L) DMFS and OS are also being collected in KEYNOTE-716, however these are event-driven outcomes and the number of events required to enable analysis have not yet been reached. Currently, at IA2, reported events have reached [redacted] DMFS events and [redacted] OS events, representing only [redacted] and [redacted] of the final number of events needed for analysis, respectively. [30]
All other reported outcomes	No additional clinical outcomes were measured in the trial

Other comments	Part two is the unblinded crossover/rechallenge phase of the study in which eligible patients with disease recurrence, from either the pembrolizumab arm or placebo arm, can receive adjuvant treatment with pembrolizumab. Pembrolizumab is administered Q3W for 17 cycles after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis). Patients receive up to 35 cycles of pembrolizumab Q3W for unresectable disease recurrence (regional metastatic lymph nodes, in-transit, satellite, microsatellite metastases and unresectable distant recurrence). After the end of treatment in parts one and two, each patient will be followed for the occurrence of safety events. Patients who discontinue for reasons other than confirmed metastatic disease recurrence will be followed for disease status until metastatic disease recurrence is confirmed. Patients who initiate a non-study cancer treatment will have post-treatment DMFS follow-up until metastatic disease recurrence is documented. All patients will be followed by telephone for OS until death or the end of the study. The efficacy and safety results presented in the CS[1] are from part one only.
Adapted from Tables 5 and 7 in CS[1] with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29] AEs = adverse events; BCG = Bacille Calmette-Guérin; CS = company submission; CT = computed tomography; DMFS = distant metastasis-free survival; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQoL-5 dimension questionnaire-5 levels; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL = health-related quality of life; IV = intravenous; KPS = Karnofsky performance status; LPS = Lansky performance status; MRI = magnetic resonance imaging; N = number of patients; OS = overall survival; PD-1 = programmed (cell) death protein 1; PD-L1/2 = programmed (cell) death ligand 1/2; Q3W = every three weeks; RFS = recurrence-free survival	

ERG comment: The allocation concealment process is very briefly reported and although it is clear that treatment allocation occurred centrally using an interactive response technology system, insufficient information is given to be certain that those recruiting participants were unaware of the allocation sequence. The outcomes proposed in the trial were those listed in the NICE final scope.[2]

Inclusion criteria

In its clarification letter, the ERG queried the company on the statement that patients with: "*no more than 12 weeks between final surgical resection and randomisation, with complete surgical wound healing"* were eligible for enrolment into the KEYNOTE-716 trial (part one). The ERG asked for clarification whether patients in the KEYNOTE-716 trial needed to have achieved '*No Evidence of Disease*' (NED) following surgical resection, to be eligible for enrolment. The company replied [3] that "*Patients considered eligible for the KEYNOTE-716 trial required no evidence of disease (NED) following surgical resection. Final surgical resection is defined in the KEYNOTE-716 protocol as complete resection of melanoma and a sentinel lymph node (SLN) biopsy. If the wide excision was followed by the SLN biopsy (i.e., they were not performed at the same time), no more than 12 weeks may have elapsed between the two surgical procedures. If a second wide excision needed to be completed after SLN biopsy, this date was used to calculate the final surgical resection date. Patients also required a pathologically confirmed negative SLN biopsy, or no disease at baseline in order to meet the inclusion criteria. Initial tumour scans at Screening were performed within 28 days prior to the date of randomisation and reviewed by the site study team in order to confirm the participant had no evidence of disease at study entry. Thus, the combination of these prespecified criteria constitute NED for all patients enrolled in the KEYNOTE-716 trial*". This reply satisfied the ERG that NED had been achieved.

Concomitant medications

The ERG in its clarification letter queried the company on the statement that "*the majority of patients treated with pembrolizumab (95.4%) and placebo (92.0%) took concomitant medications*". The ERG asked for clarification about whether non-protocol specified concomitant medications were used in the management of mild, moderate and severe AEs in this trial (protocol violations), and also asked if the company could tabulate and discuss the most frequently reported categories of concomitant medications, by arm. The company responded[3] by stating that: "*A list of frequently reported concomitant medications (≥5% in one or more treatment group) by treatment arm is presented in Appendix L.4 of Submission Document B. The most common concomitant medications categories that were reported in >40% of patients in either treatment arm were ophthalmologicals, analgesics, stomatological preparations, corticosteroids for systemic use, antidiarrheals/intestinal anti-inflammatory/anti-infective agents, and corticosteroids for dermatological preparations. Among these categories, the following were reported more frequently in the pembrolizumab group than in the placebo group:*

- *Corticosteroids for systemic use ([redacted] patients in the pembrolizumab arm versus [redacted] patients in the placebo arm)*
- *Antidiarrheals/intestinal anti-inflammatory/anti-infective agents ([redacted] patients in the pembrolizumab versus [redacted] patients in the placebo arm)*
- *Corticosteroids for dermatological preparations ([redacted] patients in the pembrolizumab arm versus [redacted] patients in the placebo arm)*".

The company therefore did not directly respond to the ERG question about whether *non-protocol* concomitant medications had been used. Perusal of the study protocol[30] showed that systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest (ECI) that is suspected to have an immunologic aetiology are prohibited, unless administered under a certain dose, or if they are inhaled or topical. It is unclear from the clarification letter response[3], and from Appendix L4 of document B[15], whether the corticosteroids used concomitantly transgressed these boundaries or fulfilled the criteria for legitimate use. Therefore, further clarification on this point is required.

Impact of Coronavirus disease 2019 (COVID-19)

The ERG notes that no comment was made in the company's first submission relating to the impact of coronavirus disease 2019 (COVID-19) on the KEYNOTE-716 trial. The ERG asked in the clarification letter for information on the effects of COVID-19 in terms of recruitment, treatment administration and follow-up. The company replied that: "*in March 2020, the countries with recruitment sites for KN-716 reported a high-level impact on recruitment due to COVID-19. It was reported that there was a high probability that the last patient in (LPI) planned for 30 June 2020 would be delayed due to the impact of COVID-19. Six out of the sixteen countries stopped or limited recruitment at this time, including the United Kingdom, Italy, France, Germany, Spain and Chile. Japan was added as a new country for recruitment in March 2020 at which time, any impact on recruitment due to COVID-19 was unforeseen. However, in June 2020, Japan requested an extension to continue enrolment until November 2020 due to the pandemic surge. Standard operating procedures for study conduct, monitoring and oversight were adhered to during the COVID-19 pandemic and a risk-based approach, consistent with Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance, was used to assess and mitigate impact on study conduct. There were no changes in the planned analyses due to the COVID-19 pandemic. All protocol deviations in Part 1 of the KEYNOTE-716 study that were associated with the COVID-19 pandemic were similar across treatment groups. Most were visit deviations (e.g., missed, delayed or early) or dose deviations (e.g., missed or delayed). No patient's data were excluded from analyses due to a protocol deviation associated with the COVID-19 pandemic, and no protocol deviations that occurred due to the COVID-19 pandemic were considered important by patients or study sites."* A summary of protocol deviations considered by the trial authors to be associated with COVID-19 and which had the potential to impact interpretation of trial results, is provided in Table 3.4.

Table 3.4: Accounting of selected protocol deviations associated with COVID-19 (ITT population)

	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Subjects with ≥1 visit deviation, n (%)	[redacted]	[redacted]	[redacted]
≥1 visit missed	[redacted]	[redacted]	[redacted]
≥1 visit where dosing was scheduled	[redacted]	[redacted]	[redacted]
≥1 visit delayed	[redacted]	[redacted]	[redacted]
≥1 visit where dosing was scheduled	[redacted]	[redacted]	[redacted]
Subjects with ≥1 dose deviation, n (%)	[redacted]	[redacted]	[redacted]
≥1 dose missed	[redacted]	[redacted]	[redacted]
≥1 dose delayed	[redacted]	[redacted]	[redacted]
Subjects with ≥1 imaging scan deviation	[redacted]	[redacted]	[redacted]
≥1 imaging scan missed	[redacted]	[redacted]	[redacted]

	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
≥1 imaging scan delayed	[redacted]	[redacted]	[redacted]
≥1 imaging scan early	[redacted]	[redacted]	[redacted]
≥1 imaging scan other	[redacted]	[redacted]	[redacted]
Subjects with ≥1 survival assessment deviation	[redacted]	[redacted]	[redacted]
≥1 survival assessment missed	[redacted]	[redacted]	[redacted]
Subjects with ≥1 safety assessment deviation	[redacted]	[redacted]	[redacted]
≥1 imaging scan missed	[redacted]	[redacted]	[redacted]
≥1 imaging scan delayed	[redacted]	[redacted]	[redacted]
≥1 imaging scan early	[redacted]	[redacted]	[redacted]
≥1 imaging scan other	[redacted]	[redacted]	[redacted]

Based on the company's response to the clarifications letter[3]
ITT = intention to treat.

In their response to the clarification letter, the company also stated that: *"As indicated in Table 10, Document B of the company submission, a total of [redacted] deaths associated with COVID-19 were recorded in the KEYNOTE-716 trial. In addition, [redacted] patients discontinued study medication due to AEs associated with COVID-19, a further [redacted] patients discontinued due to a physician decision associated with COVID-19, [redacted] patient discontinued due to relapse/recurrence associated with COVID-19, and [redacted] patients chose to withdraw for reasons associated with COVID-19."*[3]

This response satisfied the ERG that the impact of COVID-19 had been adequately accounted for in the running of the study.

3.2.2 Statistical analyses of the KEYNOTE-716 trial

The statistical analyses used for the primary endpoint, alongside the sample size calculations and methods for handling missing data are presented in Table 3.5.

Table 3.5: Summary of statistical analyses for the primary analysis in KEYNOTE-716

Hypothesis objective	The primary hypothesis of the study was to demonstrate if pembrolizumab is superior to placebo with respect to RFS as assessed by the site investigator
Statistical analysis	A non-parametric KM method was used to estimate the RFS curve in each treatment group. The treatment difference in RFS was assessed by the stratified log-rank test, with a stratified Cox proportional hazard model with Efron's method of tie handling used to assess the magnitude of the treatment difference between the treatment arms. The HR and 95% CI from the stratified Cox model with a single treatment covariate were reported. KM estimates and the corresponding 95% CIs at specific follow-up time-points were provided for RFS. As disease assessment occurred periodically, and recurrence could occur at any time between assessments, the true date of the events occurring was approximated by the date of the first assessment at which event is objectively documented. Patients not experiencing a first recurrence event are censored at the last disease assessment. Two sensitivity analyses of RFS were conducted; one in which new primary melanomas were counted as RFS events, and another in which the following different censoring rules applied:

	Patients experiencing recurrence or death after ≥2 consecutive missed disease assessments or after new anti-cancer therapy (if any), were censored at the last disease assessment prior to the date of that event occurring. Patients not experiencing recurrence or death and initiated on a new anti-cancer therapy, were censored at the last disease assessment prior to initiating the new anti-cancer therapy.
Sample size, power calculation	The study was designed to have 92% power to detect a 40% reduction in the risk of recurrence (HR of 0.60), using a log-rank test with 2-sided alpha level of 5% and 1:1 randomisation of pembrolizumab to placebo. It was calculated that 954 patients would need to be randomised 1:1 between pembrolizumab and placebo with the following assumptions: RFS follows a cure model with a long-term RFS of 50% and the 60-month RFS estimated to be 68%. An enrolment period of 16 months and at least 32 months follow-up. A yearly drop-out rate of 4.7%. The final analysis of RFS in this the study was event driven, intended to be conducted after 179 RFS events were observed among all patients (expected to be ~48 months after first patient was randomised).
Data management, patient withdrawals	The primary efficacy analysis and safety analysis used all available data from all patients in the respective populations (ITT and ApaT), irrespective of premature discontinuation from the study medication.
Adapted from Table 9 in CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report)[29] ApaT = all participants as treated; CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; RFS = recurrence-free survival	

ERG comment: The statistical approach appears to be rigorous and correct.

3.2.3 Baseline characteristics of the KEYNOTE-716 trial

A total of 976 patients were randomised to receive pembrolizumab (N=487) or placebo (N=489). Overall, baseline characteristics were well-balanced between the two treatment arms. The mean (standard deviation (SD)) age was [redacted] ([redacted]) years in the pembrolizumab group and [redacted] ([redacted]) years in the placebo group. The median age (range) was 60.0 (16, 84) years in the pembrolizumab group and 61.0 (17, 87) years in the placebo group. Both groups contained more males than females. The majority of patients were of white ethnicity, which is expected as fair skin type is a risk factor for melanoma.[31] Across both groups, 64.0% of patients had stage 2B melanoma and 34.8% of patients had stage 2C melanoma.

Clinical experts confirmed that the baseline characteristics of patients in the KEYNOTE-716 are representative of the population in the UK.[32] Furthermore, data published by PHE reports that 58% of patients diagnosed with stage 2B or 2C melanoma in 2016 and 2017 were male, whilst 42% were female. Of patients diagnosed in this period, 94% were white, 57% had stage 2B melanoma and 43% had stage 2C.[33] The CS[1] states that the baseline characteristics of patients in the KEYNOTE-716 trial reflect these data, and as such, can be considered generalisable to the population in England.

A summary of the baseline characteristics of patients enrolled in the KEYNOTE-716 trial is presented in Table 3.6.

Table 3.6: Baseline characteristics of patients in the ITT population of KEYNOTE-716

Characteristic	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
Sex, n (%)			
Male	300 (61.6)	289 (59.1)	589 (60.3)
Female	187 (38.4)	200 (40.9)	387 (39.7)
Age (Years), n (%)			
12–17	1 (0.2)	1 (0.2)	2 (0.2)
18–64	302 (62.0)	294 (60.1)	596 (61.1)
≥65	184 (37.8)	194 (39.7)	378 (38.7)
Mean	[redacted]	[redacted]	[redacted]
Median	60.0	61.0	61.0
Race, n (%)			
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Black or African American White	[redacted]	[redacted]	[redacted]
White	435 (89.3)	439 (89.8)	874 (89.5)
Missing	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
US	95 (19.5)	80 (16.4)	175 (17.9)
Non-US	392 (80.5)	409 (83.6)	801 (82.1)
ECOG, n (%)†			
0	454 (93.2)	452 (92.4)	906 (92.8)
1	32 (6.6)	35 (7.2)	67 (6.9)
2	0	1 (0.2)	1 (0.1)
N/A	[redacted]	[redacted]	[redacted]
KPS Status, n (%)‡			
100 – Normal. No complaints. No evidence of disease	[redacted]	[redacted]	[redacted]
N/A	[redacted]	[redacted]	[redacted]
T-Stage, n (%)			
T3a	[redacted]	[redacted]	[redacted]
T3b	200 (41.1)	201 (41.1)	401 (41.1)
T4a	113 (23.2)	116 (23.7)	229 (23.5)

Characteristic	Pembrolizumab (N=487)	Placebo (N=489)	Total (N=976)
T4b	172 (35.3)	172 (35.2)	344 (35.2)
Nodal Involvement, n (%)§			
NX	[redacted]	[redacted]	[redacted]
N0	[redacted]	[redacted]	[redacted]
N1C	[redacted]	[redacted]	[redacted]
Metastatic Staging, n (%)¶			
M0	[redacted]	[redacted]	[redacted]
M1C	[redacted]	[redacted]	[redacted]
M1D	[redacted]	[redacted]	[redacted]
Overall Cancer Stage, n (%)			
IIA	[redacted]	[redacted]	[redacted]
IIB	309 (63.4)	316 (64.6)	635 (64.0)
IIC	171 (35.1)	169 (34.6)	340 (34.8)
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Stratification, n (%)			
Paediatric Age (12–17)	[redacted]	[redacted]	[redacted]
IIB T3b >2.0–4.0 mm with ulceration	[redacted]	[redacted]	[redacted]
IIB T4a >4.0 mm without ulceration	[redacted]	[redacted]	[redacted]
IIC T4b >4.0 mm with ulceration	[redacted]	[redacted]	[redacted]

Adapted from Table 8 in CS[1], with primary sources: MSD Data on File (KEYNOTE-716 Clinical Study Report);[29] Luke et al. 2021. Presented at Society for Melanoma Research congress.[28]
†ECOG is not applicable for paediatric patients.
‡KPS is not applicable for adult patients.
§NX indicates the regional lymph nodes cannot be evaluated; N0 indicated there is no cancer in regional lymph nodes; N1C indicates presence of in-transit, satellite, and/or microsatellite metastases.[34]
¶M0 indicates no metastatic spread; M1C indicates the cancer has spread to a non-CNS location; M1D indicates the cancer has spread to the CNS.[34]
CNS = central nervous system; CS = company submission; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; N = number of patients; N/A = not applicable; US = United States

ERG comment: The listed baseline characteristics demonstrate high levels of comparability between treatment arms. Given the law of large numbers and the fact that this was a randomised trial, it can be assumed that other characteristics which were not measured would be similarly distributed.

The CS[1] estimation of two characteristics of the UK population with stage 2B and 2C melanoma from the referenced PHE document[33] has been checked and is correct, showing that 94% of patients are white, and that 57% of patients are at stage 2B (thus implying 43% will be at stage 2C). However, the CS[1] statement that the UK population with stage 2B and 2C melanoma is reflected by the participants in the trial is not correct. The ERG noted that 89.5% of participants in the trial were white, and [redacted] were stage 2A, 64% were stage 2B, and 34.8% were stage 2C (with a remaining [redacted] stage 3C, [redacted] stage 4 and [redacted] missing). Although there is only a small difference between the UK population and trial participants for ethnicity, the percentage difference between the UK population and the trial participants

for the proportion of 2B participants is higher, at around 7%. This difference is important given that patients with 2B melanoma generally have a more favourable prognosis than those with 2C melanoma.[1] It is possible that the larger prevalence of people with 2B melanoma in the trial compared with the UK population might overestimate therapeutic benefits for the UK population with 2B and 2C overall. This might arise because given a certain level of pembrolizumab effectiveness, pembrolizumab could show more beneficial relative effects (versus placebo) against less severe than more severe disease (in the same way that a given dose of painkiller may tend to ease a less severe headache more readily than a severe one). The ERG requested clarification related to this issue, asking for sub-group analyses of RFS, OS and DMFS, one with patients with stage 2B and the other with patients with stage 2C disease. The company responded[3] by stating that: "*randomised patients in KEYNOTE-716 were stratified by T-staging and subgroup analyses by baseline T-category were performed for recurrence-free survival (RFS), as presented in Section B.2.7 of Document B of the Company submission. Subgroup analyses by T-staging was pre-specified over the American Joint Committee on Cancer (AJCC) staging; T-staging is static, whereas AJCC staging is subject to change and as such T-staging was favoured to allow interpretation to remain consistent when the AJCC is updated. All subgroup analyses on the KEYNOTE-716 trial are not statistically powered to detect differences in efficacy and any additional subgroup analysis by AJCC staging (compared with pre-specified analyses based on T-staging) would be conducted post-hoc. As such, subgroup analyses for RFS, separated by patients with stage 2B and stage 2C disease, have not been provided here but are presented in Table 14.2-12 and Table 14.2-13, and Figure 14.2-11 and Figure 14.2-12 of the study CSR. As explained in the clarification call of 14 March 2022 OS and DMFS data are not yet available as of the second interim analysis (IA2) data cut-off presented in this submission, due to insufficient events occurring to enable analysis of these endpoints*."

The sub-grouped data signposted by the clarification response in Tables 14.2-12 and 14.2-13 in the study CSR[29] suggests that pembrolizumab is more effective relative to placebo in stage 2B (HR [redacted]) than stage 2C patients (HR [redacted]), and underlines the ERG point that a trial sample that has a greater proportion of stage 2B patients than the general UK population will tend to yield overly optimistic measures of effect. The data for T staging signposted in document B yield similar results that lend themselves to similar interpretations.

The issues around the larger proportion of patients with less severe disease (stage 2B melanoma) in KEYNOTE-716 compared with the population seen in UK clinical practice has been noted by the ERG as a key issue.

3.2.4 Risk of bias assessment of the KEYNOTE-716 trial

A quality assessment of the KEYNOTE-716 trial was provided in the CS[1] using the Cochrane ROB2[18] tool for randomised trials the results of which are presented in Table 3.7. These demonstrate low risk of bias across all areas for both efficacy (RFS) and safety (AE) outcomes.

Table 3.7: Quality assessment of the KEYNOTE-716 against ROB-2 criteria

Area of potential bias	Risk of bias within the specified outcome	
	RFS	AE
Randomisation process	Low	Low
Deviations from the intended interventions	Low	Low
Missing outcome data	Low	Low
Measurement of the outcome	Low	Low

Area of potential bias	Risk of bias within the specified outcome	
	RFS	AE
Selection of the reported result	Low	Low
Overall risk of bias	Low	Low
Based on Table 12 in CS[1] AE = adverse event; CS = company submission; RFS = recurrence-free survival		

ERG comment: The CS[1] directs the reader to the appendices for more information on the rationale for the decisions made, but the appendices do not provide any further information, apart from directing the reader back to the main document. The evaluation above assesses risk of bias for RFS and AEs but not the other completed outcome, HRQoL. Furthermore, after review of the primary sources[29, 30] the ERG does not agree with the quality assessment in terms of the randomisation process. The allocation concealment process is very briefly reported and although it is stated that treatment allocation occurred centrally using an interactive response technology system, insufficient information is given to be certain that those recruiting participants were unaware of the allocation sequence. In other aspects of risk of bias, the ERG agrees with the CS evaluation.[1] It is likely that performance bias was low as both participants and clinical/study-site personnel were blinded, although it is not described if the intervention and placebo medication were visually identical. Although [redacted] of the pembrolizumab arm and [redacted] of the placebo arm had discontinued by the time of IA2, only [redacted] and [redacted] respectively were lost to follow-up, indicating no real risk of attrition bias. Although it is not specifically stated that outcome assessors were blinded, this appears to be covered by the assertion that all study personnel were blinded. Outcome reporting bias appears to be low for these outcomes. Overall, because of the ambiguity in reporting of allocation concealment, the risk of bias has been designated as unclear for all three outcomes.

The revised ERG quality assessment, using the Cochrane ROB2[18] tool is presented in Table 3.8 for all three completed outcomes.

Table 3.8: ERG revised quality assessment of the KEYNOTE-716 against ROB-2 criteria

Area of potential bias	Risk of bias within the specified outcome		
	RFS	HRQoL	AE
Randomisation process	Unclear	Unclear	Unclear
Deviations from the intended interventions	Low	Low	Low
Missing outcome data	Low	Low	Low
Measurement of the outcome	Low	Low	Low
Selection of the reported result	Low	Low	Low
Overall risk of bias	**Unclear**	**Unclear**	**Unclear**
AEs = adverse events; HRQoL = health-related quality of life; RFS = recurrence-free survival			

3.2.5 Efficacy results of the KEYNOTE-716 trial

The NICE final scope[2] lists the following outcomes that should be covered in the technology appraisal (TA):

- OS
- RFS
- DMFS

- HRQoL
- AEs of treatment

The first four of these outcomes will now be evaluated in turn. AEs of treatment will be evaluated in Section 3.2.6.

3.2.5.1 Overall survival

OS data are not yet available from KEYNOTE-716.[1] The company explains that this is because the analyses of OS are event driven, and final analyses are expected to take place when [redacted] events have occurred. Reported events at IA2 have reached [redacted] OS events, representing [redacted] of the final number of events needed for analysis.[29]

ERG comment: Although it is appreciated that relatively low numbers of events would have meant interpretation of results would have required caution, an interim analysis of available data would have been very useful. The absence of this key outcome makes a full evaluation of this product difficult. The company was asked in the clarification letter when IA3 will be, and when OS data will be mature and included in a future interim analysis, as well as the current numbers by treatment arm. The company responded[3] stating that: "*MSD are unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm, as these data are not available. As described in response to question A13, the database lock for the IA3 analysis of KEYNOTE-716 has now occurred. Full results from this analysis, which will include DMFS events by arm, are expected to be available in June 2022.[35] MSD will ensure to inform NICE about specific dates as soon as further information is available to be shared. As explained in the clarification call on 14 March 2022, OS and DMFS data are not yet available as of the second interim analysis (IA2) data cut-off presented in this submission, due to insufficient events occurring to enable analysis of these endpoints*."

Subgroup analyses were requested by the ERG but not provided for the latter reason.[3] The absence of available data on OS has been noted by the ERG as a key issue.

3.2.5.2 Recurrence-free survival (RFS)

Adjuvant pembrolizumab treatment resulted in an improvement in RFS compared with placebo, demonstrating a 39% decreased risk of disease recurrence or death (HR = 0.61 (95% CI: 0.45, 0.82); nominal p = [redacted]). As of the data cut-off, the median RFS was not yet reached in either treatment group. Main time-to-event analysis of RFS is presented for the intention-to-treat (ITT) population in Table 3.9.

Table 3.9: Analysis of RFS (Primary Censoring Rule) (ITT Population)

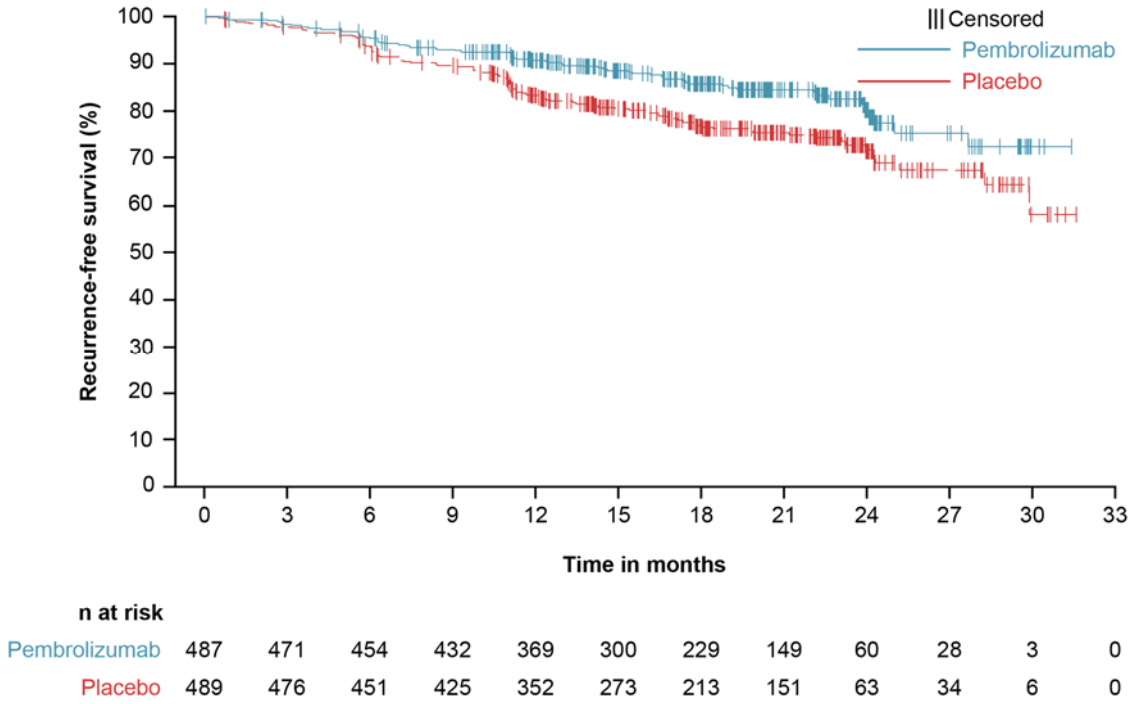
Treatment	N	Number of Events (%)	Person-month	Event Rate/100 Person-months	Median RFS† (months) (95% CI)	RFS Rate at 18 months† (%) (95% CI)
Pembrolizumab	487	72 (14.8)	[redacted]	[redacted]	NR (NR, NR)	85.8 (82.0, 88.9)
Placebo	489	115 (23.5)	[redacted]	[redacted]	NR (29.9, NR)	77.0 (72.6, 80.7)
Pairwise Comparisons					**HR‡, (95% CI)**	**Nominal p value§,¶**
Pembrolizumab versus Placebo					0.61	[redacted]

	(0.45, 0.82)	

Adapted from Table 13, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report)[29]
†From product-limit (Kaplan–Meier) method for censored data.
‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b versus T4a versus T4b).
§One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b versus T4a versus T4b).
¶ Statistical testing is nominal as RFS endpoint was met at IA1.
CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention to treat; N = number of patients; NR = not reached; RFS = recurrence-free survival

The Kaplan-Meier (KM) curves for RFS separated at month 6 and remained separated through the period assessed (Figure 3.1) with RFS rates at 12, 18, and 24 months being higher in the pembrolizumab group compared with the placebo group (Table 3.10).

Figure 3.1: Kaplan–Meier estimates of RFS (primary censoring rule) (ITT population)



Adapted from Figure 4, CS[1], with primary source: Luke et al. 2021. Presented at Society for Melanoma Research congress.[28]
CS = company submission; ITT = intention to treat; RFS = recurrence-free survival

Table 3.10: RFS rate over time

RFS rate at time point	Pembrolizumab (N=487), % (95% CI)†	Placebo (N=489), % (95% CI)†
6 months	95.6 [redacted]	93.6 [redacted]
12 months	90.8 [redacted]	83.3 [redacted]
18 months	85.8 [redacted]	77.0 [redacted]
24 months	80.5 [redacted]	71.7 [redacted]

Adapted from Table 14, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29]
†From product-limit (Kaplan–Meier) method for censored data.
CI = confidence interval; CS = company submission; NR = not reached; RFS = recurrence-free survival

Overall, fewer participants in the pembrolizumab group experienced disease recurrence during part one of the study compared with the placebo group (Table 3.11). The most frequent type of recurrence was distant metastases, and the percentage of participants with this type of recurrence for participants in the pembrolizumab group (31 (6.37%) participants) was almost half compared with the placebo group (60 (12.27%) participants). The percentage of local/regional/LRR was similar in the pembrolizumab and placebo groups.

Table 3.11: Disease status (ITT Population)

Type of first event in RFS analysis	Pembrolizumab (N=487), n (%)	Placebo (N=489), n (%)
All events	**72 (14.78)**	**115 (23.52)**
Local/Regional/Loco-regional	38 (7.80)	50 (10.22)
Local†	[redacted]	[redacted]
Regional‡	[redacted]	[redacted]
Loco-regional§	[redacted]	[redacted]
Distant¶,††	31 (6.37)	60 (12.27)
Death	3 (0.62)	5 (1.02)

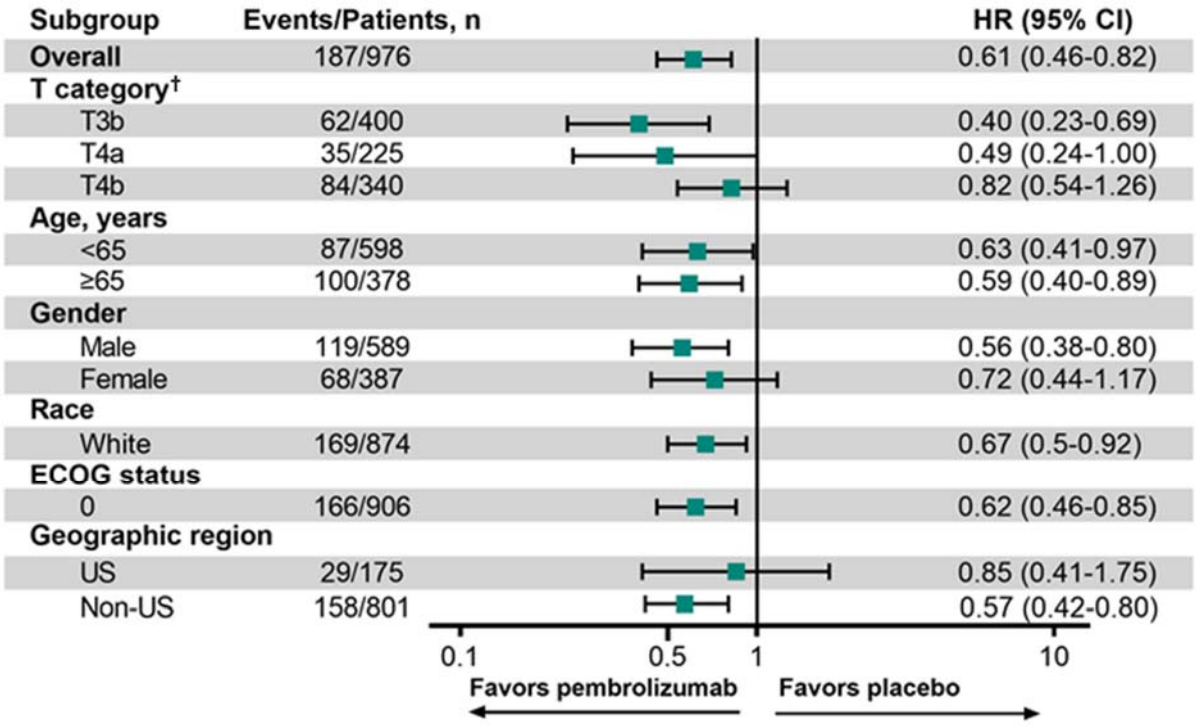
Adapted from Table 15, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report);[29] Luke et al. 2021. Presented at Society for Melanoma Research congress.[28]
†Local: tumour recurrence is in the immediate vicinity of primary tumour (i.e., skin, in transit lesions, micro-satellite metastases)
‡Regional: regional lymph node basin involvement
§Loco-regional: tumour recurrence is in the immediate vicinity of primary tumour and regional lymph node basin metastasis is noted. Tumour has not spread beyond regional lymph nodes
¶Distant: metastasis is beyond the regional lymph node basin
††Includes distant event diagnosed within 30 days from Local/Regional/Locoregional event.
CS = company submission; ITT = intention to treat; RFS = recurrence-free survival

Pre-specified subgroup analyses of RFS were conducted to determine the consistency of treatment effect across the following variables:

- T-stage (T3b versus T4a versus T4b)
- Age (<65 years versus ≥65 years)
- Sex (male versus female)
- Race (white versus non-white)
- Eastern Cooperative Oncology Group (ECOG) Performance Status (0 versus 1) or equivalent Lansky Performance Status (LPS)
- Geographic region (US or Non-US)

The results of the subgroup analysis are reported in Figure 3.2. RFS results in prespecified demographic and clinical subgroups were generally consistent with the ITT analysis, although certain subgroup factors (e.g., US participants) had a smaller number of participants and events, resulting in a wide 95% CI for the HR.

Figure 3.2: RFS stratified by prespecified subgroups



Adapted from figure 6, CS[1], with primary source: Luke et al. 2021. Presented at Society for Melanoma Research congress.[28]

Note: The KEYNOTE-716 trial was not powered for these subgroup analyses. Small sample sizes led to large CIs for these analyses.

[†]Based on actual baseline tumour stages 2B and 2C collected on eCRF.

CI = confidence interval; CS = company submission; ECOG = European Cooperative Oncology Group; eCRF = electronic case report form; HR = hazard ratio; RFS = recurrence-free survival; US = United States

ERG comment: This Section provides fairly strong evidence that pembrolizumab reduces disease recurrence, within the time limits of the trial. However, it is important to consider whether the magnitude of reduced recurrence is clinically important. The HR of 0.61 (treatment versus placebo, for recurrence) indicates a 39% reduction in *instantaneous* risk of recurrence compared to placebo, which at first sight appears to be of clinical importance. However, caution should always be taken with interpretation of the clinical importance of HRs[36] as they cannot be interpreted in the same way as risk ratios. Although the 39% reduction in hazard of recurrence is of large magnitude, this cannot be taken to imply that a similar difference in survival from recurrence will exist between the groups at longer time intervals.[36] Hence the clinical importance of this result is unclear.

Subgroup analyses by stage 2B or 2C were requested by the ERG to which the company responded that subgroup analysis by T-staging had been pre-specified and was preferred because it is "*static, whereas AJCC staging is subject to change*".[3] They also stated that subgroup analyses are not powered to detect differences in efficacy and referenced the CSR for results by stage 2B or 2C. The ERG was able to locate these results, which showed HRs of [redacted] and [redacted] for stage 2B (Table 14.2-12) and stage 2C (Table 14.2-13) respectively.[29] These results show that the HR for stage 2B is lower than for stage 2C i.e., pembrolizumab appears to be more effective in stage 2B patients.

3.2.5.3 Distant metastasis-free survival (DMFS)

DMFS data are not yet available from KEYNOTE-716.[1] The company explains that this is because the analyses of DMFS are event driven, and final analyses are expected to take place when [redacted] events have occurred. Reported events at IA2 have reached [redacted] DMFS events, representing [redacted] of the final number of events needed for analysis.[29]

ERG comment: Although it is appreciated that low numbers of events would have meant interpretation would have required caution, an interim analysis of available data would have been very useful. The absence of this key outcome makes a full evaluation of this product difficult. The company was asked in the clarification letter[3] when IA3 will be, and when DMFS data will be mature and included in a future interim analysis, as well as the current numbers by treatment arm. The company responded that, "*MSD are unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm, as these data are not available. As described in response to question A13, the database lock for the IA3 analysis of KEYNOTE-716 has now occurred. Full results from this analysis, which will include DMFS events by arm, are expected to be available in June 2022.9 MSD will ensure to inform NICE about specific dates as soon as further information is available to be shared.*

As explained in the clarification call on 14 March 2022 OS and DMFS data are not yet available as of the second interim analysis (IA2) data cut-off presented in this submission, due to insufficient events occurring to enable analysis of these endpoints."

As was the case for OS data, the ERG requested subgroup analyses which were not provideddue to the insufficient number of observed events.[3] The absence of available data on DMFS has been noted by the ERG as a key issue.

3.2.5.4 Health-related quality of life (HRQoL)

At Week 48, the completion rates for the EQ-5D-5L were [redacted] and [redacted], in the pembrolizumab and placebo groups, respectively, and the compliance rates were [redacted] and [redacted], respectively.

Analysis of the EQ-5D-5L visual analogue scale (VAS) score at Week 48 showed [redacted] (difference in LS means [redacted], 95% CI [redacted], nominal p value = [redacted]) (Table 3.12; Figure 3.3).

Table 3.12: Analysis of change from baseline in EQ-5D-5L VAS to Week 48 (FAS population)

Treatment	Baseline		Week 48		CFB to Week 48	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†,‡
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise Comparison	Difference in LS Means†,‡ (95% CI)	Nominal p value†,‡
Pembrolizumab versus Placebo	[redacted]	[redacted]

Adapted from Table 16, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29]
For baseline and Week 48, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
†Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction, stratification factor melanoma T stage (2B T3b greater than 2.0–4.0 mm with ulceration versus 2B T4aCS greater than 4.0 mm without ulceration versus 2C T4b greater than 4.0 mm with ulceration) as covariate.

Treatment	Baseline		Week 48		CFB to Week 48	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†,‡
‡ Statistical testing for PROs is nominal and is not adjusted for multiple testing. CFB = change from baseline; cLDA = constrained longitudinal data analysis; CI = confidence interval; CS = company submission; EQ-5D-5L = EuroQoL-5 Dimension Questionnaire; FAS = full analysis set; QoL = quality of life; PRO = patient-reported outcomes; LS = least squares; VAS = visual analogue scale						

Figure 3.3: Empirical mean change from baseline and 95% CI for the EQ-5D VAS over time by treatment group (FAS population)

Adapted from Figure 5, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29]
CS = company submission; EQ-5D-5L = EuroQoL-5 Dimension Questionnaire; FAS = Full analysis set; QoL = quality of life; VAS = visual analogue scale

ERG comment: There was no evidence of a between-group difference in HRQoL.

3.2.6 AEs of the KEYNOTE-716 trial

The overall frequency and type of AEs reported in KEYNOTE-716 were generally consistent with the established safety profile of pembrolizumab monotherapy.

3.2.6.1 Patient exposure

Table 3.13 gives a summary of drug exposure whilst Table 3.14 shows the proportion of patients with exposure by duration.

Table 3.13: Summary of drug exposure (ApaT population)

	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
Number of days on therapy			

	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of administrations			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Adapted from Table 17, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29]
Number of days on therapy is calculated as last dose date − first dose date +1.
ApaT = all participants as treated; CS = company submission; N = number of patients; SD = standard deviation

Table 3.14: Exposure by duration (ApaT population)

Duration of exposure	Patients, n (%)		
	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
>0 month	[redacted]	[redacted]	[redacted]
≥1 months	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]
≥9 months	[redacted]	[redacted]	[redacted]
≥10 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]

Adapted from Table 18, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29] Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
ApaT = all participants as treated; CS = company submission; N = number of patients

3.2.6.2: Summary of AEs

Table 3.15 presents a summary of AEs in the KEYNOTE-716 trial.

Table 3.15: Overview of AEs (ApaT population)

	Patients, n (%)†	
	Pembrolizumab, N=483	Placebo, N=486
Any AE	461 (95.4)	444 (91.4)
Any AE related to study drug‡	400 (82.8)	308 (63.4)
Any AE with toxicity grade 3–5	136 (28.2)	93 (19.1)
Any AE related to study drug‡ with toxicity grade 3–4§	82 (17.0)	21 (4.3)
Any SAE	[redacted]	[redacted]
Any SAE related to study drug‡	[redacted]	[redacted]
Death	[redacted]	[redacted]

	Patients, n (%)†	
	Pembrolizumab, N=483	**Placebo, N=486**
Death related to study drug‡	0 (0.0)	0 (0.0)
Any AE leading to discontinuation	[redacted]	[redacted]
Any AE related to study drug‡ leading to discontinuation	79 (16.4)	12 (2.5)
Any SAE leading to discontinuation	[redacted]	[redacted]
Any SAE related to study drug‡ leading to discontinuation	[redacted]	[redacted]

Adapted from Table 19, CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29] Luke et al. 2021. Presented at Society for Melanoma Research congress.[28]
Includes non-serious AEs up to 30 days after receiving the final dose of treatment (i.e., up to 1 year after initiating treatment in patients who completed the regimen) and SAEs up to 90 days after receiving the final dose of treatment.
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
‡Related events as determined by the Investigator.
§No grade 5 TRAEs occurred.
AE = adverse event; ApaT = all participants as treated; CS = company submission; SAE = serious adverse event; TRAEs = treatment-related adverse events

ERG comment: The overall incidence of study discontinuation related to study drug was higher on the pembrolizumab arm compared to the placebo arm in the KEYNOTE-716 trial. This issue was raised in the clarification letter, where the company were asked to discuss the most frequently reported of these AEs that led to study discontinuation. The company responded[3] as follows: "*As highlighted by the EAG and as shown in Table 21, Document B of the Company submission, the overall incidence of drug-related AEs was higher in the pembrolizumab group compared with the placebo group. The overall incidence of drug-related AEs that led to discontinuation of study intervention was also higher in the pembrolizumab group ([redacted]%) compared with the placebo group ([redacted]%). The most frequently reported of these drug-related AEs were colitis ([redacted] [[redacted]%]) and autoimmune hepatitis ([redacted] [[redacted]%]) in the pembrolizumab group, and diarrhoea ([redacted] [[redacted]%] in each group) and autoimmune hepatitis ([redacted] [[redacted]%]) in the placebo group. Colitis and autoimmune hepatitis are known adverse drug reactions for pembrolizumab.*" As part of their response, the company tabulated the incidence of all drug-related AEs resulting in treatment discontinuation reported in either group (Table 3.16).

Table 3.16: Participants with drug-related AEs resulting in treatment discontinuation by decreasing incidence (incidence >0% in one or more treatment groups) (ApaT population)

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	**Placebo, N=486**
Autoimmune hepatitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Autoimmune nephritis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Hepatitis	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Hypopituitarism	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Polyarthritis	[redacted]	[redacted]
Pulmonary sarcoidosis	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Autoimmune colitis	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Chronic gastritis	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]
Genital erythema	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Immune thrombocytopenia	[redacted]	[redacted]
Immune-mediated arthritis	[redacted]	[redacted]
Immune-mediated enterocolitis	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Lichen planus	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]
Macular detachment	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]
Myelitis transverse	[redacted]	[redacted]
Myopathy	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Palatal oedema	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Pneumonitis	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Skin fissures	[redacted]	[redacted]
Tendonitis	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Autoimmune myocarditis	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Neuralgic amyotrophy	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Polyneuropathy	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]

Adapted from clarification letter response[3] Original source: KEYNOTE-716 CSR[29]
Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
Non-SAEs up to 30 days of last treatment and SEAs up to 90 days of last treatment are included.
MedDRA V24.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database cut-off date: 21 June 2021
AE = adverse event; ApaT = all participants as treated; CTCAE = common terminology criteria for adverse events; SAEs = serious adverse events

As a further part of their response, the company stated that: *"In terms of drug-related Grade 3 to 5 AEs, overall incidence was higher in the pembrolizumab group ([redacted] [[redacted]%]) compared with the placebo group ([redacted] [[redacted]%]). Most drug-related Grade 3 to Grade 5 AEs were Grade 3 in severity in both the pembrolizumab group ([redacted] [[redacted]%]) and placebo group ([redacted] [[redacted]%]). There were [redacted] drug related Grade 4 AEs ([redacted]%) in the pembrolizumab group and [redacted] ([redacted]%) in the placebo group. There were no drug-related Grade 5 AEs.*

The most frequently reported drug-related Grade 3 to Grade 5 AEs in the pembrolizumab group (in ≥1.0% of participants) were autoimmune hepatitis, rash, colitis, diarrhoea, and increased lipase. Autoimmune hepatitis, rash, colitis, increased lipase, and diarrhoea are known adverse drug reactions (ADRs), or clinical manifestations of ADRs, for pembrolizumab. There were no drug related Grade 3–5 AEs with incidence ≥5% in one or both treatment arms." The company provided a tabulation of the incidence of all drug-related grade 3 to 5 AEs reported in either group (Table 3.17).

Table 3.17: Participants with drug-related grade 3 to 5 AEs by decreasing incidence (incidence >0% in one or more treatment groups) (ApaT population)

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Autoimmune hepatitis	[redacted]	[redacted]
Rash	[redacted]	[redacted]

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Colitis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Autoimmune colitis	[redacted]	[redacted]
Autoimmune nephritis	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]
Hypopituitarism	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood sodium decreased	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Endocrine disorder	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Immune-mediated enterocolitis	[redacted]	[redacted]

Participants with:	Patients, n (%)	
	Pembrolizumab, N=483	Placebo, N=486
Lip dry	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Myelitis transverse	[redacted]	[redacted]
Myopathy	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Palatal oedema	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Polyarthritis	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
Autoimmune myocarditis	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neuralgic amyotrophy	[redacted]	[redacted]

Based on the company's response to the clarification letter.[3] Original source: KEYNOTE-716 CSR[29]
Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
Non-SAEs up to 30 days of last treatment and SAEs up to 90 days of last treatment are included.
MedDRA V24.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database cut-off date: 21 June 2021
AE = adverse event; ApaT = all participants as treated; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs = serious adverse events

ERG comment: The ERG acknowledges this fuller set of data which was submitted in response to the request for clarification and will inform the decision making of the committee.

3.2.6.3 AEs with an incidence ≥5% in one or more treatment arms

Table 3.18 presents AEs with an incidence ≥5% in one or more treatment arms. Most AEs were grade 1 or 2; there were no grade 3–5 AEs with incidence ≥5% in either treatment arm.

Table 3.18: Participants with AEs (any grade) by decreasing incidence (incidence ≥5% in one or more treatment groups) (ApaT population)

AE, n (%)	Pembrolizumab, N=483	Placebo, N=486
Participants with one or more AE	**461 (95.4%)**	**444 (91.4)**
Fatigue	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]

AE, n (%)	Pembrolizumab, N=483	Placebo, N=486
Rash	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]

Based on Table 20 of the CS[1], with primary source: Data on File (KEYNOTE-716 Clinical Study Report).[29]
Every participant is counted a single time for each applicable row and column.
Includes non-SAEs up to 30 days of last treatment and SAEs up to 90 days of last treatment.
AE = adverse event; ApaT = all participants as treated; CS = company submission; SAEs = serious adverse events

3.2.6.4 Drug-related AEs with incidence ≥10% in one or both treatment arms

Table 3.19 shows specific drug-related AEs (any grade) with incidence ≥10% in one or both treatment arms. There were no drug related grade 3-5 AEs with incidence ≥5% in one or both treatment arms.

Table 3.19: Drug-related AEs (any grade) with incidence ≥10% in one or both treatment arms (ApaT population)

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Participants with one or more AE	**400 (82.8)**	**308 (63.4)**
Pruritus	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Arthralgia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]

Based on Table 21 of the CS[1], with primary source: Data on File (KEYNOTE-716 Clinical Study Report).[29]
Every participant is counted a single time for each applicable row and column.
Includes non-SAEs up to 30 days of last treatment and SAEs up to 90 days of last treatment.
AE = adverse event; ApaT = all participants as treated; CS = company submission; SAEs = serious adverse events

3.2.6.5 Serious adverse events (SAEs)

Table 3.20 shows SAEs with incidence ≥1% in one or both treatment arms. There were no drug-related SAEs with incidence ≥1% in one or both treatment arms.

Table 3.20: SAEs with incidence ≥1% in one or both treatment arms (ApaT population)

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Participants with one or more AE	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Squamous cell carcinoma of skin	[redacted]	[redacted]
Malignant melanoma in situ	[redacted]	[redacted]

Based on Table 22 of the CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29]
Every participant is counted a single time for each applicable row and column.
Includes SAEs up to 90 days of last treatment.
AE = adverse event; ApaT = all participants as treated; CS = company submission; SAE = serious adverse event

3.2.6.6 Adverse events of special interest (AEOSI)

Predefined AEs of special interest (AEOSI), corresponding to immune-mediated events and infusion-related reactions associated with pembrolizumab, were analysed. Overall, the type and severity of AEOSIs were consistent with the established pembrolizumab monotherapy safety profile. Most AEOSIs were grade 1 or 2 and were generally manageable with corticosteroids and/or hormone replacement therapy, and/or with treatment interruption/discontinuation. Table 3.21 summarises the rates of AEOSIs (in which ≥1 event occurred in either group); further details of the specific AEOSI subtype and severity grade can be found in Appendix L.3. of the CS appendices.[15]

Table 3.21: AEOSIs (any grade; ApaT Population)

Patients, N (%)a	Pembrolizumab, N=483	Placebo, N=486
Participants with one or more AE	**182 (37.7)**	**44 (9.1)**
Adrenal Insufficiency	12 (2.5)	0 (0)
Colitis	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypophysitis	12 (2.5)	0 (0)
Hypothyroidism	83 (17.2)	17 (3.5)
Infusion Reactions	[redacted]	[redacted]
Myasthenic Syndrome	[redacted]	[redacted]

Patients, N (%)a	Pembrolizumab, N=483	Placebo, N=486
Myelitis	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Sarcoidosis	[redacted]	[redacted]
Severe Skin Reactions	[redacted]	[redacted]
Thyroiditis	8 (1.7)	2 (0.4)
Type 1 Diabetes Mellitus	2 (0.4)	0 (0)
Uveitis	[redacted]	[redacted]

Based on Table 23 of the CS[1], with primary source: MSD Data on File (KEYNOTE-716 Clinical Study Report).[29]
AE = adverse event; AEOSI = adverse event of special interest; ApaT = all participants as treated; CS = company submission.

3.2.7 Included studies: Supporting evidence

Not applicable.

3.2.8 Ongoing studies

The CS[1] reports how KEYNOTE-716 is an ongoing RCT which will continue until the number of DMFS and OS events reaches the criteria required for the analyses to be conducted. The final analyses of DMFS and OS will take place when [redacted] and [redacted] events have been observed, respectively.

The CS[1] also describes how part 2 of KEYNOTE-716 will follow on from part 1, in which eligible patients with disease recurrence are offered further treatment with pembrolizumab for 17 cycles after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis) or up to 35 cycles of pembrolizumab Q3W for unresectable disease recurrence (unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or unresectable distant recurrence).

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison and/or multiple treatment comparison was carried out to inform clinical effectiveness estimates.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

3.6 Conclusions of the clinical effectiveness Section

The CS[1] and response to clarification[3] provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on adjuvant therapies in adult and paediatric (≥12 years) patients

with surgically resected stage 2B and 2C melanoma. Searches were conducted in September 2021. Searches were transparent and reproducible. A good range of databases and grey literature resources were searched. The reported strategies contained a number of limitations which the ERG was concerned may have adversely affected the overall recall of results.

The single RCT provided reasonably strong evidence that pembrolizumab reduces recurrence rates during the median 20-month duration of the first interim period of part 1 of the KEYNOTE-716 study.[1] Pembrolizumab led to more AEs than placebo, but serious adverse events were relatively uncommon. There was no evidence of a between-group difference in HRQoL. It is possible that longer term follow up may change this result, but this is uncertain.

The main limitations of the evidence base are the lack of data for the OS and DMFS outcomes. It is the ERG's belief that data for OS and DMFS should have been made available to facilitate decision-making.

Overall, however, it is probably safe to conclude that pembrolizumab is superior to placebo. Given that both groups also had routine surveillance, the results imply that pembrolizumab combined with routine surveillance is probably superior to routine surveillance alone (see ERG comment in Section 3.2.1). However, the lack of OS and DMFS data means that the size of the benefit is uncertain. It is also possible that any benefit would be overestimated in relation to NHS clinical practice given the apparently greater effectiveness in the stage 2B population and the likely greater proportion of such patients in the KEYNOTE-716 trial than would be observed in clinical practice.

The population defined in the NICE final scope was people aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection and who are deemed at high risk of recurrence. The KEYNOTE-716 trial only recruited one patient per treatment arm within the 12 to 17 year-old age group. Therefore, the clinical effectiveness results cannot be considered as generalisable to people in this younger age group.

Two dosing schedules for pembrolizumab are recommended: 200 mg Q3W and 400 mg Q6W. The comparability of the two dosing regimens in terms of efficacy and safety is uncertain because comparative data on clinical outcomes in stage 2 melanoma are not available.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

A SLR was conducted with the objectives to identify and select relevant studies in patients with resected high-risk stage 2 melanoma regarding; 1) cost effectiveness analysis (CEA) (CS, Appendix G); 2) HRQoL (CS, Appendix H); 3) costs and healthcare resource use (CS, Appendix I).[15]

4.1.1 Searches for cost effectiveness analysis review

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[15] The CADTH evidence-based checklist for PRESS was used to inform this critique.[13, 14] The ERG has presented only the major limitations of each search strategy in the report.

Appendices G, H and I of the CS[15] detail three individual sets of searches designed to identify and summarise published CEAs, direct and indirect costs and healthcare resource requirements, and lastly to review publications regarding health state utility values (HSUVs) in patients with resected high-risk stage 2 melanoma. The searches were conducted in two stages: an initial search in March 2021 and an update in October 2021. The same search strategies were used in the original search and updates.

A summary of the sources searched for the cost effectiveness SLR is provided in Table 4.1.

Table 4.1: Data sources for the cost effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE	Embase.com	Inception-current	15/3/21 Updated 6/10/21
Embase		Inception-current	15/3/21 Updated 6/10/21
PubMed	Internet	Inception-current	15/3/21 Updated 6/10/21
HTA Database NHS EED DARE	CRD website	Inception-close of database	15/3/21
Conferences			
AACR	Internet	2019–2021	6/4/21 Updated 18/10/21
ASCO			
ESMO			
ISPOR			
SITC			
SMR			
HTA sources			
UK (England) NICE	Internet		04/21 Updated 10/21
UK (Wales): AWMSG			
UK (Scotland): SMC			
Ireland: NCPE			

Resource	Host/Source	Date Ranges	Dates searched
Canada: CADTH/pCODR			
Germany: IQWiG/G-BA			
Australia: PBAC			
France: HAS			
INAHTA			
htai.org			
EUnetHTA			

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; DARE = Database of Abstracts of Reviews of Effects; EUnetHTA = European Network for Health Technology Assessment; ESMO = European Society of Medical Oncology; G-BA = Gemeinsamer Bundesausschuss; HAS = French National Authority for Health; HTAD = health technology assessment database; htai = International Society for the promotion of health technology assessment; IQWiG = Institute for Quality and Efficiency in Health Care; INAHTA = International Network of Agencies for Health Technology Assessment; ISPOR = International Society for Pharmacoeconomic and Outcomes Research; NCPE = National Centre for Pharmacoeconomics; NHS EED = National Health Service Economic Evaluations Database; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; pCODR = pan-Canadian Oncology Drug Review; SITC = Society for Immunotherapy of Cancer; SMC = Scottish Medicines Consortium; SMR = Society for Melanoma Research

ERG comment:

- A broad range of resources were searched for the economic SLR, including databases, conference proceedings and HTA organisations.
- "*For the cost-effectiveness studies, health-related quality-of-life (HRQoL) and costs and resource use SLRs (Appendices G, H and I, respectively), Medline and Embase were searched simultaneously via the Embase.com interface, using a single search strategy. A single search strategy was chosen based on the understanding that the Emtree indexing system utilised by the Embase database is now inclusive of all Medical Subject Headings (MeSH) terms used by Medline. Thus, this single search strategy can be considered inclusive of all records from both Medline and Embase*".[3] Whilst the ERG accepts this single approach as being adequate, the ERG considers it preferable to conduct a separate companion MEDLINE search in order to fully utilise the power of database-specific study design filters developed to make the most of an individual database's subject headings. However, on closer inspection the PubMed search which the CS reported[15] was intended to retrieve papers from PubMed in process, doesn't appear to contain any limits, and the numbers retrieved seem to suggest that this was a full search of all PubMed content, which would negate any loss of recall from the joint MEDLINE/Embase search. It is also worth noting that despite listing MEDLINE via Embase.com in the search strategy, unlike the clinical effectiveness Section only PubMed was listed in the PRISMA flow chart.
- Searches were well structured and reproducible. Initially strategies and numbers of hits retrieved were missing for both the conference proceedings and HTA searches, however these were provided after a request by the ERG at clarification.
- With regard to the HTA searches, the company reported that the *"searches did not identify any HTA submission available for patients with stage 2 melanoma".*[3] The ERG noted that searches were conducted for the keywords: "Melanoma, Stage II". For these types of grey literature resources, it may have been safer to search more broadly for the term 'Melanoma' as it is often unclear which

fields (i.e., title or full text) are being searched, or to have looked for synonyms for Stage II (i.e., Stage 2 or Stage two). Again, some resources may have automatically searched for synonyms but without rerunning the searches it is unclear what impact this may have had on the recall of results.

- In addition to the main economics searches reported in Appendices G, H and I, an additional SLR used to inform a NMA for advanced melanoma treatments was reported in Appendix O. Searches were listed for MEDLINE, Embase and CENTRAL databases, ClinicalTrials.gov and manual searches of four conference proceedings. No search strategies were reported in the initial CS[15] but were provided at clarification[3] and appeared appropriate

Table 4.2: Data sources searched for HRQoL studies (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE Embase	Embase.com	Inception-current	15/3/21 - Updated 6/10/21
PubMed	Internet	Inception-current	15/3/21 - Updated 6/10/21
CDSR CENTRAL	Wiley	Inception-current	15/3/21
Additional searches			
Reference checking			
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials			

- After a query from the ERG at clarification, the company confirmed that there had been a mix-up in the reporting of strategies in the HRQoL and Resources Use appendices and that Tables 18 to 21 (Appendix H) should be switched with Tables 25 to 29 (Appendix I) to rectify this.
- As well as the searches listed above the CS reported that "*The same data sources described in Section G.2.1 were also used for this SLR*".[15]
- Despite listing MEDLINE via Embase.com in the search strategy, only PubMed was listed in the PRISMA flow chart. Please see the point regarding joint MEDLINE/Embase searches in the cost effectiveness comments.

Table 4.3: Data sources searched for cost/resource use studies (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE Embase	Embase.com	Inception-current	15/3/21 - Updated 6/10/21
PubMed	Internet	Inception-current	15/3/21 - Updated 6/10/21
Additional searches			
Reference checking			

- After a query from the ERG at clarification the company confirmed that there had been a mix-up in the reporting of strategies in the HRQoL and Resources Use appendices and that Tables 18 to 21 (Appendix H) should be switched with Tables 25 to 29 (Appendix I) to rectify this.

- Despite listing MEDLINE via Embase.com in the search strategy, only PubMed was listed in the PRISMA flow chart. Please see the point regarding joint MEDLINE/Embase searches in the cost effectiveness comments.
- As well as the searches listed above the CS reported that "*The same data sources described in Section G.2.1 were also used for this SLR*".[15]

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies are presented in Table 4.4.

Table 4.4: Eligibility criteria for the systematic literature reviews

	Inclusion criteria
Patient population	Patients (≥12 years) with resected high-risk stage 2 melanoma. Studies which assessed mixed age children were included only if sub-group data for children ≥12 years was reported
Intervention	There was no restriction on the interventions
Comparator	There was no restriction on the comparison interventions
Outcomes(s) 1 (Published economic evaluations)	Cost effectiveness/utility analysis (cost effectiveness and/or cost-utility, ICER/ICUR, cost/QALY, cost/LYG, cost/DALY)
Outcomes(s) 2 (HRQoL studies)	Utility/disutility data associated with disease and AEs
Outcomes(s) 3 (Cost/resource use studies)	Direct costs: • Medication costs • Outpatients visit costs • Hospitalisation costs (emergency department or hospital visits) • Laboratory costs • Diagnostic costs (e.g., magnetic resonance imaging) • Physician costs • Non-medication treatment costs Indirect or other costs of interest: • Productivity loss of patient (wages lost from absences) • Out-of-pocket expenses • Travel costs for patient Resource use estimates (e.g., number of hospitalisations and length of stay, drug utilisation, physician visits, outpatient visits, total number of emergency visits)
Study design 1 (Cost effectiveness analysis studies)	Relevant study designs included in the review were: • CEAs • Cost-utility analyses • Cost-benefit analyses • Cost-minimisation analyses • Budget impact models • Cost consequence studies • All economic evaluation studies based on models

	Inclusion criteria
Study design 2 (HRQoL studies)	Relevant study designs included in the review were: • RCTs • Non-RCTs • Single-arm trials • Cross-sectional and longitudinal database studies • Registry studies • Pragmatic clinical trials • Cohort studies/longitudinal studies (retrospective) • Cohort studies/longitudinal studies (prospective) • Case-control studies • Analysis of hospital records/database
Study design 3 (Cost/resource use studies)	Relevant study designs included in the review were: • Cost studies/surveys/analyses • Database studies collecting cost data (e.g., claims databases, electronic health records and hospital records) • Resource surveys
AEs = adverse events; ICER = Incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LYG = life years gained; QALY = quality-adjusted life years; RCTs = randomised controlled trials	

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	Consistent with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Partly consistent with reference case (utility based on standard gamble)

Element of health technology assessment	Reference case	ERG comment on CS
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Consistent with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case

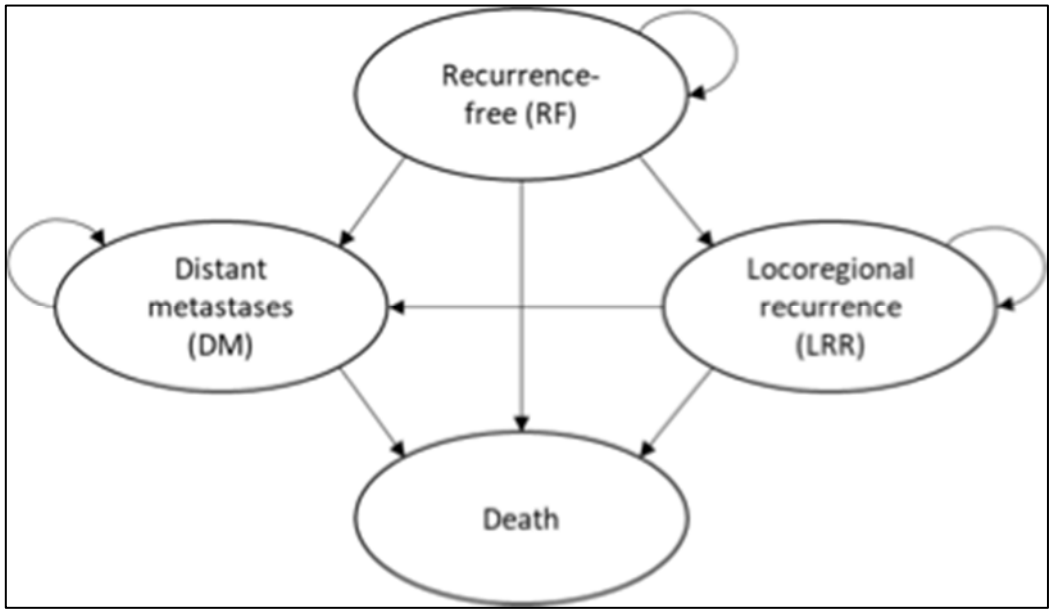
CS = company submission; ERG = Evidence Review Group; EQ-5D = EuroQol-5 Dimension; HRQoL = health related quality of life; NHS = National Health Service; NICE = National Institute for Heath and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

A cohort state-transition model with a one-week cycle length was developed that consisted of four health states: RF, LRR, DM, and death. Survival time and time spent in the LRR, and DM health states depended upon the efficacy and market shares of subsequent therapies in these health states. The DM state consisted of a pre-progression and a post-progression substate. The company argued this was done to capture the costs and outcomes of subsequent therapies that patients may receive after DM recurrence. Utility and costs in the DM state was computed as a weighted average of utilities and costs in the pre- and post-progression sub-states. The model was programmed in Microsoft Excel®. Figure 4.1 shows the model structure.

All patients start in the RF health state and the transitions from this health state were based on KEYNOTE-716. Transitions from the LRR health state were based on real-world evidence from the US Oncology Network (USON)[37] as data are not yet available from KEYNOTE-716, and assumed equal between the intervention and comparator. Transitions from the DM health state to death were estimated using data from the KEYNOTE-006 trial (phase 3 trial among ipilimumab-naïve patients with unresectable or advanced melanoma) and an NMA.

Figure 4.1: Model structure



Based on Figure 7 of the CS
CS = company submission.

ERG comment: The main concern of the ERG relates to the substates in the DM state. The ERG asked for the exact definition, implementation and justification for the use of the DM sub-states (clarification question B1).

The company clarified that time spent in the pre-progression DM sub-state equals PFS as measured from the time of initiating the first-line treatment for advanced melanoma. The time spent in the post-progression DM sub-state equals OS-PFS, both measured from the time of initiating the first-line treatment for advanced melanoma. This was calculated for each first-line treatment option. Mean OS and PFS, for pembrolizumab and the comparator separately, were calculated as a weighted average based on market share on which patients received subsequent treatment (and if treated, which treatment). The ratio PFS:OS was then calculated for the intervention and comparator. This ratio was used to determine the relative weight of subsequent treatment costs, disease management costs and utility values, in the pre- and post- progression DM sub-states. The company justified their approach by stating it made their model more in line with previous assessment in advanced melanoma (that typically used a three state model) and also facilitated the use of relevant input data. The company submitted an adapted model that enabled an analysis without the post-progression DM sub-state.

According to the ERG the use of a model structure with pre- and post-progression DM sub-states is reasonable. As a consequence of using market share data to inform the type of first-line and subsequent treatment for advanced melanoma for pembrolizumab and the comparator separately, transition probabilities from the DM health states to death (and costs and utilities) differ over the entire remaining modelled time horizon. Therefore, the market share of subsequent treatments for pembrolizumab and the comparator is likely influential on the modelled outcomes. It should be noted that this also applies to the LRR health state. See also Sections 4.2.6 and 4.2.9.

4.2.3 Population

The population in the economic model consists of patients with stage 2B or 2C melanoma who have undergone complete resection. This is in line with the anticipated licence for pembrolizumab and the

scope of the current appraisal. Baseline characteristics of the model patient cohort reflected the patients enrolled in the KEYNOTE-716 trial. The proportion of patients with BRAF-mutation positive melanoma (used for subsequent treatments) was based on the KEYNOTE-054 trial as BRAF mutation status was not captured in KEYNOTE-716. The key baseline patient characteristics in the economic model are listed in Table 4.6.

Table 4.6: Key baseline patient characteristics used in the economic model

Characteristic	Value	Source
Age	59.3 years	KEYNOTE-716
Age <18 years	0.2%	KEYNOTE-716
Female	39.7%	KEYNOTE-716
Stage 2B/2C	64.8% / 35.2%	KEYNOTE-716
Weight among adults, mean (SD)	[redacted]	KEYNOTE-716
Weight among paediatrics, mean (SD)	[redacted]	KEYNOTE-716
BRAF mutation positive†	43.3%	KEYNOTE-054

Based on Table 24 CS.[1]
† BRAF status was used to ensure the market shares of BRAF-targeted agents in the locoregional recurrence and distant metastases health states did not exceed the proportion of patients who were BRAF mutation positive.
CS = company submission; SD, standard deviation

ERG comment: The main concern of the ERG related to the potential difference in outcomes between patients with 2B or 2C melanoma. The ERG asked the company to perform subgroup analyses of RFS, OS and DMFS, one with patients with stage 2B and the other with patients with stage 2C disease. The company showed subgroup specific RFS results and explained that OS and DMFS results are not yet available due to insufficient events at the second interim analysis data cut-off.

4.2.4 Interventions and comparators

The intervention considered in the CS was pembrolizumab as fixed dose intravenous infusion of 400 mg over 30 minutes Q6W for adults and 2 mg/kg Q3W for children.[1] Treatment was continued for approximately 12 months (equivalent to 17 cycles of 200 mg Q3W) or until disease recurrence, toxicities leading to discontinuation, or physician/patient decision (as stated in the KEYNOTE-716 protocol).[30] This was in line with the anticipated marketing authorization. The SmPC for pembrolizumab allows treatment to be administered at a dose of either 200 mg Q3W or 400 mg Q6W across all monotherapy indications.[4] In KEYNOTE-716 the Q3W dosing was used. The company reported that clinical experts favoured the Q6W dosing schedule for pembrolizumab as it reduces the number of clinic visits, whilst maintaining the results observed with Q3W dosing with no increase in toxicity. Therefore, the Q6W dosing was anticipated to be utilized by most clinics in UK practice and was used for the base case analysis. A scenario analysis explored the Q3W dosing.

The comparator was routine surveillance (no active treatment), which is in line with the NICE scope. The content of routine surveillance was based on observations in the control arm of KEYNOTE-716.

ERG comment: The main concerns of the ERG relate to the use of Q6W pembrolizumab dosing in the base case. The ERG asked the company to further justify the use of Q6W dosing in their base case analysis and to explore the impact of using a mixture of Q3W and Q6W in a scenario analysis. The company clarified that the SmPC for pembrolizumab was amended in March 2019 following EMA approval to allow treatment to be administered at a dose of Q6W in addition to the already approved

dose of Q3W across all monotherapy indications (see also Section 2.2 of this report). The company conducted scenarios on the dosing schedule (assuming that only the treatment costs would be affected by changing the dosing to Q3W). All patients on Q3W dosing resulted in an ICER of £5,300 per QALY gained.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS PSS perspective, and the time horizon is lifetime. Discount rates of 3.5% are applied to both costs and benefits.

ERG comment: This is in line with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

Transition probabilities starting from the RF, LRR, and DM health states were estimated based on the KEYNOTE-716 trial, real-world data from the USON and the KEYNOTE-006 trial respectively. Transitions to the death health state were adjusted (if required) to ensure these would not be lower than all-cause mortality rates in the UK (sourced from the Office for National Statistics life tables 2017-2019).

4.2.6.1 Transition probabilities from RF health state

Transition probabilities starting from the RF health state (to the LRR, DM and death health states) were estimated based on survival analyses of individual patient-level data from the KEYNOTE-716 trial, using the parametric multistate modelling approach. Parametric models were used to estimate the cause-specific hazards of each transition (i.e., RF to LRR, RF to DM, and RF to death) over time within the adjuvant pembrolizumab and routine surveillance arms. Within each cycle of the model, the probabilities of each of these transitions (as well as the composite probability of any RFS failure event) were calculated as a function of all three cause-specific hazards. This approach was similar to the methodology employed in TA766.

To account for competing risks, patients were censored at the end of follow-up or upon the occurrence of the competing event. Specifically:

- RF to LRR: Patients who experienced a DM or death prior to LRR were censored
- RF to DM: Patients who experienced a LRR or death prior to DM were censored
- RF to death: Patients who experienced a LRR or DM prior to death were censored

Parametric models were separately fitted to each treatment: pembrolizumab and routine surveillance (assuming the same parametric distribution for both treatments). Specifically, for RF to LRR and RF to DM, six parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) were considered while for RF to death only the exponential distribution (i.e., constant transition over time) was considered due to the small number of events observed in the KEYNOTE-716 trial for this transition. The transition probabilities from the RF health state depends upon all three cause-specific hazard functions. Therefore, to select the most suitable base case parametric functions, 54 different combinations of parametric functions were considered separately. The CS base case parametric functions were selected based on three criteria: 1) statistical fit; 2) visual assessment and 3) clinical plausibility of long-term extrapolations.[1]

For statistical fit the company did not use the AIC but stated that the AIC is not suitable when modelling competing risks, hence the mean squared error was therefore used as an alternative to assess statistical fit to the observed data. Also, the company indicated that the proportional hazard assumption was

examined by considering the scaled Shoenfeld residuals (from a Cox proportional hazard model), these plots provided support for the proportional hazard assumption (clarification response Figure 8). Moreover, visual assessment of fit was performed specifically considering predicted versus observed cumulative incidence curves for the three individual transitions starting from the RF state (CS, Appendix M).[15] Finally, clinical plausibility of long-term extrapolations was considered by excluding crossing RFS curves (i.e., higher long-term RFS under routine surveillance compared with pembrolizumab) due to clinical implausibility and comparison with external sources (CS, Table 28) as well as expert opinion.[1]

Tables 26 and 27 of the CS as well as Appendix M of the CS provide an overview of the parametric survival models estimated by the company.[1, 15] Twelve of the 54 combinations met the clinical plausibility requirements. Seven of these 12 used the exponential distribution for the RF to DM transition and had a less optimal visual and statistical fit to the KEYNOTE-716 data. Therefore, the remaining five combinations were prioritised by the company (Weibull-Generalised gamma; Gompertz-Generalised gamma; Lognormal-Lognormal; Generalised gamma-Lognormal; Log-logistic-Lognormal) and comparisons with external data are provided in CS, Tables 29-31 and CS, Figures 8 to 11.[1] The three curve combinations that used Lognormal for the RF to DM transition provided the best fit to the external data, and the Lognormal-Lognormal combination yielded RFS predictions that were closest to the external sources at the most time points over 10 years. The two functions that used Generalised gamma for the RF to DM transition produced RFS projections that were above the external data at all time points after 2 years. The company concluded that the Lognormal-Lognormal combination for RF to LRR and RF to DM, respectively, was most consistent with external sources for routine surveillance RFS over 10 years and provided a middle-ground estimate in terms of the treatment benefit of pembrolizumab versus routine surveillance. Consequently, the Lognormal-Lognormal parametric function combination was selected for the CS base case.[1]

The company stated that clinical experts agreed that the risk of recurrence decreases over time such that the likelihood of disease recurrence after 10 years is extremely small, although would not reach zero. In other words, patients who remain recurrence-free at 10 years are highly unlikely to have a recurrence. According to the company, it is likely that the flattening of the curve observed in published real-world cohorts and described by clinical experts has not yet been reached in the KEYNOTE-716 trial at IA2 (median follow-up 20.5 months). This is supported by clinical experts who felt that the long-term estimates after 10 years produced by the parametric functions were pessimistic and underestimated RFS. To address this under prediction of RFS, the company assumed that the per cycle risk of recurrence for patients remaining in the RF health state after 10 years would reduce by 95% (consistent with TA569, TA632, and TA761). Specifically, the company assumed the risk (relative to the parametric function) begins to linearly decrease from 7 years until the 95% risk reduction is reached at 10 years.

4.2.6.2 Transition probabilities from locoregional recurrence (LRR) health state

Transitions from the LRR health state (to DM and death health states) were informed using real-world data from USON selecting patients who underwent surgical resection of stage 2B or 2C melanoma and were subsequently identified as having an LRR (see CS, Appendix M for details about the USON cohort).[15] Based on the subset of patients who had no adjuvant therapy, these real-world USON data were used to estimate exponential parametric functions for 1) time to DM and 2) time to death. To account for competing risks, patients were censored at the end of follow-up or upon the occurrence of the competing event.

Input from clinical experts indicated that, in current practice, patients with stage 2B/2C melanoma who had a LRR would be considered to have resectable stage 3 melanoma and would be eligible to receive

systemic adjuvant therapy with one of three treatments recommended by NICE in the adjuvant setting: pembrolizumab, nivolumab or dabrafenib + trametinib. The market share of these treatments and their relative efficacy were combined to estimate the transition probabilities. The relative efficacy (versus no adjuvant treatment) was based on HR (for DM-free survival) from the KEYNOTE-054 trial (pembrolizumab) and COMBI-AD trail (dabrafenib + trametinib). For nivolumab, the relative effectiveness was assumed equal to pembrolizumab (CS, Table 34).[1]

4.2.6.3 Market shares of subsequent treatments in LRR health state

For routine surveillance, market shares of subsequent treatment regimens for the LRR health state were sourced from Ipsos Oncology Monitor market research as this was the most robust source available for the UK setting. As the Ipsos dataset only included counts of treated patients, the estimated proportion of patients who received no systemic adjuvant therapy was obtained from market research of current UK treatment practices.

For pembrolizumab, clinical experts advised that they consider patients to have 'one shot' at adjuvant therapy as there is currently no evidence on the efficacy of repeated treatment with adjuvant therapy, and they were not sure funding for further adjuvant therapy would be available; it was therefore deemed unlikely that patients treated with adjuvant pembrolizumab in the stage 2B/2C setting would receive further adjuvant therapy after recurrence. Consequently, no further systemic adjuvant therapy for the LRR health state was assumed after initial treatment with pembrolizumab (CS, Table 36).[1]

4.2.6.4 Transition probabilities from distant metastasis (DM) health state

Transitions from the DM health state (to the death health state) were estimated based on survival analyses of individual patient-level data from the KEYNOTE-006 trial (multicentre, randomised, open-label phase 3 trial among ipilimumab-naïve patients with unresectable or advanced melanoma), using exponential parametric functions for both OS and PFS. Notably, PFS was only used to calculate the ratio between mean PFS and mean OS, which was subsequently used to estimate utility values and disease management costs within the DM state (accounting for the proportion of time spent pre- versus post-progression within this state).

The transition from the DM health state to death was assumed to depend on the first-line subsequent treatment in the DM health state. Treatment options in the model were based on the regimens currently approved by NICE and used in clinical practice for the treatment of advanced melanoma: pembrolizumab, nivolumab, nivolumab + ipilimumab, ipilimumab, dabrafenib + trametinib, encorafenib + binimetinib, and dacarbazine chemotherapy. Second-line therapies were also included in the DM health state but were only used to estimate cost.

The market share of the first-line treatments in the DM health state and their relative efficacy were combined to estimate the transition probabilities. The relative efficacy (versus pembrolizumab) was based on the HR (for PFS and OS) from a fixed-effects NMA, assuming proportional hazards, of trials conducted in advanced melanoma (aligned with the approach used in TA766), see CS, Table 38 and CS, Appendix O.[1, 15]

4.2.6.5 Market shares of subsequent treatments in DM health state – first-line

Market shares of subsequent treatment regimens for the DM health state were sourced from the Systemic Anti-Cancer Treatment (SACT) report. The treatment regimens observed in SACT were reflective of the NICE guidance for systemic anticancer therapies in stage 4 melanoma, with the exception that minimal use of IO monotherapy was observed. According to the company this suggests that, based on the 2-year follow-up reported by the SACT dataset, IO rechallenge for patients having a

DM recurrence within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice. Therefore, it was assumed that a small percentage of patients who entered the DM state more than 2 years after adjuvant treatment initiation would receive rechallenge with pembrolizumab monotherapy and the SACT market shares of other non-targeted regimens were proportionally adjusted. In addition, clinicians stated that for patients that initially received routine surveillance, IO monotherapies (pembrolizumab or nivolumab) are expected to be a common choice. Therefore, for this strategy, the company sourced the market share of pembrolizumab in the DM health state on the Ipsos Oncology Monitor, and the other market shares (sourced from SACT) were proportionally lowered to account for pembrolizumab usage, except for dabrafenib + trametinib and encorafenib + binimetinib these were not proportionally lowered (CS, Table 55).[1]

4.2.6.6 Market shares of subsequent treatments in DM health state – second-line

In addition, a subset of patients in the DM health state were assumed to go on to receive second-line therapy for advanced melanoma following progression in the DM health state. The proportion of patients assumed to receive no active second-line therapy (due to death, deterioration of performance status (fitness), patient/clinician choice, or participation in a clinical trial) was sourced from the Ipsos Oncology Monitor (calculated as the ratio between the number of patients on second-line versus first-line regimens) and ratified by clinical experts. The distribution of second-line regimens for the routine surveillance arm was sourced from the Ipsos Oncology Monitor and confirmed by clinicians to be acceptable for the UK setting. In the pembrolizumab arm, market shares were also obtained from the Ipsos Oncology Monitor. However, as in the first-line setting (in the DM health state), it was assumed that patients who reached the second-line setting less than 2-years after adjuvant pembrolizumab initiation would not be rechallenged with IO monotherapy. As such, the market shares of pembrolizumab and nivolumab monotherapy were set to 0% for the first 2 years and the other market shares were proportionally increased to account for pembrolizumab and nivolumab usage, except for dabrafenib + trametinib and encorafenib + binimetinib these were not proportionally increased. After 2 years, a [redacted] share of pembrolizumab was permitted to reflect the rechallenge strategy described by clinical experts, and the shares of nivolumab + ipilimumab and ipilimumab were proportionally decreased (CS, Table 56).[1]

4.2.6.7 Extrapolation + potential waning of treatment effect

No waning of treatment effectiveness was assumed for transitions from the RF health state i.e., transition probabilities from the RF health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon. According to the company, for the LRR and DM health states, it was assumed that there was no ongoing benefit of adjuvant pembrolizumab after recurrence. However, transition probabilities from the LRR and DM health states differed between arms based on the respective market shares of subsequent treatments received in these health states (for the whole duration of the time horizon).

ERG comment: The main concerns of the ERG relate to a) parametric models to estimate transition probabilities from the RF health state; b) assumed risk reduction for the patients in the RF health state; c) no treatment waning was assumed; d) transitions from the LRR and DM health states were assumed constant over time and e) the HR for the transition from LRR to death.

a) The company provided an extensive description (in the CS[1] and in response to clarification question B4[3]) how the parametric models to estimate transition probabilities from the RF health state were selected (CS base case: Lognormal-Lognormal for RF to LRR and RF to DM respectively).[1] Nevertheless, out of a total of 54 candidate combinations, the company

prioritised five combinations (all based on parametric models separately fitted to each treatment arm, defined as approach #1 in the CS):[1] Weibull-Generalised gamma; Gompertz-Generalised gamma; Lognormal-Lognormal (CS base case); Generalised gamma-Lognormal (CS scenario); Log-logistic-Lognormal (CS scenario), see also clarification response Tables 21 and 22.[3] CS, Table 70 indicates that the relative impact on the ICER is potentially substantial (CS scenario 2). Notably, not all prioritised combinations were explored in the scenario analyses reported in CS, Table 70.[1] Therefore, the ERG explored the remaining prioritised combinations, i.e., Weibull-Generalised gamma and Gompertz-Generalised gamma in scenario analyses.

b) In response to clarification question B5,[3] the company indicated that "*Active treatment strategies for stage 2 melanoma are a relatively recent development in melanoma research, and therefore there is limited long-term published evidence reporting on the risk of recurrence over time in the stage 2 setting. Accordingly, MSD are not aware of a published study that explicitly evaluates the change in recurrence risk over time*". However, the company provided evidence indicating that the large majority (>90% according to clarification response Table 23) of relapses occur in the first 5 years. Moreover, clinical experts were "*highly supportive of the assumption that any patients who reached 10 years without recurrence were very unlikely to subsequently have a recurrence*". Hence the company's statement that it is likely that the flattening of the curve has not yet been reached in the KEYNOTE-716 trial at IA2 (median follow-up 20.5 months) seems consistent with published real-world cohorts and clinical opinion. The company helpfully explored the impact of this assumption by providing a scenario in which the risk reduction assumption is not applied, this increased the ICER to £12,626 per QALY gained (deterministic CS base case ICER: £4,616 per QALY gained).[1]

c) Transition probabilities from the RF health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon, i.e., no treatment waning was assumed. The company justified this by stating that there are two approaches through which pembrolizumab is anticipated to provide a lasting treatment effect, firstly the 'immune surveillance' mechanism of action of pembrolizumab and secondly the removal of residual micro-metastases (as adjuvant treatment is intended to supplement surgery, the company expects that adjuvant pembrolizumab will increase the proportion of patients who have no residual micro-metastatic disease and who will therefore never have disease recurrence). Moreover, the company provided supporting statements based on evidence from KEYNOTE-716, KEYNOTE-054, KEYNOTE-006, KEYNOTE-001, CheckMate238 and EORTC-18071. Based on the above, the company does not believe it is appropriate to implement treatment waning in the economic model (and hence no scenario analyses is provided).

d) The transitions from the LRR and DM health states were estimated based on an exponential distribution, assuming a constant transition probability over time. In the CS[1] the company stated that the "*exponential distribution is typically 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. Given the memoryless nature of Markov modelling, 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.*". While the ERG agrees that it is computationally convenient and preferred from a parsimony principle, it is important to explore the plausibility of assuming constant probabilities over time. In clarification response B4 (Table 18), the company indicated that "*exponential distributions for the cause-specific hazards of LRR→DM and LRR→Death produced a suitably close fit with time from LRR to DM or death among patients who receive no adjuvant treatment following LRR*", this was illustrated in Figure 5 of the clarification

response. Although it is, according to the ERG reasonable to use an exponential distribution for intermediate health states, i.e., the LRR and DM health states (given the reasons mentioned above), the clinical plausibility of constant probabilities over time is less clear given the limited information provided to justify this assumption.

e) CS Table 34 reports the HRs of DMFS failure versus no adjuvant treatment used for transitions from the LRR health state.[1] Although this is not explicitly mentioned by the company, the ERG believes that these HRs are also used for estimating the transition from LRR to death. This assumption was not appropriately justified and hence its plausibility is unclear to the ERG. Therefore, the ERG adopted the scenario analysis, wherein transition probabilities for patients receiving a subsequent adjuvant treatment in the LRR state were estimated using Electronic Health Record (EHR) data.

4.2.7 Adverse events

The main source of evidence on AEs used for intervention and comparators was the KEYNOTE-716 trial. Grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm were considered in the economic model. In addition, diarrhoea of grades 2 or higher was also considered based on the high expected cost of managing this AE (i.e., need for hospitalisation) even for grade 2 events and to ensure consistency with previous NICE appraisals.

Risks of the included AEs for patients treated with pembrolizumab and routine surveillance were obtained from all-cause AE event rates observed in KEYNOTE-716 (CS Table 41).[1] Mean durations of each AE per episode, and the mean number of episodes per patient with each AE, were collected from KEYNOTE-716 using pooled data from both treatment arms and were used to estimate the duration of each AE disutility regardless of subgroup or adjuvant treatment arm.

ERG comment: No comments.

4.2.8 Health related quality of life (HRQoL)

4.2.8.1 HRQoL data identified in the review

According to the CS,[1] the SLR identified one study reporting utility values in early stage melanoma and four studies reporting utility values in stage 3-4 melanoma. Out of these, the company used the study of Beusterien et al. 2009[38] in which a standard gamble was used to elicit societal preferences from the UK general population, to inform the post-progression DM utility.

4.2.8.2 HRQoL data from clinical trials

HRQoL was measured in KEYNOTE-716 using the EuroQoL-5D-5L (EQ-5D-5L) at baseline (cycle 1), every fourth cycle while on treatment (cycles 5, 9, 13, 17; i.e., every 12 weeks), every 12 weeks during year 2 (week 60, 72, 84, and 96 from baseline), every 6 months during year 3 (month 30 and 36 from baseline), at the treatment discontinuation visit, and at the 30-day follow-up visit. In part 2 (crossover/rechallenge after recurrence), measurements were collected at baseline (cycle 1 of part 2), during treatment at cycles 9, 17 and 35, and at 24 and 48 weeks during the first year off treatment. In line with the NICE reference case, EQ-5D-5L measurements collected in KEYNOTE-716 were mapped to the EQ-5D-3L using the crosswalk method developed by van Hout et al (2012).[39] The EQ-5D-5L value set was explored in a scenario analysis.

Utility values for the RF, LRR and DM health states were derived via repeated measures regression analyses (linear mixed-effects model with patient-level random effects). At each visit where HRQoL was assessed, the corresponding EQ-5D score was used to estimate utility and visits with missing EQ-

5D responses were excluded from the analysis. The analyses were pooled across treatment arms to estimate the average utility for all patients in the trial, as the company stated that there was no clinically meaningful difference in HRQoL between the pembrolizumab and placebo arms of the KEYNOTE-716 trial. Two regression models were conducted with EQ-5D utility as the dependent variable: one to estimate the RF health state utility and AE disutility, and one to estimate the LRR and DM health state utilities.

Pre- versus post-progression utilities in the DM health state could not be separately estimated using the KEYNOTE-716 data due to limited follow-up data and the relatively small number of patients. The company therefore informed the pre-progression DM utility based on KEYNOTE-716 and used the study of Beusterien et al. 2009[38] to inform the post-progression DM utility. Then, a single utility value for the DM health state was calculated as a weighted average of the pre- and post-progression states, based on the proportion of time spent in each (i.e., the ratio of PFS:OS (CS Table 39)).[1] As the market shares of subsequent treatments in the advanced setting affect the estimated efficacy and thereby the PFS:OS ratio which vary by adjuvant treatment arm, the weighted average utility will also differ for patients that initially received adjuvant pembrolizumab vs routine surveillance.

4.2.8.3 Disutility values

The disutility of an active grade 3+ AE was estimated to be [redacted] (using the same regression model that was used to estimate RF utilities), representing the difference in utility between RF without toxicity versus RF during any grade 3+ AE in KEYNOTE-716. The same disutility was applied to grade 2+ diarrhoea. Disutilities associated with each AE were applied as a one-off utility decrement in the first model cycle.

4.2.8.4 Health state utility values

All HSUVs used in the economic model were based on data from KEYNOTE-716, except for the post-progression DM utility, which was based on Beusterien et al. 2009.[38] A summary of all utility values used in the CEA is provided in Table 4.7.

To account for potential decreases in utility with age, age-adjusted utilities were applied in the model to account for the increasing age of the cohort over time using the algorithm developed by Ara and Brazier 2010.[40]

Table 4.7: HSUVs

Health state	Utility value	SE	Source
RF (toxicity free)	[redacted]	[redacted]	KEYNOTE-716
LRR	[redacted]	[redacted]	
DM (pre-progression)	[redacted]	[redacted]	
DM (post-progression)	0.5900	0.0200	Beusterien et al. 2009[38]
Death	0	-	-
AE disutility[1]	[redacted]	[redacted]	KEYNOTE-716

Based on CS Table 45.[1]
[1] This AE disutility was applied to the RF (toxicity free) utility, adjusted by the frequency of AEs, to estimate the utility for RF with toxicity
AEs = adverse events; CS = company submission; DM = distant metastases; LRR = locoregional recurrence; RF = recurrence-free

ERG comment: The main concerns of the ERG relate to a) the potential overestimation of the RF health state utility, and b) the source of informing the DM (post progression) health state utility.

a) To calculate the RF health state utility, the company conducted a regression analysis including a binary indicator for grade 3+ AEs and a binary indicator for any other grade (i.e., grade<3) AEs. The company stated, however, that the model only considered grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial. Therefore, including low grade AEs (grade<3) as a binary indicator in the regression model rather than assuming these to be implicitly included in the RF health state utility likely overestimated the utility value of the RF health state ([redacted]). Instead of using two separate regression models to estimate the utility values of the RF state and the LRR and DM states, the ERG would have preferred that the company conducted one regression model including binary indicators for being in the LRR state, being in the DM state and grade 3+ AEs. Although suboptimal and awaiting the company's utility analysis based on one regression model, the ERG selected [redacted] (intercept of regression model 2) to inform the RF utility in its base case.
b) The company stated that it was not possible to generate utility values for pre- versus post-progression in the DM health state due to limited follow-up data and small patient numbers in the KEYNOTE-716 trial. The company consequently sourced the utility value for the post-progression DM health state from a study of Beusterien et al. 2009[38] which used a standard gamble approach to elicit utilities for advanced melanoma health states from the UK general population. The ERG questions the use of a standard gamble approach to elicit utilities and considers the post-progression DM utility (0.59) to be low compared to the pre-progression DM utility ([redacted]). The ERG considered the company's scenario analysis in response to question B12b, using the utility for progressed disease (0.7) sourced from KEYNOTE-006 (TA366; based on the EuroQol-5D), to be more plausible and adopted this in its base case.

4.2.9 Resources and costs

The cost categories included in the model were intervention costs (including treatment acquisition and administration costs), health state costs (including regular surveillance/monitoring costs and subsequent treatment costs), costs of managing AEs and terminal care costs.

Unit prices were based on the NHS reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and Monthly Index of Medical Specialities (MIMS).

4.2.9.1 Resource use and costs data identified in the review

Although details regarding cost and resource use identification were provided in Appendix I,[15] the company did not summarise in the CS whether any of the identified studies could be used to inform cost and resource use in the economic model.

4.2.9.2 Treatment costs

As per the anticipated licence, the model considered a 400 mg intravenous IV infusion of pembrolizumab Q6W for adults, and weight-based dosing of 2 mg/kg Q3W for children. The list price of pembrolizumab was £2,630.00 per 100 mg vial, therefore the list drug cost per administration was £10,520.00 for adults and [redacted] for children (based on mean paediatric weight in KEYNOTE-716). No vial sharing was assumed, and to prevent over-dosing, it was assumed that the final dose of the pembrolizumab Q6W regimen within the 12-month treatment period would be 200 mg based on the available vial presentations for pembrolizumab. A PAS is in place for pembrolizumab, which makes

pembrolizumab available to the NHS for a discount of [redacted]. The relative dose intensity (RDI) from KEYNOTE-716 ([redacted]) was applied to account for any delays or interruptions in administration.

Pembrolizumab is administered via a 30-minute intravenous infusion, which was costed, consistent with other NICE submissions for pembrolizumab, based on Healthcare Resource Group (HRG) code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) from NHS Reference Costs 2019/20.

4.2.9.3 Health state costs

Health state costs were based on resource use estimates sourced from the literature and were expected to be the same for patients that initially received adjuvant pembrolizumab and routine surveillance.

4.2.9.3.1 Recurrence-free health state

Resource use for patients remaining in the RF health state consisted of regular surveillance activities to identify recurrences. Frequencies were based on NICE guideline 14[8] and the surveillance policy for patients with stage 2B/2C resected melanoma outlined in a position paper developed by UK clinicians (CS Table 48). Unit costs for each resource were sourced from NHS Reference Costs 2019/20 (CS Table 49), applied to annual resource use estimates, and then converted to resource use cost per cycle for inclusion in the model.[1]

4.2.9.3.2 Locoregional recurrence (LRR) health state

A proportion of patients received salvage surgery upon entry to the LRR health state. The type of surgery, the proportion of patients having each surgery type, and the mean number of surgeries per patient were based on the KEYNOTE-716 trial. The frequency of regular surveillance activities was sourced from NICE guideline 14 and the UK position paper used to inform the RF state (CS Table 50).[1] In addition, UK clinical experts advised that patients suspected of having a recurrence would undergo an image-guided biopsy to confirm the recurrence. Costs of salvage surgeries were sourced from NHS Reference Costs 2019/20102 and were applied as a one-off cost on entry to the LRR state (CS Table 51).[1] Unit costs for clinic visits and imaging resources were sourced from NHS Reference Costs 2019/20 as per the RF health state.

Subsequent treatments in LRR health state

In addition, patients in the routine surveillance arm who entered the LRR state were assumed to be eligible for adjuvant therapy with pembrolizumab, nivolumab, or dabrafenib + trametinib. Drug acquisition and administration costs for adjuvant therapies were applied as lump-sum costs upon entry into the LRR state. The dosing schedule for each drug was based on the schedule included in the corresponding NICE recommendation and in line with the SmPC. Unit costs per pack or vial of treatment (list price) were sourced from MIMS (CS Table 52). Drug administration costs for adjuvant therapies were sourced from NHS Reference Costs 2019/20 and the PSSRU 2021 (CS Table 53).[1] The mean duration of each adjuvant treatment was estimated using observed time on treatment in the corresponding clinical trial (maximum duration 52 weeks), which were used to calculate the exponential rate of discontinuation. Dose intensity was assumed to be 100% for all treatments in the LRR state.

4.2.9.3.3 Distant metastatic health state

Medical resource use in the DM state were outpatient clinic visits, inpatient stays, laboratory tests and imaging. Resource use frequencies were sourced from NICE TA319. In addition, UK clinical experts advised that patients suspected of having a recurrence would undergo an image-guided biopsy to confirm the recurrence. Unit costs were sourced from NHS Reference Costs 2019/20 (CS Table 63),

applied to monthly resource use estimates, and then converted to resource use cost per cycle for inclusion in the model.[1]

As the DM state consisted of both pre- and post-progression DM, in each treatment arm disease management costs per cycle for the DM state were computed as a weighted average of resource use associated with pre- versus post-progression DM, based on the estimated proportion of time spent progression-free.

Subsequent treatments in DM health state

All patients who entered the DM health state were assumed eligible for treatment in the advanced setting with one of the treatment regimens currently recommended by NICE and used in clinical practice (IO combination or monotherapy, targeted therapies).

The proportion of patients in the pembrolizumab arm receiving subsequent treatment in the pre-progression DM state were sourced from the SACT report. The company stated that IO rechallenge within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice, and therefore only a small percentage of patients entering the DM state more than 2 years after adjuvant treatment were retreated with subsequent pembrolizumab. Market shares of subsequent treatments in the routine surveillance arm were also based on SACT data. However, as IO monotherapies are common in the metastatic setting for patients who have not received adjuvant pembrolizumab, the market share of pembrolizumab was sourced from the Ipsos Oncology Monitor, and shares of non-targeted agents from SACT were proportionally lowered (CS Table 55).[1]

In addition, a subset of patients was assumed to also receive subsequent treatment in the post-progression DM state (for both arms based on the Ipsos Oncology Monitor and confirmed by clinicians to be acceptable for the UK setting). As in the pre-progression DM state, only a small percentage of patients entering the DM state more than 2 years after adjuvant treatment were retreated with second-line (CS Table 56).[1]

Acquisition and administration costs for the advanced melanoma setting were applied as one-off costs in the DM health state. Based on the estimated discontinuation rate, the mean total cost in the pre- and post-progression DM state was estimated, and the mean treatment cost per treatment arm was then calculated as a weighted average of all treatment regimens using the pre- and post-progression DM market shares specified for each arm. Unit costs were sourced from MIMS (CS Table 57).[1] No vial sharing was assumed in the company's base case but was explored in a scenario analysis. Drug administration costs for advanced melanoma therapies were sourced from NHS Reference Costs 2019/20 and the PSSRU 2021 (CS Table 59).[1] Duration of subsequent therapies in the pre-progression DM state was estimated using the exponential rates of PFS failure to estimate discontinuation rates (CS Table 60).[1] A relative dose intensity of 100% was assumed for all agents. In the post-progression DM state, mean time on treatment was assumed to be 21 weeks for all regimens (consistent with NICE TA319 and TA366), with the exception of ipilimumab (maximum of 12 weeks as per the NICE guidance (CS Table 61).[1]

4.2.9.4 Costs of managing adverse events

Unit costs of AEs were sourced from NICE TA319 where available and inflated to 2020 using the health component of the Consumer Price Index from the ONS. For AEs of which melanoma-specific costs were not available from TA319, costs were obtained from the NHS Reference Costs 2019/20 (CS Table 64).[1]

4.2.9.5 Terminal care costs

Patients who transitioned to the death health state were assumed to incur a one-off cost associated with palliative/terminal care if death was melanoma-related (i.e., if they occurred from the DM state). Consistent with TA366 and TA766, terminal care costs were based on costs during the last 90 days before death as reported by Georghiou & Bardsley 2014,[41] including services such as emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs. Terminal care costs were inflation-adjusted to 2020 GB£ using the health component of the Consumer Price Index from the ONS (CS Table 65).[1]

ERG comment: The main concerns of the ERG relate to a) assumptions regarding the proportions of patients receiving subsequent treatments in the LRR and DM health states, b) clinical plausibility of subsequent treatment duration in the DM health state, and c) implementation of terminal care costs.

a) The company stated that for the pembrolizumab arm, it was deemed unlikely that patients treated with adjuvant pembrolizumab in the stage 2B/2C setting would receive further subsequent therapy after LRR as there is currently no evidence on the efficacy of repeat treatment with adjuvant therapy, and clinical advisors were not sure funding for further subsequent therapy would be available. Consequently, all patients in the pembrolizumab arm who had a LRR recurrence were assumed to have no further systemic subsequent therapy. However, Table 58 of Appendix P reported utilisation of subsequent treatments after LRR in the KEYNOTE-716 trial and showed that a substantial proportion of patients in the pembrolizumab arm (and similar to the placebo arm) were treated with subsequent therapies, including systemic therapies such as pembrolizumab and nivolumab, after LRR. In question B15b of the clarification letter, the ERG requested a scenario analysis assuming the same proportion of patients in the pembrolizumab arm who had a LRR recurrence would receive subsequent treatment as was given in the routine surveillance arm. The company did not provide this and stated that such scenario analysis was deemed to be implausible based on clinical expert opinion and is highly unlikely to reflect clinical practice. Nevertheless, in line with the KEYNOTE-716 trial evidence, the ERG in its base case assumed equal proportions of patients receiving subsequent treatment after LRR in the pembrolizumab and routine surveillance arm. In addition, the company sourced the proportion of patients receiving subsequent treatments in the pre- and post-progression DM states from SACT and the Ipsos Oncology Monitor respectively. The company stated that subsequent treatment data from KEYNOTE-716 for patients who developed DM were incomplete with respect to the use of combination regimens and were based on a small number of patients. The company further stated minimal use of IO monotherapy was observed in the SACT data, suggesting that IO rechallenge within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice. This was also assumed in the second-line setting. However, the ERG noticed in Table 59 of Appendix P that subsequent treatments after DM in the KEYNOTE-716 were roughly similar between the pembrolizumab and placebo arm. Although the ERG acknowledges that subsequent treatment use after DM in the KEYNOTE-716 trial was based on small patient numbers, the ERG conduced a scenario analysis assuming equal proportions of patients receiving subsequent treatment after DM in the pembrolizumab and routine surveillance arms.
b) In the DM state, apart from ipilimumab and nivolumab + ipilimumab, no maximum treatment duration for subsequent treatments was assumed in the economic model. The British Association of Dermatology Guidelines[42] supports this assumption by stating that for stage 4 melanoma, treatment with pembrolizumab or other immunotherapy agents "are given as an intravenous infusion for as long as they keep the cancer under control". Subsequent treatment

duration in the pre-progression DM state was based on exponential rates of PFS failure, whereas subsequent treatment duration in the post-progression DM state was based on a mean time on treatment of 21 weeks to be consistent with NICE TA319 and TA366. It is unclear to the ERG whether these assumptions regarding subsequent treatment duration in the DM state are clinically plausible. For pembrolizumab, the total subsequent treatment costs in the DM state were [redacted], and for routine surveillance these were [redacted] (increment [redacted]). These costs are a driver of the economic model and hence, the ERG considered this may be a point of attention to the committee. To assess the impact of subsequent treatment costs in the DM state, the ERG conducted an extreme scenario analysis excluding subsequent treatment acquisition costs in the DM state for both arms, which lead to a substantial increase of the ICER.

c) The company assumed that patients who died incur a one-off cost associated with palliative/terminal care if death was melanoma related. As a result, terminal care costs were only applied to patients who transitioned to the death state from the DM state, assuming that deaths occurring directly from the RF or LRR states had causes other than melanoma. The ERG does not agree on this, as patients in any health state could die from causes involving terminal care, and the ERG in its base case therefore assumed terminal care costs for all patients that transitioned to the death state regardless of which state they transition from.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The probabilistic CS base case cost effectiveness results (1,000 simulations) indicated that pembrolizumab is both more effective (incremental QALYs of [redacted]; 95% percentiles: [redacted]) and more costly (additional costs of [redacted]; 95% percentiles: [redacted]) than routine surveillance amounting to an ICER of £6,761 per QALY gained (Table 5.1 and CS Figure 14). For the deterministic analyses the ICER was estimated to be £4,616 per QALY gained. The probability of pembrolizumab being cost-effective compared to routine surveillance at a threshold of £30,000 per QALY gained was 77% (CS Figure 15).[1]

Most of the QALYs were gained in the RF health state (incremental QALYs in the RF, LRR and DM health states were [redacted] respectively) and the difference in costs in the RF, LRR and DM health states were [redacted] respectively (CS Appendix J Table 34).[15] Most costs were incurred due to (subsequent) treatments in the RF, LRR and DM health state (incremental treatment costs in the RF, LRR and DM health states were [redacted] respectively; CS Appendix J Table 35).[15] According to the company the disaggregated results illustrated that by reducing the incidence of recurrences, health outcomes are improved and most of the costs of adjuvant treatment with pembrolizumab can be offset by reducing the number of patients that need to be treated with expensive subsequent management strategies.

Table 5.1: Probabilistic company base case analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Routine surveillance	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	6,761
ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years					

Overall, the technology is modelled to affect QALYs by:

- Reducing the incidence of recurrences (i.e., transition from the RF health state to the LRR and DM health states)

Overall, the technology is modelled to affect costs by:

- Adjuvant treatment costs in the RF health state
- Subsequent treatment costs in the LRR and DM states
- Disease management costs in the DM state

ERG comment: The main concerns of the ERG relate to a) the proportion of benefits accrued beyond the observed data and b) the disaggregated costs.

a) According to clarification response Table 28, the proportion of RFS benefit (i.e., increment) accrued beyond the observed data period is substantial ([redacted]). Although the company argued that this is plausible, this remains an uncertainty. Moreover, for OS, the life years gained beyond the observed data period was not provided by the company as OS was not included as part of the pre-specified analyses for the second interim analysis of KEYNOTE-716.
b) As noted in the ERG comments of Section 4.2.9, the plausibility of the costs incurred in the DM health state ([redacted] for pembrolizumab and routine surveillance respectively), as opposed for instance the costs incurred in the RF health state ([redacted] for pembrolizumab and routine surveillance respectively) is unclear. Particularly when

considering that patients remain 9.09 and 6.68 life years in the RF health state and 1.87 and 2.42 in the DM health state when considering pembrolizumab and routine surveillance respectively CS Appendix Table 34).[1]

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) were related to estimated (progression-free) survival in the DM health state, patient weight, costs in the DM health state and the probability of transitioning from LRR to DM (CS Figure 16).[1]

Modelling assumptions that relate to transitions from the RF health state and alternative market shares of subsequent therapy in the LRR and DM health states had the greatest upwards effect on the ICER (CS Table 70).[1]

ERG comment: The main concerns of the ERG relate to the parameters included in the DSA. It is notable, based on CS Section B.3.8.2,[1] the number of parameters included in the DSA was limited (e.g., the transition probabilities from the RF health states, which are potentially key parameters given the description in Section 5.1, were not incorporated in the DSA).

5.3 Model validation and face validity check

5.3.1 Face validity assessment

Clinical experts were consulted via an advisory board and through additional individual engagements to validate the efficacy inputs (e.g., the plausibility of long-term RFS, DMFS, and OS) and other key model decisions (e.g., assumptions about post-recurrence treatments) from a clinical perspective, to ensure that the model was reflective of the UK setting.

5.3.2 Technical verification

To verify the results of the cost effectiveness model, internal quality control procedures were undertaken by the model developer team to ensure that the mathematical calculations are being performed correctly and are consistent with the model's specifications. The model was also independently reviewed by two external health economists, who evaluated the model from an overall health economics perspective.

5.3.3 Comparisons with other technology appraisals

To provide further validation of the outcomes modelled from the DM state, which accounts for most deaths in the first half of the model, an additional check was conducted which considered the plausibility of the modelling assumptions in this health state, as per the methods employed by the ERG in TA766. The expected survival in the DM state predicted by the economic model was compared to the life years estimated for the pembrolizumab arm in the economic model considered in the 2015 NICE appraisal of pembrolizumab monotherapy for untreated advanced melanoma (TA366). In the current model, the expected survival (in the DM health state) ranged from [redacted] years, based on the first-line market shares applied in each arm; this is highly comparable to the 5.08 life years in the TA366 model. This provides reassurance that the current modelling of this health state is reasonable, and thus the predicted OS is likely to be plausible.

5.3.4 Comparison with external data used to develop the economic model

The validity of the model was also assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs. For example, the RFS curves predicted for the two arms of KEYNOTE-716 were plotted alongside the observed KM curves for RFS to ensure that the curves are well-aligned during the trial period.

According to the CS, the modelled outputs were highly consistent with the RFS data observed in KEYNOTE-716, and RFS and DMFS outputs for routine surveillance were closely aligned with results reported in published real-world cohorts (CS Figures 8 and 10).[1]

To validate that the competing risks approach to survival modelling employed in the economic model produced plausible composite RFS results, independent parametric survival analysis of the RFS data from KEYNOTE-716 was conducted based on fitting six standard parametric models (exponential, Weibull, Gompertz, Lognormal, Log-logistic, and Generalised gamma) to patient-level data from the pembrolizumab and placebo arms of KEYNOTE-716. Based on Bayesian Information Criterion (BIC) statistics and visual assessment, the Log-logistic RFS distributions appeared to provide the best balance between goodness-of-fit in the pembrolizumab arm and goodness-of-fit in the routine surveillance arm, ranking as the third- and second best-fitting distributions in these arms, respectively. Comparison of the projections estimated by the Log-logistic function in this independent analysis with the projected RFS estimated in the base case economic model demonstrates a close alignment in the 10-year RFS generated via these two approaches (until the 10-year risk reduction assumption is applied) (CS Figure 17A).[1] In the scenario where the 10-year risk reduction is not applied (CS Figure 17B),[1] the RFS predicted by the Log-logistic function continues to align closely with the composite RFS estimated by the model. This provides further reassurance that the model produces credible results and that the parametric functions selected to model the intermediate health states are appropriate.

5.3.5 Comparison with external data not used to develop the economic model

Model predictions were compared against observed data from three published external studies that reported long-term RFS and/or OS in real-world cohorts of patients diagnosed with the American Joint Committee on Cancer (AJCC) 8th edition stage 2B or 2C melanoma. These three external studies were conducted in distinct patient cohorts (including two US-based cohorts and one European cohort). Survival projections in the routine surveillance arm were also validated against long-term RFS, DMFS, and OS observed in a real-world study using USON electronic health records. UK clinicians confirmed that these datasets were generalisable to the UK setting and therefore suitable for use as validation sources.

The estimated OS results for routine surveillance (CS Figure 11) were slightly higher than reported by the real-world evidence.[1] However there have been significant improvements in the treatment of metastatic disease in the last 10 years which have substantially improved survival outcomes for patients with metastatic melanoma. Note that the study by Bajaj et al, 2020[43] does represent a relatively more recent cohort (patients enrolled 2010–2016) which therefore may partly capture recent treatment improvements. However, the study is limited by the small cohort size (n=90) and therefore the OS curve, particularly the second half, should be interpreted with caution. Consequently, it is likely that all the external studies somewhat underestimate the true OS for patients with contemporary diagnoses.

ERG comment: The company helpfully provided further details and clarifications regarding the model validation (clarification questions B8, B9, B23-B27) regarding the technical verification as well as comparison with external data and other technology appraisals, this supported the validity of the economic model.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020.[44]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base case. This base case included multiple adjustments to the original base case presented in the previous Sections. These adjustments made by the ERG form the ERG base case and were subdivided into three categories (derived from Kaltenthaler 2016):[45]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base case

Adjustments made by the ERG, to derive the ERG base case (using the CS base case[1] as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base case. The 'FE' adjustments were combined, and the other ERG analyses were performed also incorporating these 'FE' adjustments given the ERG considered that the 'FE' adjustments corrected unequivocally wrong issues.

6.1.1.1 Matters of judgement

1. Alternative utility estimate for RF (Section 4.2.8)
   A HSUV of [redacted] was adopted for the RF health state
2. Alternative utility estimate for DM post progression (Section 4.2.8)
   A HSUV of 0.7 was adopted for DM post progression
3. Alternative subsequent treatment proportions/market share in LRR health state (Section 4.2.9)
   For patients that initially received pembrolizumab, subsequent treatment proportions/market share (LRR health state) was assumed equal to routine surveillance
4. Alternative implementation of end of life costs (Section 4.2.9)
   End of life costs implemented regardless of health state from which patients died

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base case.

6.1.2.1 Exploratory scenario analyses

1. Alternative transition probabilities from the RF health state (Section 4.2.6)
   The Weilbull-Generalised gamma distributions were selected
2. Alternative transition probabilities from the RF health state (Section 4.2.6)
   The Gompertz-Generalised gamma distributions were selected
3. Alternative transition probabilities in the LRR health state (Section 4.2.6)
   Transition probabilities for patients receiving a subsequent adjuvant treatment in the LRR health state were estimated using electronic health record (EHR) data
4. No subsequent treatment costs in the DM health state (Section 4.2.9)
   No subsequent treatment acquisition costs for the DM health state
5. Alternative subsequent treatment proportions/market share in DM health state (Section 4.2.9)
   For patients that initially received pembrolizumab, subsequent treatment proportions/market share (DM health state) was assumed equal to routine management
6. Alternative model structure for DM health state
   Assume no progression in the DM health state

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Additional evidence or analyses required
The use of separate regression models for the estimation of RF utility and AE disutility (regression model 1), and LRR and DM utilities (regression model 2).	4.2.8	Methods	Single regression model including binary indicators for being in the LRR state, being in the DM state and grade 3+ AEs.	Unclear	No	Yes
Plausibility of assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs.	4.2.9	Bias and indirectness	1. Analyses assuming equal proportions of patients receiving subsequent treatment after LRR and DM in the pembrolizumab and routine surveillance arm. 2. Extreme scenario analysis excluding subsequent treatment acquisition costs in the DM state. 3. Analysis assuming terminal care costs for all patients that transitioned to the death state.	Unclear (overall impact)	Partly	Yes

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator

[b] Explored

AE = adverse event; DM = distant metastases; ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; LRR = locoregional recurrence; MJ = matters of judgement; RF = recurrence free

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base case was presented, which was based on various changes compared to the company base case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the ERG base case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. Finally, Table 6.4 provides the results of the probabilistic CS base case[1] and ERG base case analysis. The submitted model file contains technical details on the analyses performed by the ERG (e.g., the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base case

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	4,616
Company base case + 1 Alternative utility estimate for RF							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	4,790
Company base case + 2 Alternative utility estimate for DM post progression							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	4,764
Company base case + 3 Alternative subsequent treatment proportions/market share in LRR health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	10,045
Company base case + 4 Alternative implementation of end of life costs							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	5,047
ERG base case (1-4)							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	11,107

DM = distant metastases; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; LY = life year; QALY = quality-adjusted life year; RF = recurrence free

Table 6.3: Deterministic scenario analyses (conditional on ERG base case)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ERG base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	11,107
ERG base case + 1 Weilbull-Generalised gamma distributions for transition probabilities from the RF health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	10.721	[redacted]	[redacted]	[redacted]	[redacted]	22,537
ERG base case + 2 Gompertz-Generalised gamma distributions for transition probabilities from the RF health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	10.719	[redacted]	[redacted]	[redacted]	[redacted]	4,231
ERG base case + 3 Alternative transition probabilities in the LRR health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.921	[redacted]	[redacted]	[redacted]	[redacted]	11,075
ERG base case + 4 No subsequent treatment costs in the DM health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	19,035
ERG base case + 5 Alternative subsequent treatment proportions/market share in DM health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	729
ERG base case + 6 Alternative model structure for DM health state							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.967	[redacted]	[redacted]	[redacted]	[redacted]	10,708

DM = distant metastases; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; LY = life year; QALY = quality-adjusted life year; RF = recurrence free

Table 6.4: Probabilistic CS base case and ERG base case

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.980	[redacted]	[redacted]	[redacted]	[redacted]	6,761
ERG base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	9.980	[redacted]	[redacted]	[redacted]	[redacted]	13,550

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

6.3 ERG's preferred assumptions

The estimated ERG base case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 5.1, was £13,550 per QALY gained. The probabilistic ERG base case analyses indicated cost effectiveness probabilities of 61% and 71% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was assuming alternative subsequent treatment proportions/market share in LRR health state. The ICER increased most in the scenario analysis with alternative assumptions regarding transition probabilities from the RF health state and assuming no subsequent treatment costs in the DM health state.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness model was consistent with the NICE reference case. The most prominent issues highlighted by the ERG were 1) handling of subsequent treatments after recurrence (both in terms of cost and effectiveness); 2) estimation of transition probabilities from the recurrence free health state; 3) estimation of HSUVs; 4) implementation of terminal care costs and 5) the proportion of RFS benefit (i.e., increment) accrued beyond the observed data period.

The CS base case probabilistic and deterministic ICERs were £6,761 and £4,616 per QALY gained, respectively.[1] In addition to the abovementioned issues, in the clinical effectiveness sections, it was highlighted that there is uncertainty about the comparability of the efficacy and safety profiles of the two recommended doses of pembrolizumab (i.e., 200 mg Q3W and 400 mg Q6W). A scenario analysis, conducted by the company, assuming that only the treatment costs would differ between the two recommended doses of pembrolizumab (i.e., assuming equal efficacy and safety), changed the ICER from £4,616 per QALY gained (for 400 mg Q6W) to £5,300 per QALY gained (for 200 mg Q3W).

The ERG base case probabilistic and deterministic ICERs were, based on the ERG preferred assumptions highlighted in Section 6.1, £11,107 and £13,550 per QALY gained, respectively. The most influential adjustment was assuming alternative subsequent treatment proportions/market share in LRR health state. The ICER increased most in the scenario analysis with alternative assumptions regarding transition probabilities from the RF health state and assuming no subsequent treatment costs in the DM health state.

7. END OF LIFE

The CS (Section B.2.13.3) stated that pembrolizumab does not meet the NICE end of life criteria in the indication of resected stage 2 melanoma with high risk of recurrence.[1]

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

'*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 EAG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the EAG 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 Monday 9 May** 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.

Section 1: Factual inaccuracies

Decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 – 'The NICE final scope lists the following outcomes that need to be covered in the technology appraisal (TA)'	Please amend to: 'The NICE final scope lists the following outcomes that ~~**need to be covered**~~ **are recommended for inclusion** in the technology appraisal (TA)'	The NICE manual states that 'As far as possible, the scope identifies the main measures of outcomes that are relevant to estimating clinical effectiveness'. This suggests that the outcomes included in the final scope are not required but are recommended for inclusion in the technology appraisal.	Changed to "should be covered"

Clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 – 'No data were provided for OS or DMFS and this hinders a full evaluation of effectiveness and cost effectiveness of the product' Page 14 – 'No data were provided for OS or DMFS'	Please amend this to: Page 11 – 'No data were ~~**provided**~~ **available** for OS or DMFS and this hinders a full evaluation of effectiveness and cost effectiveness of the product' Page 14 – 'No data were ~~**provided**~~ **available** for OS or DMFS'	The current wording implies that MSD chose not to provide these data. This is not the case. Data for OS and DMFS are not yet available from KEYNOTE-716 and therefore it has not been possible for MSD to provide this information at the stage of the submission.	Not a factual inaccuracy
Page 12, Table 1.3 – 'There is uncertainty about the comparability of the efficacy	Please amend to: 'There is uncertainty about the comparability **of the efficacy and safety profiles of the two**	The use of both doses of pembrolizumab have been approved by the EMA and deemed to have no clinically significant	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
and safety profiles of the two recommended doses of pembrolizumab.'	**recommended doses of pembrolizumab in stage 2 melanoma, however both doses are deemed to have no clinically significant differences in efficacy or safety by the EMA and were subsequently approved for use**.'	differences in efficacy or safety. The Q6W regimen is widely used in clinical practice with no negative impact on outcomes. MSD consider this to be important context that should be included when discussing this potential uncertainty. Whilst data have been provided to the EMA on the efficacy and safety of both regimens, MSD agree that there are no data for this in stage 2 melanoma specifically, and therefore this wording should be updated to discuss the indication specifically. From a decision problem perspective we chose to align the posology of pembrolizumab to that which is anticipated in the real-world setting. An option exploring the impact of Q3W has been presented in the cost-effectiveness analysis.	
Page 13 – 'Patients with stage 2B melanoma not only have a better prognosis than those with stage 2C, but subgroup analyses appear to show a better outcome from stage 2B'	Please amend to: 'Patients with stage 2B melanoma **may** have a better prognosis than those with stage 2C based on historical data. In KEYNOTE-716 subgroup analyses **suggest that pembrolizumab may be more effective relative to placebo in stage 2B than 2C in improving RFS,** although the study was not formally powered to detect statistically significant associations in subgroups,'	MSD disagrees with this sentence, as the current wording is vague and open to misinterpretation. Further, the current sentence does not reflect the statistical considerations from KEYNOTE-716. The study was not powered to detect such differences and as such conclusive statements like that included in the original EAG report should not be made in isolation.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 – "The trial population for the KEYNOTE-716 RCT is not a good reflection of that seen in UK clinical practice in terms of the distribution of different stages of melanoma."	MSD requests that this sentence is either deleted or amended accordingly to: "The trial population for the KEYNOTE-716 RCT **may not be** a good reflection of that seen in UK clinical practice in terms of the distribution of different stages of melanoma **when compared to data from PHE. However, the differences in staging between KEYNOTE-716 and PHE datasets are small, particularly considering that one source is a Phase 3 study and the other is real world data from patients diagnosed within the NHS.**	The current wording is vague and open to misinterpretation. MSD believes that the study is fully generalisable to the UK population based on expert opinion sought during the development process. Subtle differences in cancer sub-staging versus historical data should not be unnecessarily inflated by the EAG in their assessment of evidence. Therefore, **we caution against comparisons between the two different data sources with different levels of reporting (Phase 3 clinical trial versus a real-world setting). The level of reporting across these sources may differ (i.e. the percentage of patients unclassified in the real-world setting could affect such comparisons). Consequently, such comparisons should be interpreted with caution.**	Partly changed, i.e., "may not be" incorporated.
Pages 21–22 – 'The update of this Section with the amendment allowing for a 400 mg Q6W regimen was issued after authorisation by the European Medicines Agency (EMA; application II/0102) and was stated to have been based on interim efficacy and safety results	Please amend to: 'The update of this Section with the amendment allowing for a 400 mg Q6W regimen was issued after authorisation by the European Medicines Agency (EMA; application ~~II/0102~~ **II/0062**) ~~and was stated to have been based on interim efficacy and safety results from Cohort B in the open-label KEYNOTE-555 trial.'~~	The EMA application number to allow 400 mg Q6W dosing for monotherapy indications was II/0062. Therefore, please update the application number and remove reference to the data submitted as this refers to a different EMA application.	Text amended to summarise information about the earlier application (II/0062). The text relating to the subsequent application (II/0102) was retained as it is relevant to the decision problem.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
from Cohort B in the open-label KEYNOTE-555 trial.'			
Page 23 – 'The company responded that: "*MSD are unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm, as these data are not available*" and "*Full results from this analysis, which will include DMFS events by arm, are expected to be available in* [redacted]"'	Please either remove the second quotation from this sentence or amend this to: 'The company responded that: "*MSD are unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm, as these data are not available.*" Full results from **the IA3 analysis**, "*which will include DMFS events by arm, are expected to be available in* [redacted]"'	The two quotations from the EAG relate to separate data cuts from the KEYNOTE-716 trial. Either the second quotation should be removed, or additional context added to clarify this.	Edited accordingly.
Page 25, Table 3.1 – reported dates searched for SMR and ESMO 2021 stated as 18/9/21	Please correct to **28/09/21**	Please correct the typographical error.	Edited accordingly
Page 30 – 'An SLR and consequent network meta-analysis (NMA) was performed to identify and synthesie RCT evidence…'	Please correct to 'An SLR and consequent network meta-analysis (NMA) was performed to identify and **synthesise** RCT evidence…'	Please correct the typographical error.	Edited accordingly
Page 31 – 'Attempts to ensure allocation concealment were made by use of an interactive voice response system.'	Please correct to: 'Attempts to ensure allocation concealment were made by use of an interactive ~~**voice**~~ response **technology** system.'	A voice system was not specified in the CSR or Protocol, please align to the wording used in Document B.	Edited accordingly. Added the relevant information as a quotation and signposted the relevant sections in Document B.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32, Table 3.3 – Inclusion criteria '…or a KPS score ≥50 (for patients'	Please correct to '…or a KPS score ≥50 (for patients **>16 and <18 years old)**'	Please complete the sentence with the missing information.	Edited accordingly and added Table 7 of the CS (which is where this information comes from) to the source material indicated in the ERG Table 3.3 footnote
Page 40 – '…64% were stage 2B, and 34.8% were stage 3B'	Please correct to '64% were stage 2B, and 34.8% were stage **2C**'	Please correct the typographical error.	Edited accordingly
Page 40-41 – 'Although there is only a small difference between the UK population and trial participants for ethnicity, the percentage difference between the UK population and the trial participants for the proportion of 2B participants is much higher, at around 11%.'	Please amend to: 'Although there is only a small difference between the UK population and trial participants for ethnicity, the percentage difference between the UK population and the trial participants for the proportion of 2B participants is ~~**much**~~ higher, at around **7**%.'	The difference in proportion of 2B patients in the UK (57%) compared with the trial population (64%) is 7%, as opposed to 11% as reported in the EAG report. Furthermore, the EAG have not clarified how this proportion has been quantified as '**much** higher', and therefore removal of the word 'much' would be appropriate. Finally, MSD believes that the study is fully generalisable to the UK population based on expert opinion sought during the development process.	Edited accordingly ('*much*' deleted and the percentage corrected to 7%).
Page 41 – 'For example, using the approximate trial ratio of 2B:2C participants (0.64:0.36) …'	Please delete the sentence or provide additional clarity that the KEYNOTE-716 trial is currently ongoing and that the study was not powered to detect differences by subgroups.	This is a crude analysis that can potentially mislead the reader – please either delete or amend as per our request to avoid this issue. The KEYNOTE-716 trial is currently ongoing, and the study was not powered to detect differences by subgroups. Further, this crude analysis fails to account for any patients for which	Edited accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		staging information may not be available in the real-world setting.	
Page 42 – 'the ERG does not agree with the quality assessment in terms of the randomisation process. The allocation concealment process is very briefly reported and although it is stated that treatment allocation occurred centrally using an interactive response technology system, insufficient information is given to be certain that those recruiting participants were unaware of the allocation sequence'	Please amend this paragraph to reflect the information provided in the study publication.	This paragraph does not reflect all the available information on the randomisation element of the trial design. Further information on the randomisation and masking procedures employed in the KEYNOTE-716 trial are reported in the primary study publication (Luke et al, Lancet 2022; 399: 1718–29). This publication states: "*All patients were randomly assigned (1:1) centrally using an interactive response technology system…Only local pharmacists were aware of treatment assignments, whereas clinical investigators, patients, and those collecting or analysing the data were masked to treatment assignment during part 1 of the study*".	Not a factual inaccuracy. The ERG report was completed on 26 April 2022 and based on the available information. The cited publication was included in issue 10336 of The Lancet which was published on 30 April 2022. Whilst the publication was available online on 31 March 2022, the ERG was not aware of the paper at the time of completing the ERG report.
Page 43 – 'Full results from this analysis, which will include DMFS events by arm, are expected to be available in [redacted].9'	Please check citation at the end of this sentence	Please amend the incorrect formatting of this citation.	Edited accordingly
Page 43 – 'This response from the company is confusing. It seems at first to suggest that numbers of events by arm are not	Please remove this text as this does not accurately represent the response from the Company.	MSD disagrees that the clarification response was confusing, and the rationale has also been discussed with the EAG during the clarification TC. Reasons for why OS and DMFS data were not	Edited accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
available (even though total study events are provided) because the database is locked for blinding purposes, but then suggests that numbers of events by arm are not available because the numbers of events are too small. These appear to be two completely separate reasons. Further clarification is required.'		available from IA2 or IA3 were provided separately; the EAG appear to have interpreted these separate reasons to relate to the same data. As per the response to Questions A13 and A18 of the clarification questions, MSD have stated that DMFS and OS data were not available at IA2 due to the small numbers of DMFS and OS events that had occurred at that timepoint (i.e. insufficient total DM and death events had occurred to trigger the event-driven analyses of these endpoints). There has therefore been no assessment of DM and death events by treatment arm. The point raised on database lock having occurred recently related to the IA3 analysis only, data from which are not yet available and timelines for its availability will be shared with NICE in due course. The data from IA3 will include results of the interim DMFS analysis and provide DM events by treatment arm. This point was separate to the discussion of the small numbers of events meaning DMFS and OS data from IA2 are unavailable.	
Page 46 – 'Pre-specified subgroup analyses of RFS were conducted to determine the consistency of treatment	Please add the following to the list of bullet points: **'Geographic region (US or Non-US)'** Please also add that the study was not powered to detect	Please add this subgroup for completeness, and to align with the subgroups presented in Figure 3.2.	Edited accordingly (subgroup added to bullet point list)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
effect across the following variables'	differences at subgroup level although results remained consistent with the ITT population.		
Page 47 – 'The ERG's view on this is similar to that in relation to the company's response about OS data (outlined in Section 3.2.5.1 above). The company's response regarding DMFS data is confusing, seeming initially to suggest that numbers of events by arm are not available (even though total study events are provided) because the database is locked for blinding purposes, whilst also suggesting that arm-level events are unavailable because the numbers of events are too small. These appear to be two separate reasons and further clarification is required.'	Please remove this text as this does not accurately represent the response from the Company. We have provided sufficient explanation regarding this issue on several different occasions.	Please see the response directly above.	Edited accordingly.
Page 48 – 'The lack of any clear benefit for HRQoL, measured with EQ-5D-5L, in the pembrolizumab arm compared to the placebo arm	Page 48 – Please amend this sentence to reflect the correct interpretation of the HRQoL assessment.	This sentence does not correctly reflect the context in which HRQoL was assessed in the KEYNOTE-716 trial. Patients are disease-free at baseline with good HRQoL and therefore adjuvant	Wording amended on both pages to reflect the ERG's observation of no evidence of a between-group difference in HRQoL.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
is an important finding, but this is not highlighted nor discussed in the CS.' Page 58 – 'However, there is no evidence that HRQoL is improved'	Page 58 – Please remove this sentence as it does not reflect the correct interpretation of the HRQoL assessment.	treatment is not intended to provide a benefit in HRQoL. Instead, the analysis seeks to assess whether adjuvant treatment is associated with a decrement to HRQoL. The trial demonstrated similar results between the treatment groups, therefore the correct interpretation is that adjuvant treatment with pembrolizumab is not associated with a HRQoL decrement compared with routine surveillance.	
Page 58 – 'The comparability of the two dosing regimens in terms of efficacy and safety is uncertain because comparative data on clinical outcomes are not available.'	Please amend to: 'The comparability of the two dosing regimens in terms of efficacy and safety is uncertain because comparative data on clinical outcomes **in stage 2 melanoma** are not available.'	As above, the EMA review considered a wider evidence base than that reported by the EAG and therefore comparative data are available from other studies. MSD agree however that there are no data for this in stage 2 melanoma specifically, and therefore this wording should be updated to discuss the indication specifically. As noted above, from a decision problem perspective MSD chose to align the posology of pembrolizumab to that which is anticipated in the real-world setting. An option exploring the impact of Q3W has been presented in the cost-effectiveness analysis.	Edited accordingly.
Page 60 – Table 4.1 "Data sources for the cost-	Please add in the abbreviation with regards to **C** in Data ranges column to clarify to the reader. This is missing	Please amend for clarity.	Edited accordingly in Table 4.1. Similar changes made to Tables 3.1, 4.2 and 4.3.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
effectiveness systematic review".	from the list of abbreviations which accompany the table.		

Cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63, Table 4.5 – Measuring and valuing health effects, ERG states 'Partly consistent with reference case (utility based on standard gamble)'	Partly consistent with reference case (utility **for the post-progression DM state measured using EQ-5D but valued using** standard gamble)'. Trial-based EQ-5D data have been used to estimate utilities for all other health states. This methodology is consistent with technology appraisals.	The utilities for the RF, LRR and pre-progression DM states were derived using EQ-5D data from the KEYNOTE-716 trial and valued using the UK value set which used the time trade off method. As explained within the submission, it was not feasible to inform the post-progression DM utility from KEYNOTE-716. It is only the post- progression DM state that uses an EQ-5D utility valued using standard gamble. This is not clear from the current wording in the table.	Not a factual error
Page 65 – 'The company justified their approach by stating it made their model more in line with previous assessment in advanced	The company justified their approach by stating it made their model more in line with previous assessments in advanced melanoma (that typically used a three-state model) **and**	The CS states that the model structure was aligned with the recent appraisal of pembrolizumab for the	Not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
melanoma (that typically used a three state model) and also facilitated the use of relevant input data'	**adjuvant melanoma (TA766)** and also facilitated the use of relevant input data.	adjuvant treatment of stage 3 melanoma (TA766). Further clarification was provided in response to question B1 regarding alignment with previous appraisals in advanced melanoma. As both advanced and adjuvant indications informed the model structure, both should be referenced in the EAGs summary. Currently, this sentence only reflects the metastatic melanoma models which were developed using a partition survival model approach and therefore normally require 3 health state modelling.	
Page 69-70 and 76 – 'According to the company this suggests that, based on the 2-year follow-up reported by the SACT dataset, IO rechallenge for patients having a DM recurrence within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice. Therefore, it was assumed that a small percentage of patients who entered the DM state more than 2 years after	According to the company this suggests that, based on the 2-year follow-up reported by the SACT dataset, IO rechallenge for patients having a DM recurrence within 2 years of adjuvant treatment initiation is currently uncommon in clinical practice. **This was supported by UK clinical experts, who also advised that rechallenge would be an option for some patients after 2 years**. Therefore, it was assumed that **patients were ineligible for rechallenge in the first 2 years after adjuvant pembrolizumab initiation,**	As is, this sentence suggests that the model permitted rechallenge after 2 years *because* it was uncommon in the first 2 years in SACT. Instead, rechallenge after 2 years was permitted for a small proportion of patients because clinical experts advised that this is what is seen in clinical practice.	Not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
adjuvant treatment initiation would receive rechallenge with pembrolizumab monotherapy and the SACT market shares of other non-targeted regimens were proportionally adjusted.'	**and** a small percentage of patients who entered the DM state more than 2 years after adjuvant treatment initiation would receive rechallenge with pembrolizumab monotherapy. The SACT market shares of other non-targeted regimens were proportionally adjusted.		
Page 70 – 'No waning of treatment effectiveness was assumed for transitions from the RF health state i.e., transition probabilities from the LR health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon' Page 71 – 'Transition probabilities from the LR health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon, i.e., no treatment waning was assumed.'	Please amend as follows: Page 70 – 'No waning of treatment effectiveness was assumed for transitions from the RF health state i.e., transition probabilities from the **RF** health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon Page 71 – 'Transition probabilities from the **RF** health state were assumed to be different for pembrolizumab and routine surveillance for the whole duration of the time horizon, i.e., no treatment waning was assumed.'	The model assumes that the transition probabilities from the ***RF state*** are different for pembrolizumab and routine surveillance for the duration of the time horizon, not those from the LRR state.	Edited accordingly.
Page 70 – 'According to the company, for the LRR and DM health states, it was assumed that there was no ongoing benefit of adjuvant pembrolizumab after recurrence. However, transition probabilities from the LRR and	~~According to the company,~~ 'For the LRR and DM health states, it was assumed that there was no ongoing benefit of adjuvant pembrolizumab **for stage 2 melanoma after disease** recurrence **(i.e. after transition from the RF state)**. However, transition probabilities from the LRR and DM health states differed	This assumption is what was applied in the model, not MSD's opinion or assumption. Please specify that this sentence refers to adjuvant treatment in the stage 2 setting to ensure	Not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
DM health states differed between arms based on the respective market shares of subsequent treatments received in these health states (for the whole duration of the time horizon).'	between arms based on the respective market shares of subsequent treatments received in these health states (for the whole duration of the time horizon).'	readers do not confuse with adjuvant treatment after LRR. The market shares applied in the LRR and DM health states are independent of the efficacy of adjuvant pembrolizumab.	
Page 70-71 – 'Nevertheless, out of a total of 54 candidate combinations, the company prioritised five combinations (all based on parametric models separately fitted to each treatment arm, defined as approach #1 in the CS):…' 'Notably, not all prioritised combinations were explored in the scenario analyses reported in CS, Table 70.1 Therefore, the ERG explored the remaining prioritised combinations, i.e., Weibull-Generalised gamma and Gompertz-Generalised gamma in scenario analyses.'	'Nevertheless, out of a total of 54 candidate combinations, the company prioritised five **combinations based on statistical fit, visual fit and plausibility of RFS projections** (all using parametric models separately fitted to each treatment arm, defined as approach #1 in the CS) …' Notably, **the Weibull-Generalised gamma and Gompertz-Generalised gamma** prioritised combinations were **not** explored in the scenario analyses reported in CS, Table 70 **as they provided a very poor fit to the external DMFS data and therefore were not considered to produce clinically plausible estimates for this population**. Therefore, the ERG explored the remaining prioritised combinations, i.e., Weibull-Generalised gamma and Gompertz-Generalised gamma in scenario analyses. Please provide some rationale to justify exploring these scenarios. It would also be very helpful to present these extrapolations vs	The Weibull-Generalised gamma and Gompertz-Generalised gamma combinations were not explored in scenario analyses as they produced a very poor fit to the external DMFS data from USON (CS Figure 10) and were therefore not considered clinically plausible. Not mentioning this rationale implies that these combinations were intentionally excluded without justification which was not the case and may be misinterpreted by the readers. MSD request that the EAG provide some additional rationale to justify considering these combinations in scenario	Not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	the Company base case in a figure to give context to the impact of the scenarios.	analyses, and further information to help the reader to understand the context of these scenarios and whether these are clinically relevant.	
Page 72 – 'CS Table 34 reports the HRs of DMFS failure versus no adjuvant treatment used for transitions from the LRR health state. Although this is not explicitly mentioned by the company, the ERG believes that these HRs are also used for estimating the transition from LRR to death. This assumption was not appropriately justified and hence its plausibility is unclear to the ERG'	We have justified our selection and instead request the following change. "CS Table 34 reports the HRs of DMFS failure versus no adjuvant treatment used for transitions from the LRR health state. Although this is not explicitly mentioned by the company, the ERG believes that these HRs are also used for estimating the transition from LRR to death." ~~This assumption was not appropriately justified and hence its plausibility is unclear to the ERG~~'	The EAG's assumption is correct in that the same HRs were used for the transitions to death as for DM transitions. However, this approach is implicitly justified because the HRs from the trials are for DMFS which includes both DM events and death events. MSD were unable to identify separate HRs for DM and death.	Not a factual error
Page 72 – 'Therefore, the ERG adopted the a) scenario analysis, wherein transition probabilities for patients receiving a subsequent adjuvant treatment in the LRR state were estimated using Electronic Health Record (EHR) data.'	Please provide a description of what is meant by 'a) scenario analysis' or remove the 'a)' as appropriate.	MSD are unclear as to what is referred to by the 'a) scenario analysis' and suspect it may be a typographical error. MSD assume this refers to the settings applied in the EAG base case – please confirm.	Edited accordingly.
Page 73 – 'A summary of all utility values used in the CEA is provided in Table 4.4'	A summary of all utility values used in the CEA is provided in **Table 4.7'**	MSD suspect there may be a typographical error and	Edited accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		should refer to Table 4.7 instead of Table 4.4.	
Page 74 – 'The list price of pembrolizumab was £2,630.00 per 100 mg vial, therefore the list drug cost per administration was £10,520.00 for adults and £[redacted] for children (based on mean paediatric weight in KEYNOTE-716)'	The list price of pembrolizumab was £2,630.00 per 100 mg vial, therefore the list drug cost per administration was £10,520.00 for adults and £[redacted] for children (based on mean paediatric weight in KEYNOTE-716).	There was a typographical error in the CS for which MSD apologise. The incorrect value presented unredacted in the CS was the RDI-adjusted value. To protect the RDI value we ask that is value is treated as commercial in confidence. The list price for children, based on the mean paediatric weight in KEYNOTE-716 with no RDI, should be £[redacted]. However, we can confirm that this was correctly applied in the cost-effectiveness model. We ask that this value is treated as CIC to protect the RDI value which feeds into the cost calculations for Pembrolizumab in the overall population and the clinical data around the mean paediatric weight used to estimate the adjusted list price cost.	Not a factual error (this is in the ERG report as retrieved from the CS). Confidentiality marking was edited accordingly (see below).

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 – 'Consequently, all patients in the pembrolizumab arm who had a LRR recurrence were assumed to have no further systemic subsequent therapy.'	Consequently, all patients in the pembrolizumab arm who had a LRR recurrence were assumed to have no further systemic **adjuvant** subsequent therapy.	Patients in the pembrolizumab arm who have a LRR are specifically assumed not to have further *adjuvant* therapy, however further systemic therapy is permitted for patients who subsequently move from LRR to DM (i.e. systemic treatment for metastatic melanoma).	Not a factual error
Page 80 – 'In the current model, the expected survival ranged from [redacted] years, based on the first-line market shares applied in each arm; this is highly comparable to the 5.08 life years in the TA366 model.'	In the current model, the expected survival **in the DM state** ranged from [redacted] years, based on the first-line market shares applied in each arm; this is highly comparable to the 5.08 life years in the TA366 model.	For clarity, this sentence should specify that this is the survival in the DM state, not from the start of adjuvant treatment. It should also be noted that the committee extensively discussed DM setting survival and be consistent with prior TA366 projections. We ask that this is explicitly stated to avoid any confusion.	Edited accordingly.
Page 82 – The EAG lists three types of adjustments used to define the new base case: FE, FV, and MJ. However, only MJ adjustments are discussed.	Please clarify whether any FE and FV adjustments were implemented – if not, please state that no FE and FV issues were identified.	For transparency in interpreting the changed implemented in the model.	Not a factual error

Section 2: Marking of confidential information

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 35, data related to concomitant medications permitted in the KEYNOTE-716 trial (3.2.1)	Missing academic in confidence highlighting	Corticosteroids for systemic use ([redacted] patients in the pembrolizumab arm versus [redacted] patients in the placebo arm) Antidiarrheals/intestinal anti-inflammatory/anti-infective agents ([redacted] patients in the pembrolizumab versus [redacted] patients in the placebo arm) Corticosteroids for dermatological preparations ([redacted] patients in the pembrolizumab arm versus [redacted] patients in the placebo arm)".	Edited accordingly. Note: this query arose from errors in the CS and was not an error by the ERG.
Page 40, data related to the baseline characteristics of the KEYNOTE-716 trial (3.2.3)	Missing academic in confidence highlighting	The EAG noted that 89.5% of participants in the trial were white, and [redacted] were stage 2A, 64% were stage 2B, and 34.8% were stage 3B (with a remaining [redacted] stage 3C, [redacted] stage 4 and [redacted] missing).	Edited accordingly.
Page 41, data related to the subgroup patient population of the KEYNOTE-716 trial (3.2.3)	Missing academic in confidence highlighting	…pembrolizumab is more effective relative to placebo in stage 2B (HR [redacted]) than stage 2C patients (HR [redacted]),	Edited accordingly.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 42, data related to discontinuation in the KEYNOTE-716 trial (3.2.4)	Missing commercial in confidence highlighting	Although [redacted] of the pembrolizumab arm and [redacted] of the placebo arm had discontinued by the time of IA2, only [redacted] and [redacted] respectively were lost to follow-up…	Edited accordingly.
Page 47, data related to the clinical efficacy by stage 2B or 2C in the KEYNOTE-716 trial (3.2.5.2)	Missing academic in confidence highlighting	The EAG was able to locate these results, which showed HRs of [redacted] ([redacted]) and [redacted] ([redacted]) for stage 2B (Table 14.2-12) and stage 2C (Table 14.2-13) respectively.	Edited accordingly.
Page 47, data related to difference in LS means for HRQoL (3.2.5.4)	Missing academic in confidence highlighting	Analysis of the EQ-5D-5L visual analogue scale (VAS) score at Week 48 showed similar results between the treatment groups (difference in LS means [redacted], 95% CI [redacted] to [redacted], nominal p value = [redacted])	Edited accordingly.
Page 48, Figure 3.3	Missing academic in confidence highlighting	Please mark Figure 3.3 as academic in confidence	Edited accordingly.
Page 72-73, marking of utility data from KEYNOTE-716 trial	Utility estimates from KEYNOTE-716 were correctly marked as CIC by the EAG, reflecting the marking in the CS. However, MSD wish to mark utilities as AIC going forward to aid transparency in the appraisal process.	Utility and disutility values and SEs from KEYNOTE-716 can be marked AIC. MSD will provide updated documents with the amended marking of these data.	Section 4.2.8 edited accordingly.
Page 72, Table 4.7 utility value for DM state	The DM (post-progression) utility and SE from Beusterien et al, 2009 is marked as CIC.	The DM (post-progression) utility and SE from Beusterien et al, 2009 should	Edited accordingly.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
	MSD have confirmed that health state utilities in the table pertaining to KEYNOTE-716 can also be marked as AIC.	be unredacted as it is from published literature and is therefore not confidential information. **MSD will provide updated documents with the corrected marking of this data point.**	
Page 74, list price for paediatric patients	The list price of pembrolizumab for children is unmarked, however this should be CIC as the mean paediatric weight from KEYNOTE-716 is not published.	The list price of pembrolizumab was £2,630.00 per 100 mg vial, therefore the list drug cost per administration was £10,520.00 for adults and £[redacted] for children (based on mean paediatric weight in KEYNOTE-716). The calculation is also dependent on RDI which is considered as Commercial in Confidence at this stage as it feeds into the drug cost calculations for list and PAS prices. **MSD will provide updated documents with the corrected marking of this data point.**	Edited accordingly.
Page 75, reference to PAS for pembrolizumab	[redacted]	A PAS is in place for pembrolizumab, which makes pembrolizumab available to the NHS for a discount [redacted].	Not a factual error

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

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 **Friday 17th June 2022.**

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 [redacted], all information submitted under [redacted], and all information submitted under [redacted] 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	**Dionysios Ntais**
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: The results described in the CS are not generalisable to adolescent patients (aged 12 to 17 years) because only one patient in this age category was allocated to each treatment arm of the included RCT (2 patients in total).	**NO**	**MSD does not agree with the EAG's comment pertaining to the generalisability of KEYNOTE-716 to the adolescent population. This opinion is primarily driven by the limited recruitment observed in the pivotal RCT. Melanoma incidence across all cancer substages in adolescents remains low across the UK (and other geographies) which explains the low recruitment numbers in KEYNOTE-716 and other melanoma trials over time. This does not indicate that the study results are not generalisable in this patient population. The European Medicines Agency (EMA) has endorsed the positive risk-benefit profile of pembrolizumab for this indication which includes adolescent patients, therefore such opinions are unsubstantiated.** MSD has prepared a submission ensuring that the population is aligned with the population in the final scope issued by NICE, namely: "***People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection (at high risk of recurrence*)**.**" This indication is in line with the recommended change to the terms of the marketing authorisation for pembrolizumab, with a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) received on 19th May 2022 for the use of pembrolizumab for the "*adjuvant treatment of adults and adolescents aged 12 years and older with stage 2B or 2C melanoma and who have undergone complete resection*"; this update to the licence also extended the previous approval for adjuvant treatment of stage 3 melanoma and treatment of advanced (unresectable or metastatic) melanoma from adults only to also include adolescent patients [1]. MSD acknowledges that only two adolescent participants were enrolled in KEYNOTE-716. Recruitment of adolescents into the trial was challenging due to the rarity of melanoma in younger

		age groups, therefore this is not uncommon or unexpected. In England in 2019, across all disease stages, there were only 23 melanoma diagnoses among the 15–19 years age group, seven in the 10–14 age group and five in the 1–9 age group [2]. More recent data from across the EU5 region (Germany, Spain, France, Italy and the UK) reported similarly low population estimates with an incidence of just [redacted] patients aged under 20 with stage 2melanoma in 2021 from a total of just [redacted] patients across all stages [3]. The rarity of adolescent melanoma has meant that adjuvant treatment for patients in this age group has been understudied. Indeed, other trials aimed at studying adolescents have only recruited few patients due to the very low incidence. In the KEYNOTE-051 trial, for example, despite recruitment occurring at 30 hospitals worldwide, only approximately one advanced melanoma patient per year has been recruited since 2015 [4]. The licence extension recommended by the CHMP is supported by extrapolation of efficacy data from adult to adolescent patients from the KEYNOTE-006 (pembrolizumab Q2W/Q3W versus ipilimumab for ipilimumab-naïve patients with unresectable metastatic melanoma), KEYNOTE-054 (pembrolizumab versus placebo for patients who have received complete resection of high-risk stage 3 melanoma) and KEYNOTE-716 (pembrolizumab versus placebo for patients with surgically resected high-risk stage II melanoma) trials [5]. The CHMP accepted an extrapolation based on the following: (1) similarity of melanoma disease biology between adults and adolescents, and (2) similar pharmacology of drug effect and similar exposure-response for efficacy and safety. The KEYNOTE-051 trial (an ongoing phase 1/2 open-label trial of pembrolizumab in advanced paediatric cancer), provided supportive efficacy data in classical Hodgkin lymphoma (cHL) for paediatric patients and safety data in paediatric patients with different tumour types [6]. An indirect conclusion on exposure-response was drawn based on the demonstrated similarity in exposure-response relationship and pharmacokinetic profile between adult and paediatric patients in cHL, with the assumption that the flat exposure-response relationship seen in adults across multiple tumour types is preserved in paediatric patients across indications. Based on these justifications, the CHMP determined that an extrapolation of data from adult to adolescent melanoma was appropriate [5]. As a way to address potential uncertainty in the adolescent population, the ERG have suggested to “conduct further RCTs that focus on the recruitment of people aged from 12–17 years”.

		However, due to the rarity of melanoma in this age group, and the timeframe of the appraisal, this option is not a feasible or practical suggestion. Currently, there is a high unmet need in the adolescent melanoma population for adjuvant treatment options that lower the risk of recurrence. As novel therapies for adults with melanoma have been demonstrated to lead to clinically and statistically meaningful improvement in outcomes [7] [8], treatment options for adolescent patients with high-risk and advanced melanoma are still limited. Pembrolizumab would provide an effective systemic treatment option to adolescent patients with completely resected stage 2B and 2C melanoma; exclusion of adolescent patients from any recommendation could raise issues of equality resulting from the differential treatment options available between adults and adolescents. Due to the very small patient population, the budget impact of offering pembrolizumab to patients aged 12–17, with stage 2B or 2C cutaneous melanoma who have undergone complete resection, is minimal, particularly when considering the substantial unmet need that could be addressed for these patients by the introduction of pembrolizumab as a treatment option. Finally, the decision to align the population in the decision problem to that of the licensed indication for stage 2B and 2C melanoma may also potentially save additional administration burden to clinicians who would otherwise opt to secure access for adolescent patients via alternative routes such as individual funding requests assuming that a final positive recommendation was issued by NICE covering only the adult population [9].
Key issue 2: The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W. No clinical data are available to demonstrate the comparability of efficacy and safety outcomes between the two dosing regimens therefore the relative effects are	**NO**	**MSD disagrees with the EAG's comments pertaining to the alternative dosing schedule for pembrolizumab (once every three weeks [Q3W] or once every six weeks [Q6W]). Clinical evidence, alongside dose/exposure modelling and simulation of dose/exposure relationships for efficacy and safety, has demonstrated that there are no clinically significant differences in efficacy or safety among the different posology options. Based on this evidence the EMA has approved the use of pembrolizumab as Q6W. Within the adjuvant setting, both clinicians and patients prefer the less frequent administration option for convenience and for resource management. Although clinical assessment of this issue falls outside the remit of the EAG, we note that the choice of Q6W or Q3W has a very limited impact on the ICER but mimics the use of pembrolizumab in the NHS which we sought to replicate in our base-case.**

uncertain.		The recommended dose of pembrolizumab in adults across indications, in monotherapy and combination settings, as reported in the Summary of Product Characteristics (SmPC), is "*either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes*" [10]. This is based on the EMA II/0062 regulatory procedure through which the alternative dosing regimen of 400 mg Q6W was approved for all approved monotherapy indications. The modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab showed that there are no clinically significant differences in efficacy or safety among the doses of 200 mg Q3W, 2 mg/kg Q3W, and 400 mg Q6W as monotherapy. Therefore, dose comparability, in terms of the risk/benefit profile, has already been demonstrated and then evaluated by regulators and was considered applicable to all indications [11]. In addition, in the II/0102 procedure, the European Commission (EC) Decision was issued on the basis of interim results from KEYNOTE-555, an interventional, pharmacokinetic study in patients with unresectable advanced melanoma. Additional data/analysis from studies KEYNOTE-021, -189, -407 (non-small cell lung cancer), -048 (head and neck squamous cell carcinoma), and -426 (renal cell carcinoma) were provided. As such, there is a wide evidence base demonstrating the comparability of the Q3W and Q6W dosing schedules in terms of efficacy and safety [11]. While the dosing regimens are comparable in terms of efficacy and safety outcomes, clinical experts have indicated a preference for the Q6W regimen due to practical reasons associated with the less frequent dosing [12]. This has been demonstrated in an ongoing real-world study of the prescribing pattern of pembrolizumab across [redacted]. The Q6W frequency of administration is an important topic that clinical experts commented on in the recent CDF exit evaluation for KEYNOTE-054 (TA766) as well as during the development of this KEYNOTE-716 submission [14]. Therefore, from a decision problem perspective, MSD chose to align to the anticipated usage in the NHS (Q6W dosing) in the base case, however an option exploring the impact of Q3W was presented in the cost-effectiveness analysis. A number of scenarios considering varying ratios of the Q3W and Q6W doses were also presented in the company response to the clarification questions for which no notable impact on cost-effectiveness was observed. Given the breadth of available evidence and clinical expert opinion in support of the comparable

		safety and efficacy of the Q3W and Q6W regimens, MSD considers alignment to Q6W dosing to be fully justified, reflecting anticipated UK clinical practice.
Key issue 3: There is a larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in UK clinical practice. This may result in an overestimation of the therapeutic benefits of the product for the overall population with stage 2B or 2C melanoma in the UK.	**NO**	**MSD considers that the KEYNOTE-716 study is fully generalisable to the UK population based on expert opinion sought during the appraisal development process. Clinical experts have confirmed at an advisory board that the baseline characteristics of patients in the KEYNOTE-716 are representative of the population in England [12].** A comparison between the KEYNOTE-716 population and Public Health England (PHE) data indicates that that a slightly lower proportion of patients have stage 2B melanoma – and therefore a slightly higher proportion of patients have stage 2C melanoma – in clinical practice compared with KEYNOTE-716. However, the observed differences in staging between the KEYNOTE-716 and PHE datasets are relatively small (64.0% versus 57.0% for stage 2B, and 34.8% versus 43.0% for stage 2C), particularly considering that one source is a Phase 3 study and the other is real world data from patients diagnosed within the NHS [15]. Caution should be applied when interpreting a comparison between two different data sources as the level of reporting across these sources may differ (e.g. the percentage of patients unclassified in the real-world setting could affect such comparisons). In the clarification questions, the EAG requested sub-group analyses of recurrence-free survival (RFS), overall survival (OS) and distant metastasis-free survival (DMFS) split by patients with stage 2B and stage 2C disease. In response, MSD signposted the EAG to relevant subgroup analysis results in the second interim analysis (IA2) KEYNOTE-716 trial Clinical Study Report (CSR), with the caveat that this is a post-hoc exploratory analysis. Subgroup analyses in the KEYNOTE-716 trial were not statistically powered to detect differences in efficacy and therefore, any observed difference in efficacy of pembrolizumab in stage 2B compared with stage 2C patients could simply be due to chance. Also, considering that the difference in staging between the KEYNOTE-716 and PHE datasets is small, MSD do not consider the treatment effect measured in the trial in the overall population to represent an overly optimistic measures of effect. Overall, there are no data to conclude that there is any difference in the relative efficacy of pembrolizumab for treating stage 2B and 2C melanoma given the comparison from KEYNOTE-716 is not statistically powered. Since clinical experts consider the characteristics of the trial to be

		generalisable to UK clinical practice, there is no reason to believe that the results of the trial overestimate the potential therapeutic benefits of pembrolizumab in UK but rather reflect an accurate representation of the benefits that may be seen within the UK NHS. Therefore, MSD does not agree with the EAG's conclusions on this matter.
Key issue 4: No data were provided for OS or DMFS and this hinders a full evaluation of effectiveness and cost effectiveness of the product.	**YES**	**MSD were unable to provide the number of DMFS events and OS events reported at IA2 by treatment arm due to insufficient events occurring to enable the protocol-specified, event-driven analysis of these endpoints. However, we have been transparent throughout the HTA process and proactively notified the EAG around the likely availability of DMFS data on more than one occasion during the evidence evaluation stage. The submission has now been updated to incorporate the latest available clinical evidence which are presented below and in the appendix.** The third interim analysis (IA3) has now occurred (data cut-off: 4th January 2022) and updated RFS data, interim DMFS data and updated safety data, with 27.4 months of median follow-up (defined as time from randomisation to data cut-off), are presented in Appendix A. RFS results are consistent with those observed at IA1 (data cut-off: 4th December 2020) and final RFS results at IA2 (data cut-off: 21st June 2021). These additional data with longer follow-up confirm a continued benefit on RFS, with the Kaplan–Meier curve separated at approximately 6 months and this separation being maintained through to 37 months. At IA3, a statistically significant improvement in DMFS for pembrolizumab compared with placebo was observed. The KM curves for DMFS separated at approximately 3 months and remained separated through the period assessed, with DMFS rates remaining higher in the pembrolizumab group compared with the placebo group up to 37 months. Data remain immature with median DMFS not being reached in either treatment arm as of the data cut-off, however adjuvant pembrolizumab treatment was measured to decrease the risk of distant metastasis by 36% compared with placebo (HR 0.64; 95% CI: 0.47, 0.88; p=0.0029). These data further support that pembrolizumab provides a clinically meaningful benefit as adjuvant therapy for patients with high-risk Stage 2 melanoma. As per the protocol, the final analysis of DMFS is scheduled at the fourth interim analysis (IA4; after [redacted] observed DMFS events). The last-patient-last-visit (LPLV) for IA4 is currently projected between [redacted].

		As of IA3, [redacted] OS events were reported representing [redacted]% of the final number of events needed for analysis. The current projected timings listed below are assuming events continue to accrue as expected for the protocol specified analyses: • First interim analysis for OS (IA5; ~[redacted] events): [redacted] • Final analysis for OS (~[redacted] events): [redacted] As the OS (and DMFS) analyses are event driven, the projected timings reported above are subject to change. However, given these anticipated timelines, OS data will not be available to support this evaluation. Any non-protocol specified, premature look at OS by treatment arm would be immature, non-informative to decision making, and may affect the blinding and integrity of the trial. In the absence of OS data, clinical experts have emphasised the value of DMFS in indicating the likely OS benefit. In evaluating pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma (TA766), clinical experts explained that if a treatment makes a clinically meaningful difference to DMFS then it was likely that this would be reflected in OS; the Committee agreed that this was biologically plausible [14]. In a retrospective observational study utilising electronic health record (EHR) structured and chart review data from a US patient population, RFS and OS were found to be strongly positively correlated (Kendall's tau = [redacted]), supporting the use of RFS as a surrogate measure for OS in patients with completely resected stage 2B or 2C melanoma [16]. The surrogacy of RFS and DMFS for OS is also corroborated further by other studies in early-stage melanoma [17]. Moreover, regardless of benefit in OS, MSD believe that patients would value improvement in RFS, due to their reported fears of disease recurrence [18]. As discussed in previous Appraisal Committee deliberations during TA766, OS collection in the adjuvant setting is particularly challenging since adjuvant therapies aim to extend RFS, delay the onset of distant disease and therefore prolong OS. In the case of melanoma OS is also confounded by the availability of subsequent highly effective treatment options available for advanced/metastatic disease. The statistically significant and clinically meaningful improvement in RFS (primary endpoint) and DMFS (secondary endpoint), along with the demonstration of an extended RFS benefit with more than two years of follow-up, confirm that adjuvant pembrolizumab for high-risk stage 2B and 2C melanoma prevents or delays recurrence and

<table>
<tr><td></td><td></td><td>distant metastases. These are in turn associated with complex and costly disease management and limited survival profile despite the recent scientific advances in the treatment of metastatic melanoma. Therefore an effective adjuvant treatment for resected stage 2B/2C such as pembrolizumab is highly likely to translate to an improved OS for these patients.</td></tr>
<tr><td>Key issue 5: The use of separate regression models for the estimation of RF utility and AE disutility (regression model 1) and LRR and DM utilities (regression model 2) may have had an effect on the ICER of unclear magnitude and direction.</td><td>YES</td><td>The ERG considers that the use of separate regression models to estimate utility values from KEYNOTE-716 for the RF, LRR and DM states may have introduced bias in the estimated utility values by overestimating the utility for the DM health state. MSD considers that the alternative approach proposed by the ERG would introduce greater bias and would not be appropriate for the analysis. However, we have explored alternative regression approaches and provided a scenario analysis which demonstrates a minimal impact on the cost-effectievness results.

Firstly, MSD would like to offer some additional context relating to the methods employed in the economic analysis. The regression models were structured as follows:

<table>
<tr><th>Regression model</th><th>Intercept</th><th>Binary indicators</th></tr>
<tr><td>1: RF utility and AE disutility:
$Utility_{ij} = \beta_0 + \beta_1 AE_{ij} + e_i$</td><td>RF without AEs</td><td>RF with grade 3+ AE†
RF with grade <3 AE</td></tr>
<tr><td>2: LRR and DM utilities:
$Utility_{ij} = \beta_0 + \beta_1 Health\ Status_{ij} + e_i$</td><td>RF (± any grade AEs)</td><td>LRR (± any grade AEs)
DM (± any grade AEs)</td></tr>
</table>
†Used to calculate the disutility of grade 3+ AEs; e_i, error; i, individual; j, records.
Variables in bold represent health state utilities used in the model.

The RF utility included in the model represented patients who were toxicity free (i.e. had no AEs of any grade) while in the RF health state. In KEYNOTE-716, AEs and AEOSIs occurred during the 1-year adjuvant treatment period, and the duration of most AEs was short (i.e. a few weeks).

Any impact of these AEs on HRQoL could be expected to endure for the duration of the AE, after which HRQoL of a patient would return to that of the toxicity-free RF state. Accordingly, the impact of grade 3+ AEs was considered in the model by applying a disutility to the proportion of patients experiencing these high-grade AEs and adjusted to account for the mean duration of</td></tr>
</table>

each AE as observed in the KEYNOTE-716 trial (see CS B.3.3.5, Table 41). This enabled the HRQoL impact of these AEs to be appropriately captured in terms of incidence, magnitude, and duration whilst a patient was in the RF health state.

Whilst this approach excludes any Grade <3 AEs from the economic analysis, the impact of this is a small marginal overestimation of short-term RF utility which is expected to be negligible as 'low-grade' AEs inherently have a smaller impact on HRQoL than grade 3+ AEs (which by definition require some type of hospitalised care [outpatient or inpatient short stay]).

Inclusion of only grade ≥3 AEs is common modelling practice as it considers AEs that are expected to have a material impact on resource use and HRQoL whilst also striking a pragmatic balance between data availability and assumptions necessary to inform model utilities. For this reason Grade <3 AEs are rarely included, as the impact on resource use and HRQoL is typically small and therefore the impact on the ICER negligible. The model does account for Grade 2+ diarrhoea (disutility derived from Grade 3+ AEs) because of its importance in the clinical management of the patient and the need for some type of hospitalised care (outpatient visit or short hospital stay). The same is not the case for majority of the alternative AEs of Grade <3.

The ERG has requested that an alternative, single regression analysis be conducted to generate a utility value for the RF health state that includes grade <3 AEs. MSD understand that the structure of this regression would be as follows:

Regression model	Intercept	Binary indicators
ERG's requested approach: Single regression which includes grade <3 AEs in the RF health state	RF without grade 3+ AEs	RF with grade 3+ AEs LRR without grade 3+ AEs DM without grade 3+ AEs

However, MSD do not consider it appropriate to include the effect of grade <3 AEs in the RF health state utility, for the following reasons:

- Adjuvant treatment with pembrolizumab is continued for up to 1 year. As observed in KEYNOTE-716, AEs occur during the treatment period and the mean duration of AEs is

		typically a few weeks. Consequently, the HRQoL impact of AEs, whether grade <3 or grade 3+, would occur in the first year after adjuvant treatment initiation and endure for a relatively short time only (see CS B.3.3.5, Table 41 for AE durations applied in original submission, and the data appendix accompanying this response for the AE durations based on the IA3 analysis). In the economic model, the same RF utility value is applied over the entire time horizon, therefore it would be inappropriate to use a utility value for the RF health state that included grade <3 AEs as this would result in underestimation of the RF utility in the long term. This would have a greater bias against pembrolizumab than exclusion of grade <3 AEs (as per the base case analysis) does for pembrolizumab. • In addition, please refer to the rationale provided above with regards to the relevance of grade <3 AEs in economic modelling. On the same basis, MSD do not agree with the ERG's use of the intercept from regression model 2 to inform the utility for the RF health state in their base case analysis. This value includes the effect of 'any grade AEs' (i.e. both grade <3 and grade 3+) and applies them to the duration of the model time horizon, resulting in a long-term underestimation of the RF utility and biasing against pembrolizumab. Further, this also results in double counting of the HRQoL impact of grade 3+ AEs when the AE disutility is applied. However, the ERG's scenario does illustrate that the RF utility (which biases against pembrolizumab by underestimating long-term utility) has a very small impact on the ICER (i.e. it increased the original base case ICER from £4,616 to £4,790 per QALY). Secondly, MSD would like to address the ERG's concern relating to the use of two separate regression models. Separate regression models were conducted to enable the inclusion, in regression model 2, of adverse events (AEs) that occurred while patients were in the LRR and DM health states whilst minimising additional assumptions. This approach was used to improve the accuracy of the utilities for the LRR and DM health states as AEs would be expected in a proportion of patients who have recurrent melanoma, and the cost-effectiveness model did not separately consider AE-related disutility of subsequent treatments. To address any residual concern of the ERG relating to the use of two separate regression models, MSD have conducted an alternative utility analysis which uses a single regression model

to estimate utilities for all health states. However, this analysis is not preferred for the base case as the method requires additional assumptions relating to the interaction of AE status and health state. Full details of the analysis are provided in the data appendix accompanying this response. Results of this scenario analysis are presented in Table 1.

Regression model	Intercept	Binary indicators
AE status and health state independent covariates	**RF without AEs**	**Grade 3+ AEs† in any health state** Grade <3 AEs in any health state **LRR ± any grade AE** **DM ± any grade AE**

Variables in bold represent health state utilities used in the model.
† Used to calculate the disutility of grade 3+ AEs.

Table 1: Scenario analysis – Alternative regression models for estimating KEYNOTE-716 utilities

Scenario	Description	Results
Base case	Includes the DMFS data introduced into the model?-	ICER: £13,864
A	Approach 1: Single regression model for utilities. AE status and health state assumed to be independent covariates. LRR and DM utilities include impact of any grade AEs.	Δ costs: [redacted] Δ QALYs: [redacted] ICER: £14,020

MSD also wish to provide further rationale regarding the utility value used to model the post-progression DM health state. The post-progression DM substate is intended to reflect the entire period from progression to death and thus the HRQoL implications of this whole period should be considered. It is therefore to be expected that the utility will be substantially lower than the pre-progression DM substate. As discussed in response to clarification question B12, MSD do not consider the progressed disease utility from KEYNOTE-006 preferred by the ERG to be appropriate for the base case. Utility values in KEYNOTE-006 were collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit (i.e. immediately after progression), but no further. As a result, the utility may not capture the decrease in HRQoL associated with the toxicity of subsequent therapies and further progression, and is therefore

		likely to be overestimated. For this reason, the progressive disease utility from Beusterien et al, 2009 is preferred, as has been accepted for use in previous melanoma appraisals (TA384 and TA766).[14, 19] Based on the rationale provided above, MSD consider that the methods presented in the original submission are the most appropriate to accurately address the decision problem and minimise bias in both directions. As such, no changes to the utility methods have been applied to MSD's base case. In addition, the scenarios explored by MSD and the ERG illustrate that the impact of any uncertainty in utility values on the cost-effectiveness of pembrolizumab is minimal.
Key issue 6: The assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs may not be plausible. The ICER may increase or decrease depending on the specific assumptions made.	**YES**	The ERG raise three points related to this issue – MSD responds below to each of the above points in turn: **1. <u>"The company made assumptions regarding the proportions of patients in the pembrolizumab arm receiving subsequent treatments in the LRR and DM health states that were not in line with evidence from KEYNOTE-716 subsequent treatment data"</u>** As part of the process for determining the most appropriate market share distributions for both treatment arms in the LRR and DM health states, MSD reviewed the available data from KEYNOTE-716, several sources of market research data, and engaged in extensive discussions with UK clinical experts via a structured process. The market shares selected for the base case analysis reflected information collected across these sources, with their generalisability to UK clinical practice considered of paramount importance. ***Generalisability of subsequent treatment data from KEYNOTE-716*** Firstly, it is critical to note that KEYNOTE-716 is a global clinical trial that enrolled patients from many different markets including the USA and South America, as well as the UK and other European countries. Treatment practices can vary widely between markets, particularly between the US and Europe. To this point, several of the agents recorded as subsequent therapies after LRR and DM in the KEYNOTE-716 trial are not currently approved for use in the UK as treatments for melanoma. This indicates that the patterns of subsequent treatment observed in

		the trial may not reflect what is seen in ***UK*** clinical practice. **Secondly, the incorrect subsequent treatment data from KEYNOTE-716 were presented in Appendix P of the CS, as they did not include patients who entered part 2 of the trial or treatments indexed as adjuvant in the trial database. MSD apologise for this error. As a result, the data in Appendix P of the CS do not represent the complete subsequent treatment data from the trial.** Consequently, utilisation of subsequent treatments was underestimated and did not reflect the complete observed treatment practices. The corrected tables reporting first subsequent treatment use after LRR or after DM in KEYNOTE-716 are presented in the data appendix accompanying this response (see Appendix B, Table 38 and Table 39). ***LRR state: Plausibility of further adjuvant therapy in the pembrolizumab arm*** The ERG has proposed for its base case analysis that the market shares of subsequent therapies in the LRR state should be the same in both treatment arms. MSD disagree with this approach as it is contradictory to the advice offered by UK clinical experts who stated that they consider patients to have 'one shot' at adjuvant therapy due to the absence of data to demonstrate efficacy and uncertainty regarding funding of a second adjuvant course.[12, 20] Further, the corrected subsequent treatment data from IA3 (see accompany Appendix B) also demonstrate a marked difference in treatment approach for LRR after adjuvant pembrolizumab versus placebo. In KEYNOTE-716, [redacted]/56 ([redacted]%) of patients in the placebo arm had a subsequent therapy after LRR compared with [redacted]/46 ([redacted]%) in the pembrolizumab arm. Of these, [redacted] of treatments in the pembrolizumab arm were experimental or not approved for use in the stage 3 setting in the UK versus [redacted] in the placebo arm. **This demonstrates that most patients in the placebo arm received systemic treatment after LRR, while most patients in the pembrolizumab arm received no systemic treatment after LRR.** These observed treatment patterns support the base case assumption (and expert clinical opinion) that, in the UK, patients would not receive further systemic therapy after LRR whereas it would be common after routine surveillance. **Therefore, the assumption that patients in the pembrolizumab arm receive no further adjuvant therapy remains MSD's preferred base case.**

		DM state: Plausibility of market shares in the pembrolizumab arm As per the LRR state, the subsequent treatment assumptions for the DM state were selected based on review of available data and extensive discussions with UK clinical experts. Clinicians consistently advised that rechallenge with IO monotherapy would not be used within 18 months of adjuvant therapy initiation but may be an option for patients with later recurrences.[12, 20] Therefore for the base case analysis MSD conservatively assumed that rechallenge would occur for a small proportion of patients (5% at 1L) who had a DM ≥2 years after adjuvant treatment initiation. The two-year timepoint for rechallenge is consistent with the preferred assumption in a recent melanoma appraisal in the adjuvant setting (TA684),[21] and the treatment patterns are broadly aligned with those observed after DM in KEYNOTE-716 as shown in the corrected subsequent treatment tables accompanying this response. However, MSD do not consider it appropriate to use market shares directly from KEYNOTE-716 in the model, as they are from a global trial with a Part 2 in which pembrolizumab crossover or re-challenge was investigated. As such, treatment patterns may not reflect UK practice and the use of pembrolizumab may be over-represented. Whilst the KEYNOTE-716 subsequent treatment data are indicative, they remain immature as the trial is still ongoing and therefore they are not suitable for use in the economic modelling directly, without clinical expect elicitation for adjustment to the UK context. The ERG present a scenario in which the DM market shares for the pembrolizumab arm are assumed to be equal to the routine surveillance arm. MSD consider that this is not fully justified based on UK clinical expert opinion as the market shares for the routine surveillance arm include a large proportion of IO monotherapy use ***regardless of time of recurrence***. However, given the data now available from KEYNOTE-716 which show that [redacted]% of patients in the pembrolizumab arm received pembrolizumab monotherapy after DM, MSD highlight that the proportion of IO monotherapy use in the base case analysis (5% at 1L) may be underestimated – although this remains uncertain in the absence of real-world data with sufficient follow-up. Consequently, an additional scenario was explored in which the market shares for patients in the pembrolizumab arm who recurred ≥2 years after adjuvant treatment inititiation were assumed to be equal to the routine surveillance arm (Table 2).

Table 2: Scenario analysis – market shares and rechallenge assumptions in the DM health state

Scenario	Description	Results
Base case	-	ICER: £13,864
B	In the pembrolizumab arm, market shares for the DM state for patients who entered the DM state ≥2 years after adjuvant pembrolizumab initiation were assumed to be equal to those in the routine surveillance arm (1L and 2L)	Δ costs: [redacted] Δ QALYs: [redacted] ICER: £3,262

This scenario demonstrates that increased use of IO monotherapy rechallenge ≥2 years after adjuvant treatment initiation further increases the cost-effectiveness of adjuvant pembrolizumab. The base case assumption regarding rechallenge in the DM health state should therefore be considered conservative.

2. <u>"It is unclear whether assumptions regarding subsequent treatment duration in the DM state are clinically plausible."</u>

In the DM state, the duration of first line therapies is based on modelled progression-free survival (PFS) for each regimen, as described in CS B.3.3.3. As acknowledged by the ERG, and as per the British Association of Dermatology[22] and NICE recommendations, treatments for metastatic melanoma should be continued for "as long as they keep the cancer under control". As acknowledged by the ERG, and as per the British Association of Dermatology[22] and NICE recommendations, treatments for metastatic melanoma should be continued for "as long as they keep the cancer under control".[22] PFS is widely used as a proxy for how long the cancer is 'under control' (i.e. progression indicates that the cancer is no longer controlled) as time on treatment (ToT) is inherently correlated with PFS. Therefore, the use of PFS to model the duration of therapy (i.e. ToT) is a simple way to reflect this relationship and as such is a common modelling approach. The same approach was implemented in the recent appraisal of adjuvant pembrolizumab for stage 3 melanoma (TA766).[14]

Data from a German real-world study of pembrolizumab for advanced melanoma (Mohr et al,

2021) showed that ToT and PFS were very closely aligned at 1 year (29% and 30%, respectively)[23], supporting the use of PFS as a proxy for ToT. After 1 year there were fewer patients remaining on treatment, and the ToT curve followed an exponential trajectory. As PFS in the economic model is estimated using an exponential rate, the modelled PFS is likely to be a good approximation of ToT.

The duration of second line therapies used a simplified assumption based on data from previous NICE appraisals (TA319 and TA366 – fixed duration of 7 cycles over 21 weeks for BSC; TA357 – a mean of 6.86 cycles over 20.57 weeks based on the mean PFS in the pembrolizumab arm of KEYNOTE-002).[24-26] The concordance between these three appraisals indicates that the duration of second line therapy is likely to be representative of clinical practice. On this basis, the same approach for modelling second line therapies was used in TA766.[14]

The ERG has presented an extreme scenario in which the costs of subsequent therapies in the DM state are excluded. **MSD strongly object to this scenario, as it excludes one of the major cost benefits to the NHS of adjuvant therapy in terms of offsetting the costs of recurrent disease, therefore does not capture all the relevant costs and benefits of the intervention, and thus is not a fair assessment of cost-effectiveness.** It also does not address the issue raised by the ERG regarding clinical plausibility of treatment durations. MSD's position is that all scenarios should have potential to be clinically plausible, and therefore consider that this extreme scenario is not informative.

As an alternative approach to explore the impact of treatment duration assumptions, MSD have conducted a scenario analysis in which the exponential rate of PFS is increased by 10% (to [redacted], in line with the variation explored in the DSA) resulting in a shorter PFS and thus shorter ToT. As illustrated in Table 3, the impact on the ICER is small.

Table 3: Scenario analysis – treatment duration in the DM health state

Scenario	Description	Results
Base case	-	ICER: £13,864

		C	The exponential rate of PFS increased by 10% to [redacted], reducing the ToT for first line subsequent therapies in the DM state	Δ costs: [redacted] Δ QALYs: [redacted] ICER: £14,547

3. <u>"Terminal care costs were only applied to patients who transitioned to the death state from the DM state"</u>

The base case model considers the implications of melanoma-related deaths as these are the cause-specific deaths which can plausibly be affected by adjuvant therapy. As the model uses a lifetime time horizon, all patients in both arms will have died by the end of the model and therefore the total number of deaths captured in the model is the same in both treatment arms. Applying the terminal care costs to all-cause deaths would result in equal undiscounted terminal care costs between arms such that the impact of including terminal care costs only captures the differential timing of deaths between arms (i.e. more deaths occur earlier in the routine surveillance arm and are therefore more costly due to less discounting). Given the small incremental difference in life years between treatment arms, the impact of this differential timing on overall terminal care costs will be minimal.

In addition, there is evidence that cancer-related deaths are more costly than deaths due to other causes. Research by Georghiou and Bardsley (2014) reports that per patient healthcare costs in the last three months of life are higher for people with a cancer diagnosis compared with people without a cancer diagnosis, driven largely by an increased number of hospital admissions.[27] Recent studies of healthcare costs in England and Scotland found that cancer deaths were preceded by the most hospital admissions and day care use of any cause of death.[28, 29] This indicates that cancer-related deaths are the most relevant to consider in the model from a cost-impact perspective.

Consequently, the most accurate approach to incorporate all-cause terminal care costs in the model would be to apply differential costs for melanoma-related and non-melanoma-related deaths. However, given the impact of terminal care cost assumptions on the cost-effectiveness results is minimal, the value of this update to the model would be insignificant, and therefore MSD

		consider it most appropriate to apply terminal care costs to melanoma deaths only.

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).

Table 3 Additional issues from the ERG report

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:	N/A	N/A	N/A
Additional issue 2:	N/A	N/A	N/A

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.

Table 4 Changes to the company's cost-effectiveness estimate

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
Key issue 4: No data reported for overall survival or distant metastasis-free survival **(Report sections 1.4, 3.2.5.1 and 3.2.5.3)**	The model was based on clinical data from interim analysis 2 (IA2) of KEYNOTE-716, and transitions from the LRR health state were based on data from a real-world study.	The model has been updated to include clinical data from interim analysis 3 (IA3) of KEYNOTE-716. This includes updated RFS data, interim DMFS data, and updated safety, utility and resource use inputs from the trial. Transitions from the LRR health state are now informed by data from KEYNOTE-716.	Updated ICER: [redacted] Original base case ICER: £4,616
[redacted]	[redacted]	[redacted]	Updated ICER: [redacted] Original base case ICER: £4,616
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Revised base case ICER: £13,864

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence

[ID3908]

Technical engagement response

Appendix: Additional evidence

June 2022

File name	Version	Contains confidential information	Date
ID3908 Pembrolizumab-in-Stage2-melanoma_TE-response_Appendix [redacted].docx	1.0	No - redacted	17 June 2022

Contents

1 Background

The company evidence submission, made on 14th February 2022, was based on data from the second interim analysis (IA2) of the KEYNOTE-716 trial (data cut-off: 21st June 2021). Since the original submission, data from the third interim analysis (IA3; data cut-off: 4th January 2022) have been analysed and are subsequently presented within this appendix.

An update to Sections B.2.4.2, B.2.6 and B.2.10 of Document B of the company submission is provided in Section 2 of this appendix, with relevant updates to the economic model presented in Section 3.

2 Clinical effectiveness: KEYNOTE-716 IA3

The results presented in this appendix are based on IA3, with 158 DMFS and 234 RFS events reported as of the data cut-off. The median duration of follow-up (defined as time from randomisation to data cut-off) for all participants (ITT population) was 27.4 months (range: 14.0 to 39.4 months), with a similar median duration of follow-up across treatment groups [1].

2.1 *Patient disposition*

At the time of IA3, [redacted] patients ([redacted]%) were ongoing in the pembrolizumab-test arm ([redacted] patients [[redacted]%] had discontinued the study) and [redacted] patients ([redacted]%) were ongoing in the placebo arm ([redacted] patients [[redacted]%] had discontinued the study). During Part 1, 163 patients (33.7%) in the pembrolizumab arm and 118 patients (24.3%) in the placebo arm had discontinued treatment. Adverse event (AE) occurrence was the most common cause of patients in the pembrolizumab arm (n=85 [17.6%]) discontinuing a study drug, whereas recurrence was the most common cause in the placebo arm (n=23 [4.7%]). As of the IA3 data-cut, [redacted] patient ([redacted]%) in the pembrolizumab arm and [redacted] patients ([redacted]%) in the placebo arm had discontinued treatment during Part 2. Reasons for patients discontinuing the trial and the study treatment are reported in Table 1.

Table 1: Disposition of patients in the ITT population at the time of IA3

	Pembrolizumab (N=487)	Placebo (N=489)
Trial disposition		
Discontinued	[redacted]	[redacted]
Death	[redacted]	[redacted]
Associated with COVID-19	[redacted]	[redacted]

	Pembrolizumab (N=487)	Placebo (N=489)
Lost to follow-up	[redacted]	[redacted]
Not associated with COVID-19, no further information	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Associated with COVID-19, no further information	[redacted]	[redacted]
Not associated with COVID-19, no further information	[redacted]	[redacted]
Not associated with COVID-19, subsequently died	[redacted]	[redacted]
Participants ongoing	[redacted]	[redacted]
Participant study medication disposition in Part 1		
Started	483	486
Completed	320 (66.3)	368 (75.7)
Discontinued	163 (33.7)	118 (24.3)
AE	85 (17.6)	23 (4.7)
Associated with Covid-19	1 (0.2)	1 (0.2)
Lost to follow-up	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]
Physician decision	10 (2.1)	4 (0.8)
Associated with COVID-19	0 (0.0)	2 (0.4)
Protocol violation	[redacted]	[redacted]
Relapse/recurrence	24 (5.0)	61 (12.6)
Withdrawal by subject	40 (8.3)	27 (5.6)
Associated with COVID-19	6 (1.2)	7 (1.4)

Abbreviations: AE: adverse event; ITT: intention to treat.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long *et al.* (2022)[1].

2.2 *Primary efficacy endpoint: recurrence-free survival (RFS)*

At IA3, adjuvant pembrolizumab treatment resulted in a statistically significant improvement in RFS compared with placebo (hazard ratio [HR]: 0.64; 95% confidence interval [CI]: 0.50, 0.84). KEYNOTE-716 achieved the success criterion for the primary RFS endpoint and hypothesis based on IA1 results (IA1 HR:0.65; 95% CI: 0.46, 0.92; p=0.00658). Therefore, the descriptive IA2 and IA3 results for RFS support the primary analysis at IA1 with additional follow-up demonstrating the sustained RFS benefit.

Of note, the median RFS reached in the pembrolizumab arm (37.2 months, 95% CI: not reached [NR], NR) is anomalous as it was only reached because the last participant at risk in the pembrolizumab arm experienced an event, which also led to the drop at the tail of the Kaplan–Meier (KM) curve and therefore cannot be considered stable. Therefore, the tail of the KM curve should be interpreted with caution a number of participants continue to be

followed and whilst the numbers at risk reduce beyond month 33. Main time-to-event analysis of RFS is presented for the ITT population in Table 2.

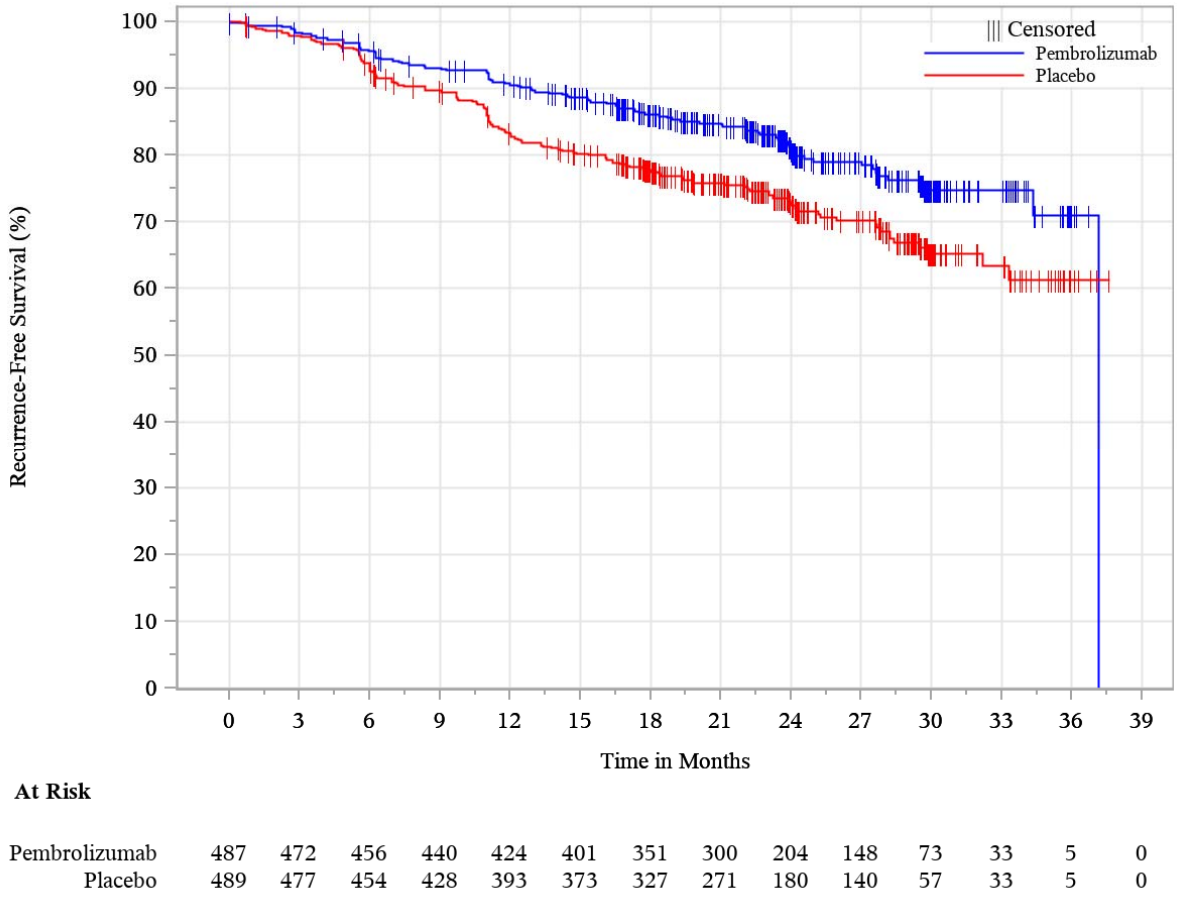
Table 2: Analysis of RFS (primary censoring rule) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/100 Person-months	Median RFS† (months) (95% CI)	RFS Rate at 24 months† (%) (95% CI)
Pembrolizumab	487	95 (19.5)	[redacted]	[redacted]	37.2 (NR, NR)	81.2 [redacted]
Placebo	489	139 (28.4)	[redacted]	[redacted]	NR (NR, NR)	72.8 [redacted]
Pairwise Comparisons					**HR‡, (95% CI)**	
Pembrolizumab vs. Placebo					0.64 (0.50, 0.84)	

†From product-limit (Kaplan–Meier) method for censored data.
‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
Abbreviations: CI: confidence interval; ITT: intention to treat; HR: hazard ratio; NR: not reached; RFS: recurrence-free survival.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

The KM curves for RFS separated at approximately 6 months (Figure 1). The result is consistent with the RFS results observed at IA1 and final RFS results at IA2. These additional data with longer follow-up further confirm a continued benefit in RFS, with RFS rates being consistently higher in the pembrolizumab group compared with the placebo group through to 37 months (Figure 1; Table 3).

Figure 1: Kaplan–Meier estimates of RFS (primary censoring rule) (ITT population)



Abbreviations: ITT: intention to treat; RFS: recurrence-free survival.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

Table 3: RFS rate over time

RFS rate at time point	Pembrolizumab (N=487), % (95% CI)†	Placebo (N=489), % (95% CI)†
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	81.2 [redacted]	72.8 [redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

†From product-limit (Kaplan–Meier) method for censored data.
Abbreviations: CI: confidence interval; RFS: recurrence-free survival.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

Overall, fewer participants in the pembrolizumab group experienced disease recurrence during Part 1 of the study compared with the placebo group (Table 4). The most frequent type of recurrence was distant metastases, and the percentage of participants with this type of recurrence in the pembrolizumab group (45 [9.24%] patients) was almost half compared with the placebo group (77 [15.75%] patients). The percentage of patients with

local/regional/loco-regional recurrence was similar in the pembrolizumab and placebo groups (46 [9.45%] vs 56 [11.46%], respectively). Overall, 10 deaths contributed to the RFS events: 4 deaths in the pembrolizumab group ([redacted]), and 6 deaths in the placebo group ([redacted]) (Table 4).

Table 4: Type of first RFS event (ITT population)

Type of first event in RFS analysis	Pembrolizumab (N=487), n (%)	Placebo (N=489), n (%)
All events	95 (20)	139 (28)
Local†, regional‡ and loco-regional§	46 (9)	56 (11)
Distant¶,††	45 (9)	77 (16)
Death	4 (1)	6 (1)

†Local: Tumour recurrence is in the immediate vicinity of primary tumour (i.e. skin, in transit lesions, micro-satellite metastases);
‡Regional: Regional Lymph node basin involvement;
§Loco-regional: Tumour recurrence is in the immediate vicinity of primary tumour and regional lymph node basin metastasis is noted. Tumour has not spread beyond regional lymph nodes;
¶Distant: Metastasis is beyond the regional lymph node basin;
††Includes distant event diagnosed within 30 days from Local/Regional/Locoregional event.
Abbreviations: ITT: intention to treat; RFS: recurrence-free survival.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

2.3 *Secondary efficacy endpoints*

2.3.1 Distant metastasis-free survival (DMFS)

Adjuvant pembrolizumab after complete resection has been shown to significantly improve DMFS in patients with resected stage 3 melanoma. In KEYNOTE-716, DMFS is defined as the time from randomisation to the first diagnosis of a distant metastasis. As detailed in the protocol, IA3 was to be performed when approximately [redacted] DMFS events have been observed, which is the first interim analysis for DMFS. As of the 4th January 2022 data cut-off, 158 DMFS events had occurred ([redacted]% information fraction).

At IA3, adjuvant pembrolizumab treatment demonstrated an improvement in DMFS compared with placebo, with fewer patients experiencing DMFS events when treated with pembrolizumab compared with placebo (63 patients [12.9%] versus 95 patients [19.4%]; HR: 0.64; 95% CI: 0.47, 0.88; p=0.00292). Median DMFS was not yet reached in either treatment group.

Main time-to-event analysis of DMFS is presented for the ITT population in Table 5.

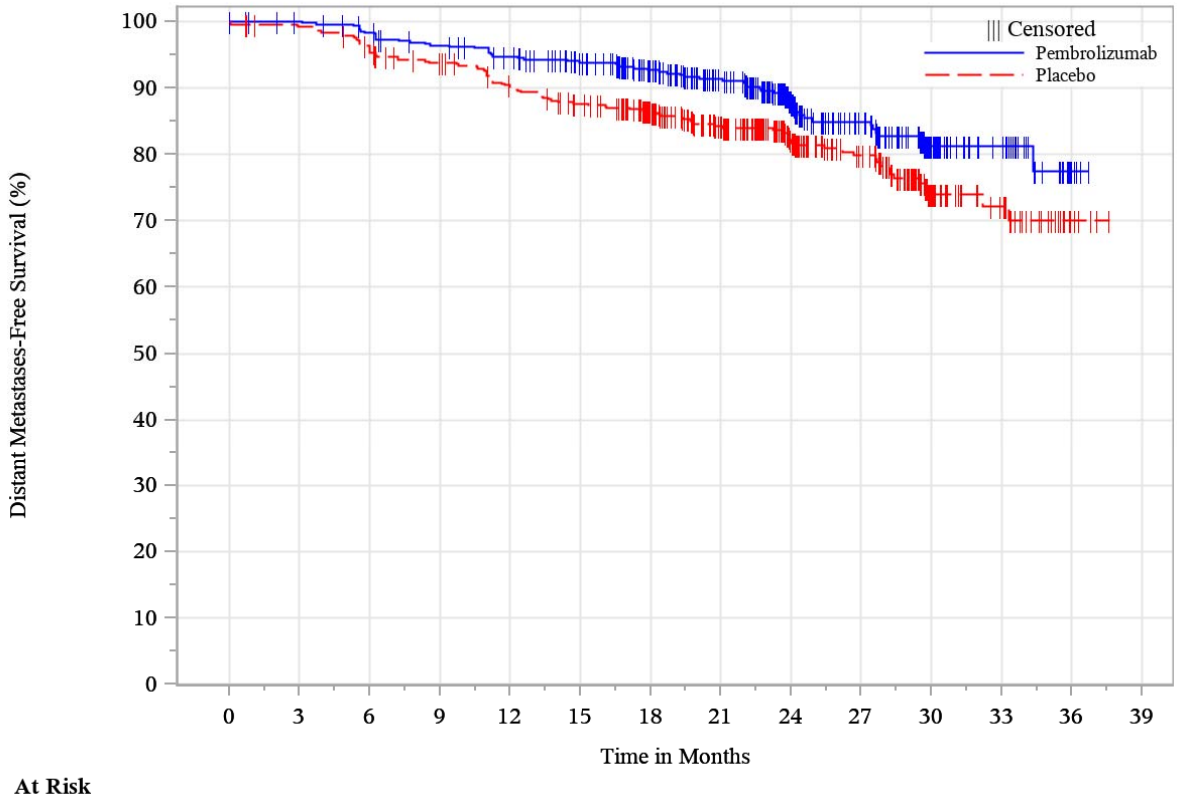
Table 5: Analysis of DMFS (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/100 Person-months	Median DMFS† (months) (95% CI)	DMFS Rate at 24 months† (%) (95% CI)
Pembrolizumab	487	63 (12.9)	[redacted]	[redacted]	NR (NR, NR)	88.1 [redacted]
Placebo	489	95 (19.4)	[redacted]	[redacted]	NR (NR, NR)	82.2 [redacted]
Pairwise Comparisons					**HR‡, (95% CI)**	**p value§,¶**
Pembrolizumab vs. Placebo					0.64 (0.47, 0.88)	0.00292

†From product-limit (Kaplan–Meier) method for censored data.
‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
§One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival; ITT: intention to treat; HR: hazard ratio; NR: not reached.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

The KM curves for DMFS separated at approximately 3 months and remained separated through the period assessed, with DMFS rates remaining higher in the pembrolizumab group compared with the placebo group up to 37 months (Figure 2; Table 6).

Figure 2: Kaplan–Meier estimates of DMFS (ITT population)



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

Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

Table 6: DMFS rate over time

RFS rate at time point	Pembrolizumab (N=487), % (95% CI)†	Placebo (N=489), % (95% CI)†
6 months	[redacted]	[redacted]
12 months	94.7 [redacted]	90.2 [redacted]
18 months	[redacted]	[redacted]
24 months	88.1 [redacted]	82.2 [redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

†From product-limit (Kaplan–Meier) method for censored data.
Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

2.3.2 Overall survival (OS)

As of the IA3 data cut-off, insufficient events had occurred to enable analysis of OS to be conducted; [redacted] OS events were reported representing [redacted]% of the final number of events needed for analysis. This secondary endpoint will be analysed at a separate future IA once the prespecified protocol criteria of target event numbers has been reached.

2.3.3 Patient-reported outcomes (PROs)

EQ-5D-5L

At Week 72, the completion rates for the EQ-5D-5L were [redacted] and [redacted], in the pembrolizumab and placebo groups, respectively, and the compliance rates were [redacted] and [redacted], respectively.

Analysis of the EQ-5D-5L visual analogue scale (VAS) score at Week 72 continued to show [redacted] (Table 7; Figure 3)[3].

Table 7: Analysis of change from baseline in EQ-5D-5L VAS to Week 72 (FAS population)

Treatment	Baseline		Week 72		CFB to Week 72		
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†,‡	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pairwise Comparison					**Difference in LS Means†,‡ (95% CI)**		**Nominal p value†,‡**
Pembrolizumab vs. Placebo					[redacted]		[redacted]

For baseline and Week 72, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

†Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction, stratification factor melanoma T stage (2B T3b greater than 2.0–4.0 mm with ulceration vs. 2B T4aCS greater than 4.0 mm without ulceration vs. 2C T4b greater than 4.0 mm with ulceration) as covariate.
‡ Statistical testing for PROs is nominal and is not adjusted for multiple testing.
Abbreviations: CFB: change from baseline; EQ-5D-5L: EuroQoL-5 Dimension Questionnaire; QoL: quality of life; PRO: patient-reported outcomes; LS: least squares; VAS: visual analogue scale.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

Figure 3: Empirical mean change from baseline and 95% CI for the EQ-5D VAS over time by treatment group (FAS population)

Abbreviations: CI: confidence interval; EQ-5D-5L: EuroQoL-5 Dimension Questionnaire; FAS: Full analysis set; VAS: visual analogue scale.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30)

At Week 72, completion rates were [redacted] and [redacted], in the pembrolizumab and placebo groups respectively, and compliance rates were [redacted] and [redacted], in the pembrolizumab and placebo groups, respectively.

Adjuvant pembrolizumab treatment resulted in a difference in LS means of [redacted] in global health status quality of life at Week 72 compared with placebo (Table 8; Figure 4).The mean changes from baseline in the global health status/QoL scores over time [redacted] (Figure 4) [4].

Table 8: Analysis of change from baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 72 (FAS population)

Treatment	Baseline		Week 48		CFB to Week 72	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means† (95% CI)**	**p value†**
Pembrolizumab vs. Placebo					[redacted]	[redacted]

†Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction, stratification factor melanoma T stage (2B T3b greater than 2.0-4.0 mm with ulceration vs. 2B T4a greater than 4.0 mm without ulceration vs. 2C T4b greater than 4.0 mm with ulceration) as covariate.
For baseline and Week 72, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Abbreviations: cLDA: constrained longitudinal data analysis; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer QoL Questionnaire; CFB: change from baseline; FAS: full analysis set; QoL: quality of life; LS: least square; N: number of patients; PRO: patient-reported outcomes; SD: standard deviation.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

Figure 4: Empirical mean CFB and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL over time by treatment group (FAS population)

Abbreviations: CI: confidence interval; CFB: change from baseline; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer QoL Questionnaire; FAS: full analysis set.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

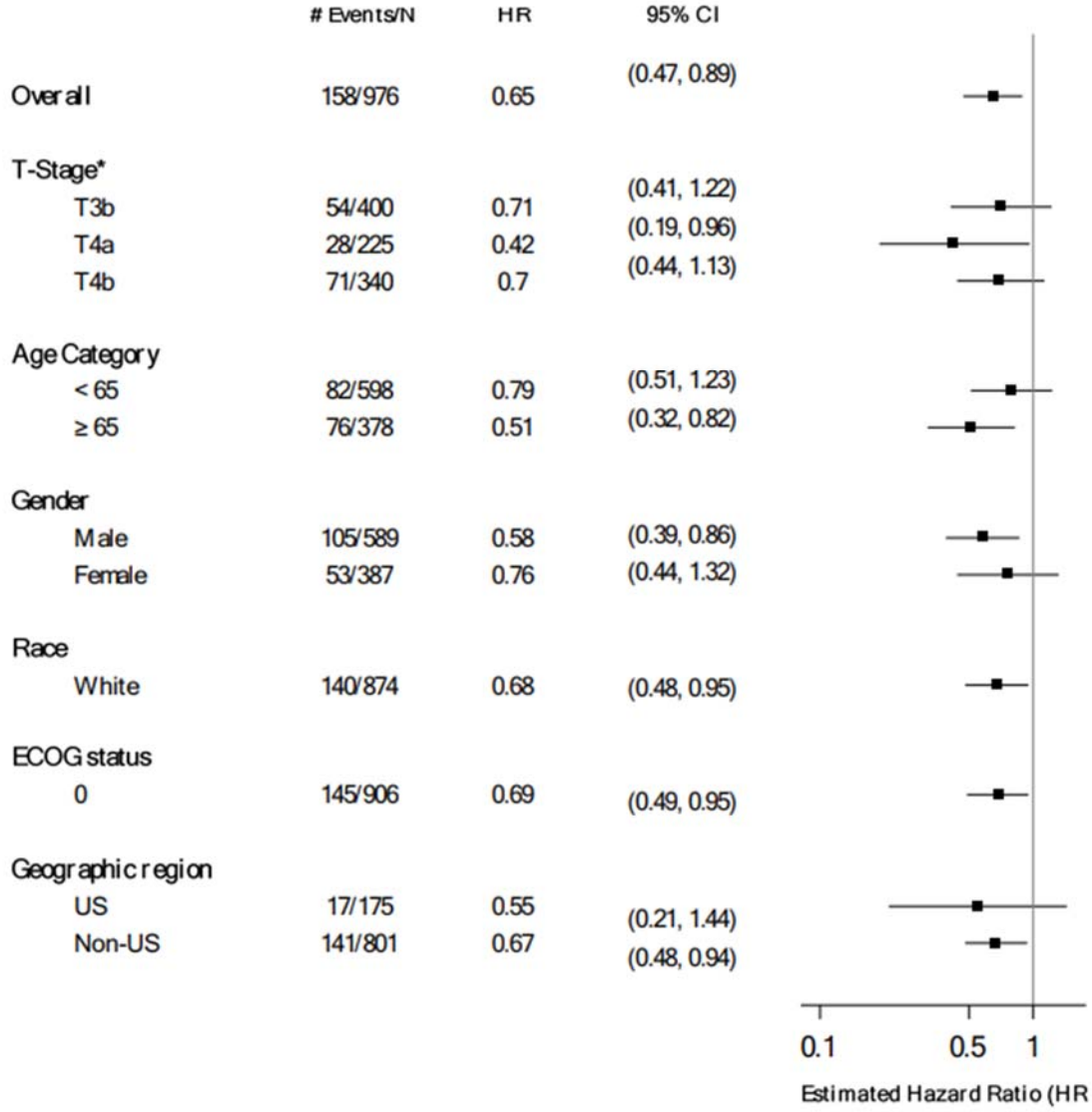
2.4 *Subgroup analysis*

Figure 5 shows the results of the subgroup analysis for RFS. RFS results in prespecified demographic and clinical subgroups at IA3 were generally consistent with the primary analysis at IA1 and with the supportive analyses at IA2. Figure 6 shows the equivalent results of the subgroup analysis for DMFS, which were generally consistent with the primary analysis for the ITT population. As at IA2, certain subgroup factors (e.g. US participants, patients with T-stage T4a) had a smaller number of participants and events, resulting in a wide 95% CI for the HR.

Figure 5: Forest plot of RFS HR by subgroup factors (ITT population)

A subgroup with number of participants < 10% ITT population is not displayed on the plot.
*Based on actual baseline tumor stage collected on eCRF
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: intention to treat; HR: hazard ratio; RFS: recurrence-free survival.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

Figure 6: Forest plot of DMFS HR by subgroup factors (ITT population)



A subgroup with number of participants < 10% ITT population is not displayed on the plot.
*Based on actual baseline tumor stage collected on eCRF
Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival; ECOG: Eastern Cooperative Oncology Group; ITT: intention to treat; HR: hazard ratio.
Source: Long et al. (2022)[1].

2.5 *Adverse reactions*

The overall frequency and type of AEs reported in KEYNOTE-716 were generally consistent with the established safety profile of pembrolizumab monotherapy.

2.5.1 Patient exposure

Table 9 gives a summary of drug exposure; Table 10 shows proportion of patients with exposure by duration.

Table 9: Summary of drug exposure (APaT population)

	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
Number of days on therapy			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of administrations			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Number of days on therapy is calculated as last dose date − first dose date +1.
Abbreviation: ApaT: all participants as treated; SD, standard deviation.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

Table 10: Exposure by duration (APaT population)

Duration of exposure	Patients, n (%)		
	Pembrolizumab, N=483	Placebo, N=486	Total, N=969
>0 month	[redacted]	[redacted]	[redacted]
≥1 months	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]
≥9 months	[redacted]	[redacted]	[redacted]
≥10 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]

Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Abbreviation: ApaT: all participants as treated.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

2.5.2 Summary of AEs

Table **11** presents a summary of AEs in the KEYNOTE-716 trial.

Table 11: Overview of AEs (APaT population)

	Patients, n (%)†	
	Pembrolizumab, N=483	Placebo, N=486
Any AE	462 (95.7)	445 (91.6)
Any AE related to study drug‡	400 (82.8)	309 (63.6)
Any AE with toxicity grade 3–5	[redacted]	[redacted]
Any AE related to study drug‡ with toxicity grade 3–5	83 (17.2)	24 (4.9)

	Patients, n (%)†	
	Pembrolizumab, N=483	Placebo, N=486
Any SAE	[redacted]	[redacted]
Any SAE related to study drug‡	[redacted]	[redacted]
Death	[redacted]	[redacted]
Death related to study drug‡	0	0
Any AE leading to discontinuation	[redacted]	[redacted]
Any AE related to study drug‡ leading to discontinuation	77 (15.9)	12 (2.5)
Any SAE leading to discontinuation	[redacted]	[redacted]
Any SAE related to study drug‡ leading to discontinuation	[redacted]	[redacted]

Includes non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
‡Related events as determined by the Investigator.
Abbreviation: AE: adverse event; ApaT: all participants as treated; SAE: serious adverse event.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

2.5.3 Adverse events

Table 12 presents AEs with an incidence ≥5% in one or more treatment arms. Most AEs were Grade 1 or 2; there were no grade 3–5 AEs with incidence ≥5% in one or more treatment arms.

Table 12: Participants with AEs (any grade) by decreasing incidence (incidence ≥5% in one or more treatment groups) (ApaT population)

AE, n (%)	Pembrolizumab, N=483	Placebo, N=486
Participants with one or more adverse event	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

AE, n (%)	Pembrolizumab, N=483	Placebo, N=486
Back pain	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column. Includes non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment.
Abbreviations: AE: adverse event; ApaT: all participants as treated.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

2.5.4 Drug-related AEs

Table 13 shows specific drug-related AEs (any grade) with incidence ≥5% in one or both treatment arms. Most drug-related AEs were Grade 1 or Grade 2 in severity in both the pembrolizumab group ([redacted]% and [redacted]%, respectively) and placebo group ([redacted]% and [redacted]%, respectively).

Table 13: Drug-related AEs (any grade) with incidence ≥5% in one or both treatment arms (ApaT population)

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Participants with one or more adverse event	400 (82.8)	309 (63.6)
Pruritus	119 (24.6)	52 (10.7)
Fatigue	103 (21.3)	92 (18.9)
Diarrhoea	90 (18.6)	56 (11.5)
Arthralgia	81 (16.8)	39 (8.0)
Rash	78 (16.1)	34 (7.0)
Hypothyroidism	77 (15.9)	13 (2.7)
Hyperthyroidism	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Alanine aminotransferase increased	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column. Includes non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment.
Abbreviations: AE: adverse event; ApaT: all participants as treated.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2]; Long et al. (2022)[1].

2.5.5 Serious adverse events (SAEs)

Table 14 shows SAEs with incidence ≥1% in one or both treatment arms. The only drug-related SAEs with incidence ≥1% in one or both treatment arms were adrenal insufficiency ([redacted] events [[redacted]%] in pembrolizumab arm; [redacted]% in placebo arm).

Table 14: SAEs with incidence ≥1% in one or both treatment arms (ApaT population)

Adverse Event	Pembrolizumab, n (%)	Placebo, n (%)
Participants with one or more adverse event	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Squamous cell carcinoma of skin	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Malignant melanoma in situ	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column. Includes serious adverse events up to 90 days of last treatment.
Abbreviations: ApaT: all participants as treated; SAE: serious adverse event.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

2.5.6 AEs of special interest

Predefined AEs of special interest (AEOSI), corresponding to immune-mediated events and infusion-related reactions associated with pembrolizumab, were analysed. Overall, the type and severity of AEOSIs remained consistent with the established pembrolizumab monotherapy safety profile. Most AEOSIs were Grade 1 or 2 and were generally manageable with corticosteroids and/or hormone replacement therapy, and/or with treatment interruption/discontinuation. Table 15 summarises the rates of AEOSIs (in which ≥1 event occurred in either group.

Table 15: AEOSIs (any grade; APaT population)

Patients, N (%)	Pembrolizumab, N=483	Placebo, N=486
Participants with one or more adverse event	[redacted]	[redacted]
Adrenal Insufficiency	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Infusion Reactions	[redacted]	[redacted]
Myasthenic Syndrome	[redacted]	[redacted]
Myelitis	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Sarcoidosis	[redacted]	[redacted]
Severe Skin Reactions	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]
Type 1 Diabetes Mellitus	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column. Includes non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment.
Abbreviation: AE: adverse event; ApaT: all participants as treated; SAE: serious adverse event.
Source: MSD Data on File: KEYNOTE-716 CSR (Data cut-off: 04 Jan 2022)[2].

3 Cost-effectiveness: Updates based on KEYNOTE-716 IA3

3.1 *Transition probabilities*

Transitions from the RF health state

Clinical data for RFS and DMFS collected from KEYNOTE-716 IA3 (data cut-off 4th January 2022) were used to update the model transition probabilities from the RF health state, using the parametric multistate modelling approach employed in the original IA2 model. As described in CS B.3.3.1, three parametric modelling approaches were explored, resulting in 54 unique combinations of parametric functions used to model the RF→LRR and RF→DM transitions. The exponential function was again used to model the RF→DM transition due to the small number of events that had occurred. Updated parameter estimates associated with all parametric models for Approaches #1–3 are provided in Appendix A. As described in CS B.3.3.1, it was assumed that the recurrence risk relative to the parametric function begins to

linearly decrease from 7 years until a 95% risk reduction is reached at 10 years. This approach reflects published evidence, and expert clinical opinion, that the risk of recurrence decreases over time and is very low after 10 years.

Selection of the updated base case combination of parametric functions for RF→LRR and RF→DM was conducted as outlined in CS B.3.3.1, considering statistical fit, visual fit, and clinical plausibility.

Statistical fit

Table 16 and Table 17 present the rankings of all 54 combinations of parametric functions from smallest to largest mean squared error (MSE) vs observed RFS in each treatment arm, for the routine surveillance and pembrolizumab arms, respectively. The MSE of the predicted DMFS curves vs the observed DMFS in KEYNOTE-716 was also assessed for each combination and is presented in the tables; long-term predictions of RFS, DMFS, and OS are also reported for each these different scenarios.

In general, the ranking of statistical fit was similar whether based on MSE relative to observed RFS or MSE relative to observed DMFS (i.e., combinations of distributions that demonstrated good statistical fit with RFS generally also showed good fit with DMFS). MSEs were generally higher for routine surveillance than for pembrolizumab, therefore the selection of base-case parametric functions prioritised statistical and visual fit, and clinical plausibility, in the routine surveillance arm. Combinations of distributions were therefore excluded if they ranked among the ten worst-fitting combinations in terms of both RFS and DMFS in the routine surveillance arm, regardless of their ranking in the pembrolizumab arm. This criterion led to the exclusion of 8 combinations in total (Weibull-Weibull, Weibull-Gompertz, Exponential-Weibull, and Exponential-Gompertz under Approaches #1 and #2; included in table below with red for MSE).

The proportional hazards assumption could not be rejected for either RF→LRR ([redacted]) or RF→DM ([redacted]) based on statistical tests. Thus, no exclusions were made based on proportional hazards testing, and combinations of distributions under Approaches #2 and #3 were retained for further consideration as base-case or scenario analyses.

Long-term predictions for both treatment arms were then checked for clinical plausibility against external sources.

Table 16: Comparison of different parametric functions to model RFS in the routine surveillance arm: Fit vs observed data and long-term extrapolations

MSE rank		Parametric functions		MSE vs. observed		Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
RFS	DMFS	RF → LRR	RF → DM	RFS	DMFS	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
Approach #1: Parametric models separately fitted to each treatment arm																							
1	4	Log-normal	Gen. gamma	0.000087	0.000105																		
2	5	Gen. gamma	Gen. gamma	0.000089	0.000106																		
3	3	Log-logistic	Gen. gamma	0.000090	0.000103																		
4	2	Weibull	Gen. gamma	0.000091	0.000103																		
5	6	Gompertz	Gen. gamma	0.000092	0.000106																		
6	1	Exponential	Gen. gamma	0.000107	0.000101																		
7	14	Gen. gamma	Log-normal	0.000119	0.000122																		
8	13	Gompertz	Log-normal	0.000123	0.000121																		
9	**15**	**Log-normal**	**Log-normal**	**0.000126**	**0.000122**																		
10	31	Gen. gamma	Log-logistic	0.000152	0.000137																		
11	17	Log-logistic	Log-normal	0.000153	0.000122																		
12	28	Gompertz	Log-logistic	0.000157	0.000136																		
13	16	Weibull	Log-normal	0.000161	0.000122																		
14	32	Log-normal	Log-logistic	0.000162	0.000138																		
15	38	Gen. gamma	Weibull	0.000166	0.000146																		
16	36	Gompertz	Weibull	0.000171	0.000145																		
17	8	Gen. gamma	Gompertz	0.000176	0.000112																		
20	19	Exponential	Exponential	0.000177	0.000130																		
21	39	Log-normal	Weibull	0.000177	0.000148																		
22	9	Log-normal	Gompertz	0.000181	0.000113																		
23	7	Gompertz	Gompertz	0.000186	0.000112																		
24	34	Log-logistic	Log-logistic	0.000196	0.000139																		
26	18	Exponential	Log-normal	0.000200	0.000126																		
28	10	Log-logistic	Gompertz	0.000206	0.000115																		
29	35	Weibull	Log-logistic	0.000206	0.000139																		
30	24	Log-logistic	Exponential	0.000209	0.000134																		
32	22	Weibull	Exponential	0.000210	0.000134																		

MSE rank		Parametric functions		MSE vs. observed		Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
RFS	DMFS	RF → LRR	RF → DM	RFS	DMFS	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
35	40	Log-logistic	Weibull	0.000215	0.000150	[redacted]																	
36	11	Weibull	Gompertz	0.000215	0.000115	[redacted]																	
38	26	Log-normal	Exponential	0.000217	0.000135	[redacted]																	
39	27	Gen. gamma	Exponential	0.000227	0.000135	[redacted]																	
40	41	Weibull	Weibull	0.000227	0.000150	[redacted]																	
41	12	Exponential	Gompertz	0.000231	0.000120	[redacted]																	
43	30	Gompertz	Exponential	0.000241	0.000137	[redacted]																	
44	37	Exponential	Log-logistic	0.000249	0.000145	[redacted]																	
48	44	Exponential	Weibull	0.000272	0.000157	[redacted]																	
Approach #2: Parametric proportional hazards models with a time-constant treatment effect																							
19	20	Exponential	Exponential	0.000177	0.000130	[redacted]																	
27	49	Gompertz	Weibull	0.000203	0.000189	[redacted]																	
34	25	Weibull	Exponential	0.000215	0.000134	[redacted]																	
37	43	Gompertz	Gompertz	0.000216	0.000157	[redacted]																	
42	29	Gompertz	Exponential	0.000237	0.000136	[redacted]																	
46	50	Weibull	Weibull	0.000268	0.000194	[redacted]																	
47	45	Weibull	Gompertz	0.000270	0.000162	[redacted]																	
51	47	Exponential	Gompertz	0.000312	0.000171	[redacted]																	
53	52	Exponential	Weibull	0.000333	0.000205	[redacted]																	
Approach #3: Parametric proportional hazards models with a time-varying treatment effect																							
18	21	Exponential	Exponential	0.000177	0.000131	[redacted]																	
25	51	Gompertz	Weibull	0.000199	0.000202	[redacted]																	
31	42	Gompertz	Gompertz	0.000210	0.000156	[redacted]																	
33	23	Weibull	Exponential	0.000211	0.000134	[redacted]																	
45	33	Gompertz	Exponential	0.000257	0.000138	[redacted]																	
49	46	Weibull	Gompertz	0.000274	0.000165	[redacted]																	
50	53	Weibull	Weibull	0.000288	0.000211	[redacted]																	
52	48	Exponential	Gompertz	0.000315	0.000174	[redacted]																	
54	54	Exponential	Weibull	0.000354	0.000222	[redacted]																	

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LRR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.
Red cells indicate that the survival estimate for routine surveillance is higher than the corresponding estimate for pembrolizumab (i.e. the curves cross). Orange cells indicate the 4-year RFS and/or DMFS estimates fall below the 4-year RFS and/or DMFS observed in KEYNOTE-054 (stage 3 melanoma). Red text indicates the combination ranked in the 10 worst-fitting combinations in terms of MSE for RFS and DMFS in the routine surveillance arm. Green cells indicate the combination considered in the base case analysis.
Long-term predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Table 17: Comparison of different parametric functions to model RFS in the pembrolizumab arm: Fit vs observed data and long-term extrapolations

MSE rank		Parametric functions		MSE vs. observed		Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
RFS	DMFS	RF → LRR	RF → DM	RFS	DMFS	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
Approach #1: Parametric models separately fitted to each treatment arm																							
1	10	Weibull	Gen. gamma	0.000043	0.000096																		
2	12	Gen. gamma	Gen. gamma	0.000043	0.000097																		
3	4	Gen. gamma	Gompertz	0.000043	0.000085																		
4	2	Weibull	Gompertz	0.000043	0.000084																		
5	11	Log-logistic	Gen. gamma	0.000043	0.000096																		
6	3	Log-logistic	Gompertz	0.000043	0.000085																		
8	13	Weibull	Weibull	0.000043	0.000099																		
9	15	Gen. gamma	Weibull	0.000044	0.000101																		
11	14	Log-logistic	Weibull	0.000044	0.000100																		
12	17	Weibull	Log-logistic	0.000044	0.000103																		
13	1	Exponential	Gompertz	0.000045	0.000077																		
14	20	Gen. gamma	Log-logistic	0.000045	0.000105																		
15	19	Log-logistic	Log-logistic	0.000045	0.000104																		
16	6	Gompertz	Gompertz	0.000048	0.000089																		
17	18	Log-normal	Gen. gamma	0.000048	0.000103																		
18	16	Gompertz	Gen. gamma	0.000049	0.000102																		
19	5	Exponential	Gen. gamma	0.000049	0.000088																		
20	8	Exponential	Weibull	0.000050	0.000091																		
21	9	Exponential	Log-logistic	0.000050	0.000094																		
22	7	Log-normal	Gompertz	0.000050	0.000091																		

MSE rank		Parametric functions		MSE vs. observed		Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
RFS	DMFS	RF → LRR	RF → DM	RFS	DMFS	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
23	22	Log-normal	Weibull	0.000050	0.000108	[redacted]																	
24	21	Gompertz	Weibull	0.000051	0.000106	[redacted]																	
25	25	Log-normal	Log-logistic	0.000052	0.000112	[redacted]																	
26	23	Gompertz	Log-logistic	0.000053	0.000110	[redacted]																	
28	27	Exponential	Log-normal	0.000054	0.000118	[redacted]																	
29	31	Weibull	Log-normal	0.000056	0.000131	[redacted]																	
32	32	Log-logistic	Log-normal	0.000058	0.000132	[redacted]																	
33	35	Gen. gamma	Log-normal	0.000059	0.000133	[redacted]																	
37	**42**	**Log-normal**	**Log-normal**	**0.000072**	**0.000142**	[redacted]																	
38	39	Gompertz	Log-normal	0.000073	0.000140	[redacted]																	
47	47	Exponential	Exponential	0.000131	0.000281	[redacted]																	
49	49	Weibull	Exponential	0.000200	0.000309	[redacted]																	
50	50	Log-logistic	Exponential	0.000207	0.000311	[redacted]																	
51	51	Gen. gamma	Exponential	0.000212	0.000312	[redacted]																	
52	52	Gompertz	Exponential	0.000255	0.000324	[redacted]																	
54	54	Log-normal	Exponential	0.000267	0.000330	[redacted]																	
Approach #2: Parametric proportional hazards models with a time-constant treatment effect																							
7	26	Exponential	Gompertz	0.000043	0.000116	[redacted]																	
10	24	Exponential	Weibull	0.000044	0.000111	[redacted]																	
27	28	Weibull	Weibull	0.000053	0.000123	[redacted]																	
34	30	Weibull	Gompertz	0.000063	0.000129	[redacted]																	
40	36	Gompertz	Weibull	0.000077	0.000134	[redacted]																	
43	41	Gompertz	Gompertz	0.000092	0.000141	[redacted]																	
46	46	Exponential	Exponential	0.000131	0.000281	[redacted]																	
48	48	Weibull	Exponential	0.000192	0.000306	[redacted]																	
53	53	Gompertz	Exponential	0.000261	0.000326	[redacted]																	
Approach #3: Parametric proportional hazards models with a time-varying treatment effect																							
30	34	Exponential	Weibull	0.000057	0.000132	[redacted]																	
31	29	Exponential	Gompertz	0.000058	0.000128	[redacted]																	
35	38	Weibull	Weibull	0.000064	0.000137	[redacted]																	

MSE rank		Parametric functions		MSE vs. observed		Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
RFS	DMFS	RF → LRR	RF → DM	RFS	DMFS	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
36	33	Weibull	Gompertz	0.000067	0.000132	[redacted]																	
39	40	Gompertz	Weibull	0.000077	0.000140	[redacted]																	
41	37	Gompertz	Gompertz	0.000078	0.000135	[redacted]																	
42	43	Exponential	Exponential	0.000088	0.000181	[redacted]																	
44	44	Weibull	Exponential	0.000100	0.000187	[redacted]																	
45	45	Gompertz	Exponential	0.000117	0.000190	[redacted]																	

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

Red cells indicate that the survival estimate for routine surveillance is higher than the corresponding estimate for pembrolizumab (i.e. the curves cross). Orange cells indicate the 4-year RFS and/or DMFS estimates fall below the 4-year RFS and/or DMFS observed in KEYNOTE-054 (stage 3 melanoma). Red text indicates the combination ranked in the 10 worst-fitting combinations in terms of MSE for RFS and DMFS in the routine surveillance arm. Green cells indicate the combination considered in the base case analysis.

Long-term predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years

Visual assessment of fit

The observed cumulative incidence of transitions from RF→LRR, RF→DM, and RF→Death in the routine surveillance and pembrolizumab arms, respectively, alongside the predicted cumulative incidence from different combinations of parametric functions, are presented in Appendix A (Figure 17 to Figure 19). Figures are also presented showing the comparison of the composite RFS and DMFS predictions with each combination of parametric functions versus the observed RFS and DMFS from KEYNOTE-716 (Appendix A, Figure 20 to Figure 21).

The interpretation of each figure is provided in Table 18. In both treatment arms, most combinations of parametric functions across all three approaches produced a close visual fit to the observed cumulative incidence of RF→LRR, RF→DM, RF→Death, and RFS and DMFS from KEYNOTE-716, and therefore no exclusions were applied based on visual inspection alone.

Table 18: Summary of findings from visual inspection of fit between predicted vs. observed RF→LRR, RF→DM, RF→Death, RFS, and DMFS

Figure	Interpretation
Figure 17: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence (RF→LRR)	All combinations of parametric functions produced a close visual fit to the observed cumulative incidence of RF→LRR.
Figure 18: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases (RF→DM)	In both arms, combinations using log-normal for the cause-specific hazards of RF→DM demonstrated good visual fit to the cumulative incidence of RF→DM. In the pembrolizumab arm, combinations using exponential for RF→DM yielded worse visual fit under Approaches #1 and #2, but good visual fit under Approach #3, In the observation arm, combinations using exponential for RF→DM under all approaches demonstrated the best visual fit during the second year of follow-up. Combinations using exponential for RF→DM were thus retained for further consideration.
Figure 19: Predicted vs. observed cumulative incidence of transitions from recurrence-free to death (RF→Death)	During the trial period, fit was indistinguishable between different combinations of parametric functions due to the very small number of observed RF→Death events in KEYNOTE-716. (*Note:* The predicted curves for RF→Death in the pembrolizumab arm were higher than the observed curve because background mortality immediately exceeded the parametrically estimated rates of RF→Death in this arm.) The large divergence seen in the long-term is due to the interplay between competing risks and background mortality: Under combinations of distributions that yield low risks of LRR and DM, more patients are estimated to die directly from RF (rather than from LRR or DM) once patients reach ages at which background mortality is high.

Figure	Interpretation
Figure 20: Predicted vs. observed RFS Figure 21: Predicted vs. observed DMFS	All combinations of parametric distributions produced close visual fits with the composite endpoints RFS and DMFS in each arm.

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LRR, locoregional recurrence; RF, recurrence-free; RFS, recurrence-free survival

Clinical plausibility (external validity)

The plausibility of long- and short-term extrapolations for routine surveillance for the 54 combinations of parametric functions was assessed by comparing the projections of RFS, DMFS and OS with data from several external sources (see CS Table 28 and CS Appendix N).

Of the 54 combinations of parametric distributions under consideration, 12 resulted in implausible crossing of the survival curves for pembrolizumab and routine surveillance (i.e., higher long-term RFS under routine surveillance than pembrolizumab very early on in the modelled time). Six of these 12 parametric distribution combinations also produced 4-year RFS and DMFS estimates that fell below the corresponding 4-year results observed in KEYNOTE-054 (trial of pembrolizumab vs. placebo as adjuvant treatment of resected high-risk stage 3 melanoma). These 12 combinations were therefore considered implausible and were excluded from consideration for the base case analysis. These exclusions are illustrated through color-coding in Table 16 and Table 17.

Predicted RFS in the routine surveillance arm was validated against long-term RFS data from two external studies. Across the Bajaj et al. (2020) study[5] and the US Oncology Network (USON) study,[6, 7] RFS for routine surveillance ranged narrowly over a 7-year period (e.g., RFS at 7 years ranged from 33.6% to 35.0%; simple average: 34.3%); 10-year RFS for routine surveillance was only available from the US Oncology Network study, at 23.2%, although there were a very small number of patients at risk at 10 years [redacted] therefore observations from this timepoint are more uncertain. Predicted DMFS in the routine surveillance arm was validated against observed DMFS from the USON study, as DMFS was not reported in Bajaj et al. (2020).

To better ensure externally valid extrapolations in the routine surveillance arm, further exclusions were applied based on the requirements that:

- predicted RFS for observation must fall within the range of these studies ±5 percentage points of the simple average of these two studies through 7 years, and;

- predicted DMFS for observation must fall within the range of the USON study ±5 percentage points through 7 years.

Thirteen combinations of distributions met these external validity requirements (see Table 19). As shown in Table 19, all but one of these 13 combinations were also within ±5 percentage points of RFS and/or DMFS in the US Oncology Network (USON) study at 10 years. RFS and DMFS estimates for routine surveillance for these 13 combinations versus the external validation sources are illustrated in Figure 7.

This shows that all combinations follow similar RFS trajectories over the first 5 years and then begin to deviate slightly after this point; the two combinations using Generalised gamma and Gompertz for the RF→LRR transition are the least consistent with the external sources and appear most likely to overestimate long term RFS. There is greater concordance amongst the 13 combinations in the DMFS projections across the full 10 years, although the Generalised gamma and Gompertz combinations still produce the highest long-term estimates versus the external sources.

All 13 curves for both treatment arms over the full model time horizon for RFS and DMFS are shown in Figure 8 and Figure 9, respectively. These illustrate that there is more variability in the long-term estimates between combinations for pembrolizumab than for routine surveillance, **therefore it was important to balance the plausibility of the routine surveillance arm with the estimated relative treatment benefit predicted by the corresponding curve in the pembrolizumab arm**.

Table 19 also summarizes the incremental RFS and DMFS benefit of pembrolizumab relative to routine surveillance under the 13 combinations of parametric distributions, and when taking the average incremental benefit of these 13 combinations. This demonstrates that, in general, combinations using the exponential function to model the RF→DM transitions produce a larger treatment benefit for pembrolizumab compared with combinations that used the log-normal function.

Table 19: External validation of modelled RFS and DMFS

MSE rank		Source	RFS %, by year								DMFS %, by year							
RFS	DMFS		1	2	3	4	5	6	7	10	1	2	3	4	5	6	7	10
Routine surveillance																		
-	-	KEYNOTE-716, placebo	83.4	73.2	65.3	-	-	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-
-	-	Bajaj et al. 2020[5]	87.4	64.6	56.7	48.7	44.2	41.4	33.6	-	-	-	-	-	-	-	-	-
-	-	USON, 2021[6, 7]	85.6	70.9	58.0	50.1	43.2	37.5	35.0	23.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	-	Pooled, Bajaj et al 2020 and USON (simple average)	86.5	67.8	57.4	49.4	43.7	39.5	34.3	-	-	-	-	-	-	-	-	-
-	-	*IA2 base case: #1/Lognormal/Lognormal*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	14	#1/Gen. gamma/Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	13	#1/Gompertz/Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	15	**#1/Log-normal/Log-normal**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	17	#1/Log-logistic/Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	16	#1/Weibull/Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	21	#3/Exponential/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	20	#2/Exponential/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	19	#1/Exponential/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	18	#1/Exponential/Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	24	#1/Log-logistic/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	22	#1/Weibull/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	23	#3/Weibull/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	25	#2/Weibull/Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab																		
-	-	KEYNOTE-716	90.8	81.2	74.7	-	-	-	-	-	[redacted]	[redacted]	[redacted]					
-	-	KEYNOTE-054[†,][8]	75.3	68.0	63.7	57.0	-	-	-	-	82.8	73.5	68.2	62.9				
-	-	*IA2 base case: Log-normal-Lognormal (Approach #1)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MSE rank		Source	RFS %, by year								DMFS %, by year							
RFS	DMFS		1	2	3	4	5	6	7	10	1	2	3	4	5	6	7	10
33	35	#1/Gen. gamma/Log-normal	[redacted]															
38	39	#1/Gompertz/Log-normal	[redacted]															
37	**42**	**#1/Log-normal/Log-normal**	[redacted]															
32	32	#1/Log-logistic/Log-normal	[redacted]															
29	31	#1/Weibull/Log-normal	[redacted]															
42	43	#3/Exponential/Exponential	[redacted]															
46	46	#2/Exponential/Exponential	[redacted]															
47	47	#1/Exponential/Exponential	[redacted]															
28	27	#1/Exponential/Log-normal	[redacted]															
50	50	#1/Log-logistic/Exponential	[redacted]															
49	49	#1/Weibull/Exponential	[redacted]															
44	44	#3/Weibull/Exponential	[redacted]															
48	48	#2/Weibull/Exponential	[redacted]															
Predicted difference (pembrolizumab vs routine surveillance)																		
-	-	#1/Gen. gamma/Log-normal	[redacted]															
-	-	#1/Gompertz/Log-normal	[redacted]															
-	-	**#1/Log-normal/Log-normal**	[redacted]															
-	-	#1/Log-logistic/Log-normal	[redacted]															
-	-	#1/Weibull/Log-normal	[redacted]															
-	-	#3/Exponential/Exponential	[redacted]															
-	-	#2/Exponential/Exponential	[redacted]															
-	-	#1/Exponential/Exponential	[redacted]															
-	-	#1/Exponential/Log-normal	[redacted]															
-	-	#1/Log-logistic/Exponential	[redacted]															
-	-	#1/Weibull/Exponential	[redacted]															
-	-	#3/Weibull/Exponential	[redacted]															

MSE rank		Source	RFS %, by year								DMFS %, by year							
RFS	DMFS		1	2	3	4	5	6	7	10	1	2	3	4	5	6	7	10
-	-	#2/Weibull/Exponential	[redacted]															
-	-	*Average of 13 combinations*	[redacted]															

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; IA2, interim analysis 2; LR, locoregional recurrence; RF, recurrence-free RFS, recurrence-free survival.

† Data represents patients with stage 3 melanoma – included here as a lower bound to the RFS estimates in the stage 2 setting.

Green cells indicate the predicted value is within ±5 percentage points of the external data for routine surveillance. **Bold** indicates the model selected for the base case analysis. # indicates the approach used for RFS fitting.

Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 7: External validation of modelled RFS and DMFS for routine surveillance
A) RFS

B) DMFS

Abbreviations: PEM, pembrolizumab; RFS, recurrence-free survival; RS, routine surveillance.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 8: Predicted RFS over lifetime horizon
A) Routine surveillance

B) Pembrolizumab

Abbreviations: PEM, pembrolizumab; RFS, recurrence-free survival; RS, routine surveillance.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Figure 9: Predicted DMFS over lifetime horizon
A) Routine surveillance

B) Pembrolizumab

Abbreviations: PEM, pembrolizumab; RFS, recurrence-free survival; RS, routine surveillance.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

Base case

Based on the assessments described above, and in line with the guidance provided in NICE DSU TSD 14,[9] parametric models separately fitted to each treatment arm (Approach #1; independently fitted models) were preferred and also appeared to provide the best balance between goodness of fit with observed data and plausibility of long-term extrapolations in both arms. When patient-level data are available, this approach is often preferred as it avoids reliance on an assumption of proportional hazards which is required for Approach #2 (constant proportional hazards) and involves fewer assumptions than are required for applying a time-varying treatment effect (Approach #3; proportional hazards with time-varying treatment effect).

Among the 13 combinations of functions in Approach #1, the **Lognormal-Lognormal** combination for RF→LRR and RF→DM, respectively, was selected for the base-case analysis based on its high MSE ranking with respect to both RFS (9th best-fitting out of 54 combinations) and DMFS (15th best-fitting out of 54) in the observation arm. In terms of statistical fit, this combination was outperformed by only two of the 13 finalist combinations (i.e., Approach #1/generalized gamma/log-normal and Approach #1/Gompertz/log-normal), both of which deviated further from external validation sources in an overestimated direction. Additionally, the Lognormal-Lognormal combination yielded moderate predictions of

incremental RFS and DMFS benefit for pembrolizumab vs. observation that were aligned with, or slightly below, the average incremental benefit across the 13 finalist combinations (Table 19).

Alternative combinations of parametric functions, including the use of Approaches #2 and #3, were tested in scenario analyses to explore more optimistic and pessimistic extrapolations, including the size of the long-term treatment benefit with pembrolizumab. The long-term RFS, DMFS and OS projections for the Lognormal-Lognormal combination are presented in Figure 10 and [redacted]

Table 20.

Figure 10: Predicted survival estimates over the modelled time horizon in the base case analysis

A) RFS

[redacted]

B) DMFS

[redacted]

C) OS

[redacted]

Table 20: Base case predicted survival estimates over the modelled time horizon

Outcome	Survival by year, %										
	1	2	3	4	5	6	7	10	20	30	40
Routine surveillance											
RFS	[redacted]										
DMFS	[redacted]										
OS	[redacted]										
Pembrolizumab											
RFS	[redacted]										
DMFS	[redacted]										
OS	[redacted]										

Abbreviations: DMFS, distant metastases-free survival; OS, overall survival; RFS, recurrence-free survival.

Transitions from the LRR health state

In the original economic evaluation, transition probabilities starting from the LRR state were estimated using a real-world database (US Oncology Network [USON]) and results from trials of adjuvant treatments for resected stage 3 melanoma, as DMFS was not included as part of the pre-specified second interim analysis (IA2) of KEYNOTE-716. Following the third interim analysis of KEYNOTE-716 (IA3; data cut-off date: 4th January 2022), data on DMFS in each trial arm were available for analysis, which allowed for the use of trial data to directly estimate the two transitions starting from the LRR state.

Patient-level time-to-event data from the trial were used to estimate cause-specific exponential rates and standard errors for transitions starting from LRR (i.e., LRR→DM, and LRR→Death) for each adjuvant treatment arm (Table 21)[a]. The analytical sample included patients in each arm who experienced LRR as their first RFS failure event. Among these patients, an exponential parametric function was fitted to time (in weeks) from entry into the LRR state until DM. Patients without this transition were censored at the end of follow-up. In both arms, no direct transitions from LRR→Death were observed; therefore, there were no censorings due to competing risk events in the sample. Because no direct transitions from LRR→Death were observed in the KEYNOTE-716 sample, the cause-specific hazard for this transition in both arms was approximated based on the exponential rate of RF→Death in the placebo arm of KEYNOTE-716 (i.e., the arm with the higher rate of RF→Death), based on the expectation that the rate of LRR→Death would be at least as high as deaths directly from the RF health state.

Table 21: Weekly exponential rates of transitions starting from LRR based on KEYNOTE-716 data (base case)

Model arm	LRR→DM		LRR→Death		Source
	Exponential rate	SE	Exponential rate	SE	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	KEYNOTE-716 IA3 trial data (data cutoff date: 04-Jan-2022)
Observation	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: DM, distant metastases; IA3, interim analysis 3; LRR, locoregional recurrence; SE, standard error.
Note: Within each cycle, the transition probability from LRR→Death is set equal to the maximum of the estimated probability based on parametric modelling and background mortality (Office of National Statistics, 2017-2019).

No adjustments were performed for rechallenge or crossover regimens within the LRR state; thus, the resulting transition probabilities incorporate any effect of crossover/rechallenge on risk of DM or death. In KEYNOTE-716, [redacted]56 [redacted]% of patients in the placebo arm who had a LRR crossed over to received pembrolizumab in Part 2 of the trial, compared with [redacted]/46 ([redacted]%) in the pembrolizumab arm. This explains why the exponential rate of LRR→DM is higher for the pembrolizumab arm than for routine surveillance. These patterns of crossover/rechallenge also support the base case assumption that patients in the pembrolizumab arm would not receive further therapy after LRR.

[a] 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 10. Briggs, A.H. and K. Claxton, *Decision modelling for health economic evaluation.* . 2011, New York (NY): Oxford University Press.

Notably, the use of KEYNOTE-716 data to model transitions from the LRR state replaces the USON and trial-based HR data used to model these transitions in the original submission based on IA2. In the updated model, the market shares described in CS Table 36 therefore only inform costs in the LRR health state and do not affect efficacy. To explore the impact of this approach on the ICER, scenarios in which the use of real-world data from USON and trial-based HRs are used (i.e. as per the approach in the original submission) are also presented.

Transitions from the DM health state

Transitions from the DM health state were modelled based on data from KEYNOTE-006 and the distribution of first-line subsequent therapies in the advanced melanoma setting and were therefore unaffected by the inclusion of IA3 data from KEYNOTE-716.

Additional validation

Independent parametric survival analysis of the updated RFS from IA3 was conducted, as described in CS B.3.10, to further validate that the competing risks approach to survival modelling employed in the economic model produced plausible composite RFS results.

Based on AIC and BIC statistics and visual assessment, the exponential and log-logistic RFS distributions appeared to provide the best balance between goodness-of-fit in the pembrolizumab arm and goodness-of-fit in the routine surveillance arm. BIC rankings supported the exponential RFS curve, ranked #1 and #2 best-fitting in the pembrolizumab and observation arms, respectively. AIC rankings supported the log-logistic RFS curve, ranked #3 and #2 best-fitting in the pembrolizumab and observation arms; the log-logistic was the only distribution that was ranked in the top 3 best-fitting curves according to BIC for both pembrolizumab and observation (Table 22). Both the exponential and log-logistic curves yielded long-term RFS predictions that were comparable to those generated by the Markov model under base-case settings (Figure 11), which demonstrated strong external validity when compared against real-world sources for RFS in stage 2B/2C melanoma.

Table 22: Validation of RFS using externally fitted parametric functions – fit statistics and output

Parametric function	AIC	BIC	Mean RFS (AUC),† years
Routine surveillance			
Base case	**N/A**	**N/A**	[redacted]
Exponential	1882.80	1887.00	[redacted]
Weibull	1882.35	1890.73	[redacted]

Parametric function	AIC	BIC	Mean RFS (AUC),† years
Log-normal	1878.48	1886.86	[redacted]
Log-logistic	1880.18	1888.57	[redacted]
Gompertz	1884.59	1892.97	[redacted]
Generalised gamma	1880.30	1892.88	[redacted]
Pembrolizumab			
Base case	**N/A**	**N/A**	[redacted]
Exponential	1368.01	1372.20	[redacted]
Weibull	1367.28	1375.65	[redacted]
Log-normal	1375.98	1384.36	[redacted]
Log-logistic	1368.00	1376.38	[redacted]
Gompertz	1366.77	1375.15	[redacted]
Generalised gamma	1368.77	1381.33	[redacted]

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; BIC, Bayesian information criterion; N/A, not applicable; RFS, recurrence-free survival.
† Undiscounted.
All values include the 95% risk reduction, as in the base case model.

Figure 11: Validation of modelled RFS versus directly fitted parametric models

[redacted]

Abbreviations: RFS, recurrence-free survival.

In addition, the plausibility of OS projections over 10 years for routine surveillance were compared with data from three external sources. These estimates are presented in Figure 12. All 13 combinations of parametric functions produced almost identical OS projections over 10 years. The estimated OS results for routine surveillance were slightly higher than reported by the real-world evidence, however, there have been significant improvements in the treatment of metastatic disease in the last 6–10 years which have substantially improved survival outcomes for patients with metastatic melanoma.

For example, in the CheckMate-067 trial in untreated advanced melanoma, 5-year OS rates for nivolumab + ipilimumab (recommended by NICE in 2016) were 52% compared with 26% for ipilimumab monotherapy (recommended by NICE in 2014).[11]). There have also been more recent advances in the management of stage 3 disease in terms of availability of adjuvant treatments, which is also expected to affect OS by improving outcomes for stage 2B/2C melanoma patients who have LRR. All the real-world studies enrolled patients who were diagnosed before these recent advances (i.e. before 2012; see CS Appendix N). Bleicher et al, 2020 enrolled patients between 2000–2017,[12] and therefore a large proportion of the cohort are likely to have recurred before these improvements were available. Note that the study by Bajaj et al, 2020 does represent a relatively more recent cohort (patients enrolled 2010–2016) which therefore may partly capture recent treatment improvements; however the study is limited

by the small cohort size (n=90) and therefore the OS curve, particularly the second half, should be interpreted with caution. Consequently, it is likely that all the external studies somewhat underestimate the true OS for patients with contemporary diagnoses.

Figure 12: External validation of modelled OS

[redacted]

Abbreviations: OS, overall survival; PEM, pembrolizumab; RS, routine surveillance.
Predictions account for a risk reduction versus the parametric function, applied linearly starting from 7–10 years.

The OS projections in the base case model are illustrated in Figure 13A. To explore the impact of the OS projections on the cost-effectiveness results, a scenario analysis was conducted in which the exponential rate used to model OS was increased such that the 5-year OS estimated by the model for routine surveillance was equal to the real-world OS rate sourced from the USON dataset (71.9%), with the purpose of lowering the OS curve to align with external sources. The exponential rate required to produce this analysis [redacted] was obtained via the Goal seek function in the Excel model. The resulting OS projections from this scenario compared with the real-world external sources over 10 years are illustrated in Figure 13B and demonstrate a close alignment with all the external sources. The cost-effectiveness results produced in this scenario are shown in Table 33, and illustrate that the absolute estimates of OS have a negligible impact on the ICER.

Figure 13: Predictions of OS – Base case and scenario analysis

A) Base case

[redacted]

B) Scenario analysis – exponential rate of OS adjusted

[redacted]

In the scenario analysis (B), the exponential rate used to model OS was increased such that the 5-year OS estimated by the model for routine surveillance was equal to the real-world OS rate sourced from the USON dataset (71.9%).

3.2 *Adverse events*

Risks of the included AEs for patients treated with pembrolizumab and routine surveillance were updated to reflect all-cause AE event rates observed in KEYNOTE-716 by IA3 (Table 23). Mean durations of each AE per episode, and the mean number of episodes per patient with each AE, were also updated accordingly.

Table 23: Risks and durations of modelled adverse events, from KEYNOTE-716 IA3

AE type†	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with the AE (weeks)	Mean duration per episode (weeks)
	Pembrolizumab	Routine surveillance		
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]

AE type†	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with the AE (weeks)	Mean duration per episode (weeks)
	Pembrolizumab	Routine surveillance		
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia‡	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
† The model considered grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial, therefore AEs (such as colitis) that occurred in <5% of patients were not included; ‡ Selected for inclusion *a priori*, but not observed in the trial by the data cut-off.

3.3 *Health-related quality of life*

The EQ-5D analysis was updated based on the IA3 data cut (4th January 2022) and consisted of the full analysis set (FAS), defined as all patients who received at least one dose of study medication and had at least one EQ-5D measurement available. As observed at IA2, compliance to the EQ-5D assessments in KEYNOTE-716 was very good and remained over [redacted] for all timepoints in both the pembrolizumab and placebo arms (Table 24). A summary of the number of patients and EQ-5D records available for use in the analyses is provided in Table 25.

Utility values for the RF, LRR and DM health states were derived via repeated measures regression analyses of patient-level EQ-5D data from the KEYNOTE-716 trial, using identical methodology as employed for IA2 (see CS B.3.4.1). These values are presented in Table 26. A summary of the utility values used in the updated economic model is provided in Table 27. Statistical testing of treatment effect using the KEYNOTE-716 IA3 data cut continued to show no significant difference in utility between the pembrolizumab and placebo arms (EQ-5D-5L: p[redacted]

by AE status, p[redacted] by health state; EQ-5D-3L: p[redacted] by AE status, p[redacted] by health state), supporting the use of pooled utilities in the model.

Table 24: EQ-5D-5L compliance rate in KEYNOTE-716 IA3

Treatment visit	Category	Patients, n (%)	
		Pembrolizumab (N[redacted]	Placebo (N[redacted]
Baseline	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 12	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 24	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 36	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 48	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 60	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 72	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 84	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Week 96	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Month 30	Missing by Design	[redacted]	[redacted]

Treatment visit	Category	Patients, n (%)	
		Pembrolizumab (N[redacted]	Placebo (N[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]
Month 36	Missing by Design	[redacted]	[redacted]
	Expected to Complete Questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance (completed per protocol)*	[redacted]	[redacted]

* Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design.
Missing by design includes: death, discontinuation, completed study treatment, translations not available, and no visit scheduled. (Database Cutoff Date: 04JAN2022).

Table 25: Sample size and number of records by health state, KEYNOTE-716 IA3

Health state	Number of patients	Number of records
RF and during grade 3+ AEs	[redacted]	[redacted]
RF and without AEs (toxicity free)	[redacted]	[redacted]
LRR	[redacted]	[redacted]
DM	[redacted]	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.

Table 26: Summary of health state utility values derived from KEYNOTE-716 IA3

Health state	EQ-5D-3L		EQ-5D-5L (scenario)	
	Mean	SE	Mean	SE
RF (toxicity free)	[redacted]	[redacted]	[redacted]	[redacted]
RF with Grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]
RF with grade <3 AE†	[redacted]	[redacted]	[redacted]	[redacted]
LRR	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free; SE, standard error.
IA3 data cut-off 4th January 2022.

Table 27: Summary of utility values used in the updated economic model

State	Utility value	SE	Source
RF (toxicity-free)	[redacted]	[redacted]	KEYNOTE-716 IA3
LRR	[redacted]	[redacted]	
DM (pre-progression)	[redacted]	[redacted]	
DM (post-progression)	0.59	0.02	Beusterien et al, 2009[13]
Death	0	-	-
AE†	[redacted]	[redacted]	KEYNOTE-716 IA3

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free; SE, standard error.
† This AE disutility was applied to the RF (toxicity free) utility, adjusted by the frequency of AEs, to estimate the utility for RF with toxicity.

Exploratory utility analysis

The ERG have requested that utility values from KEYNOTE-716 be estimated via a single regression model that includes grade <3 AEs in the RF health state. MSD consider that inclusion of grade <3 AEs in the RF health state utility is inappropriate as it will underestimate the long-term utility for patients remaining in the RF state (see full justification in the Technical Engagement response form, Issue 5). However, the use of a single regression model to estimate all utilities has been explored to partly address the ERG's request. As per the methods of linear mixed regression analysis, the definition of health states included as binary indicators in the regression must be aligned with the intercept health state such that all variables are held the same except the relevant covariate(s) defining the health state. The following approach was explored:

Description: AE status and recurrence status (i.e. health state) are treated as two independent variables where the intercept corresponds to "RF without any AEs"; "During grade 3+ AE" and "Other Grade AE" represent AEs regardless of health state; and "LRR" and "DM" represent each health state with AEs (regardless of grade).

Equation: $Utility_{ij} = \beta_0 + \beta_1 Health\ Status_{ij} + \beta_2 AE_{ij} + e_i$

Limitations: The LRR and DM states had two covariates varied (AE status and health state) with respect to the intercept which implies that the AE and health state are two completely independent variables. This was necessary to enable the analysis, as the LRR and DM with grade 3+ AE categories had a very small sample size (n[redacted] and n[redacted] respectively; Table 28) which would confer large uncertainty if these categories were estimated separately, and also to ensure consistency with the economic modelling approach.

Table 28: Number of records by health state and AE status, KEYNOTE-716 IA3 – Exploratory regression analyses

Health state	Without AE	During grade 3+ AE	During other grade AE
RF	[redacted]	[redacted]	[redacted]
LRR	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.

The utility estimates from this exploratory approach are presented in Table 29. Utility values for the RF health state are highly comparable to the estimates used in the base case approach (i.e. using two separate regression models). However, the utilities for the LRR and DM health states

deviated more from the base case values, due to the assumptions and sample size limitations necessary to enable inclusion in a single regression model.

Table 29: Summary of health state utility values derived from KEYNOTE-716 IA3 – Exploratory regression analysis

Health state	Utility	
	Mean	SE
RF (toxicity free)	[redacted]	[redacted]
RF with Grade 3+ AE	[redacted]	[redacted]
RF with grade <3 AE†	[redacted]	[redacted]
LRR	[redacted]	[redacted]
DM	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free; SE, standard error.
IA3 data cut-off 4th January 2022.

Given the limitations of this approach, MSD consider that the methods presented in the original submission are the most appropriate to accurately address the decision problem. However, the impact of the utilities generated via this alternative approach is explored in a scenario analysis.

3.4 *Other model inputs*

Intervention costs

The relative dose intensity (RDI) observed in KEYNOTE-716 at IA3 was [redacted]%, therefore the updated RDI-adjusted cost per administration (list price) was £[redacted]. This was applied to the drug acquisition cost per infusion of adjuvant pembrolizumab to account for any delays or interruptions in administration.

Health state costs: Salvage surgery in the LRR health state

Subsequent treatment in the LRR state included one-time costs of salvage surgery for a proportion of patients who enter this state. Frequencies of salvage surgery based on observed percentages of patients with each type of surgery in the KEYNOTE-716 trial, pooled across both treatment arms, were updated based on the IA3 data cut (Table 30).

Table 30: Salvage surgery resource use in the LRR state

Resource	One-off resource		Source
	% of patients	Average per patient	
ITM resection or other surgery	[redacted]	[redacted]	[redacted] patients with LRR in KEYNOTE-716

Resource	One-off resource		Source
	% of patients	Average per patient	
Lymphadenectomy	[redacted]	[redacted]	[redacted] patients with LRR in KEYNOTE-716
Skin lesion resection	[redacted]	[redacted]	[redacted] patients with LRR in KEYNOTE-716

Abbreviations: ITM, in transit metastases.
Sourced from KEYNOTE-716 interim analysis 3 (data cut-off 4th January 2022).

4 Cost-effectiveness results

4.1 *Base case*

Table 31: Base case cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,864
Routine surveillance	[redacted]	10.10	[redacted]	-	-	-	-

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

4.2 *Sensitivity analyses*

Probabilistic sensitivity analysis

Results of the PSA are shown in Table 32. The corresponding scatterplot of PSA results and cost-effectiveness acceptability curve (CEAC) are shown in Figure 14 and Figure 15, respectively. The probabilistic results are aligned to the deterministic base case and estimated that pembrolizumab was associated with [redacted] additional LYs and [redacted] additional QALYs, corresponding to a probabilistic ICER of £16,147 per QALY. The CEAC demonstrates that there is a 66.1% probability that adjuvant treatment with pembrolizumab is a cost-effective treatment strategy for patients with resected stage 2B/2C melanoma based on a WTP threshold of £30,000 per QALY. The wide distribution observed in the scatterplot is a result of iterations where opposing extreme parametric function parameters are selected in each arm such that the QALY advantage of pembrolizumab versus routine surveillance is very large or very small. As the model uses independently fitted parametric models in each arm, the parameter estimates for a given transition are not correlated between arms which magnifies this effect.

Table 32: Probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,147
Routine surveillance	[redacted]	10.10	[redacted]	-	-	-	-

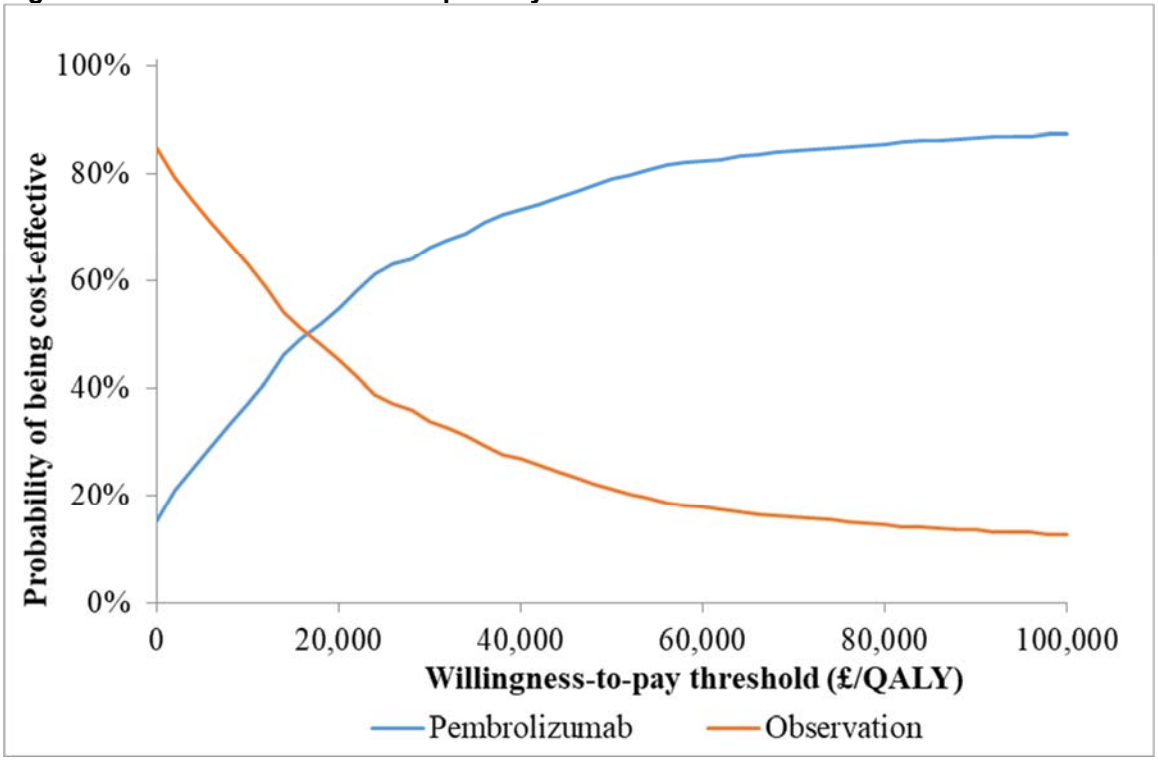
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 14: Scatterplot of PSA results

[redacted]

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 15: Cost-effectiveness acceptability curve

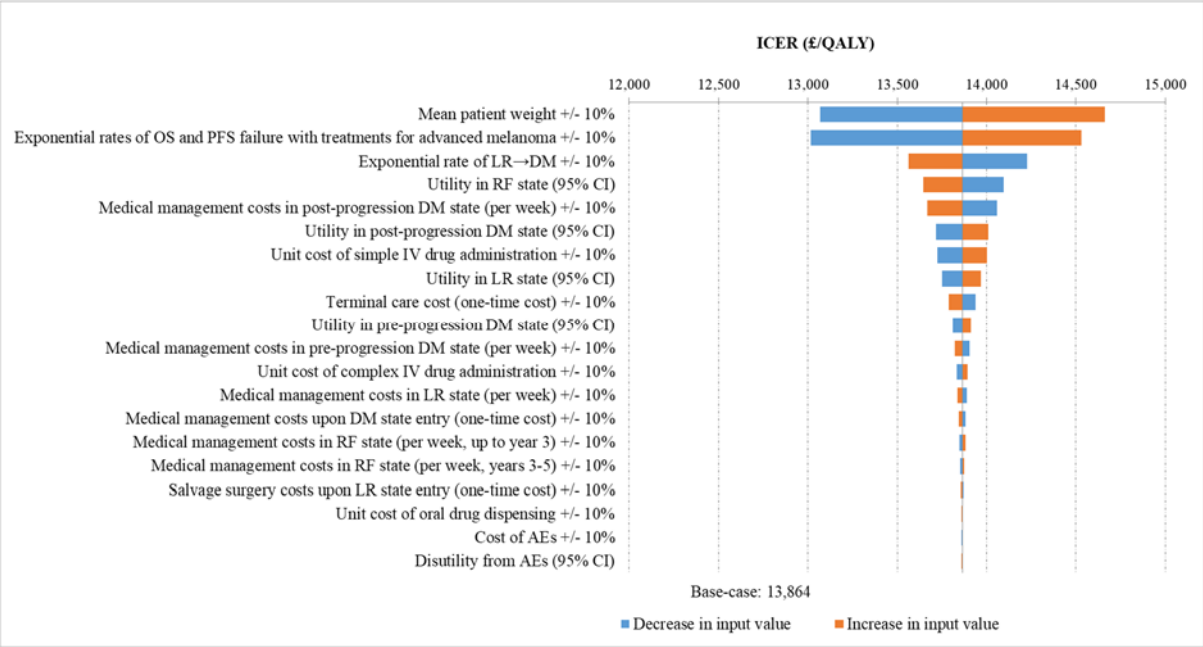


Abbreviations: QALY, quality-adjusted life year.

Deterministic sensitivity analysis

The results of the DSA are presented in a tornado diagram in Figure 16 which illustrates the 20 parameters that had the most impact on the ICER. The biggest model drivers were the exponential rates used to model OS and PFS in the DM health state, and parameters that impacted costs in the DM health state. Overall, the results show that the model is robust to changes in parameter inputs, and pembrolizumab remained cost-effective across all parameter variations.

Figure 16: Tornado diagram



Abbreviations: CI, confidence interval; DM, distant metastases; ICER, incremental cost-effectiveness ratio; IV, intravenous; LR, locoregional; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RF, recurrence-free.

Scenario analysis

A range of scenario analyses are presented in Table 33; new scenarios explored during technical engagement are indicated in bold font. These analyses demonstrate that adjuvant treatment with pembrolizumab in resected stage 2B/2C melanoma remains cost-effective across a wide range of plausible scenarios.

Table 33: Scenario analyses

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
-	**Base case**	**-**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**13,864**
1	Alternative functions for modelling of transitions from RF state (Approach #1)	**Pessimistic RFS for pembrolizumab†** **RF→LRR: Log-logistic** **RF→DM: Lognormal**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,495
2		**Alternative pessimistic RFS for pembrolizumab†** **RF→LRR: Weibull** **RF→DM: Lognormal**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,760
3		**Optimistic RFS for pembrolizumab‡** **RF→LRR: Exponential** **RF→DM: Exponential**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6,509
4		**Optimistic RFS for pembrolizumab‡** **RF→LRR: Log-logistic** **RF→DM: Exponential**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,445
5		**Alternative modelling approach** **Approach #2 (time-constant HR):**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6,509

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
	Alternative approaches for modelling transitions from RF state	**RF→LRR: Exponential** **RF→DM: Exponential**							
6		**<u>Alternative modelling approach</u>** **Approach #3 (time-varying HR):** **RF→LRR: Exponential** **RF→DM: Exponential**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,200
7	Alternative risk reduction assumptions	For patients in the RF state, an 80% risk reduction is applied at 10 years, with gradual decrease starting from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,517
8		For patients in the RF state, the 95% risk reduction is applied at 10 years, with gradual decrease starting from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,014
9		For patients in the RF state, the 95% risk reduction is applied at 5 years, with no gradual decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,732
10		For patients in the RF state, the 95% risk reduction is applied at 10 years, with no gradual decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,293
11	Reduced OS projections	**Exponential rate of OS in the DM state increased such that the modelled OS projections for routine surveillance align with the external validation sources (exp** [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,818
12		**Transitions from the LRR state are estimated using data from the**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,008

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
	Data source used to estimate transitions from the LRR state	**USON EHR database and stage 3 trials, rather than with data from KEYNOTE-716**							
13		Transitions from the LRR state are estimated using data from the USON EHR database for patient on or off adjuvant treatment, rather than with data from KEYNOTE-716	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,909
14	Alternative market shares of adjuvant therapy for stage 3 resected disease in the LRR state (base case assumes no adjuvant treatment in the LRR state for the pembrolizumab arm)	In the adjuvant pembrolizumab arm, BRAF mutation positive patients (43.3%) who enter the LRR state are eligible for adjuvant treatment with dabrafenib + trametinib, adjusted for the [redacted] of patients in the overall cohort who are expected to receive no systemic adjuvant therapy.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,877
15	Alternative market shares of systemic therapy in the DM state	No rechallenge with pembrolizumab permitted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,378
16		**In the pembrolizumab arm, market shares for the DM state for patients who entered the DM state ≥2 years after adjuvant pembrolizumab initiation were assumed to be equal to those in the routine surveillance arm (1L and 2L)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,262
17	Shorter duration of first line therapies	**The exponential rate of PFS increased by 10% to [redacted] reducing the ToT for first line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,547

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
		subsequent therapies in the DM state							
18	Only costs of first line systemic therapy in the DM state included	Costs of second line therapies in the DM state are excluded, as the model does not consider the efficacy of 2L agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,401
19	Alternative sources of utility values	EQ-5D-5L utilities sourced from KEYNOTE-716	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,178
20		Utilities sourced from KEYNOTE-054 for the LRR and pre-progression DM health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,762
21		Utilities for the DM state sourced from Middleton et al, 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,643
22		**Single regression model for utilities. AE status and health state assumed to be independent covariates. LRR and DM utilities include impact of any grade AEs**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,020
23	Alternative dosing schedule for IO therapies	Shorter dosing schedules used for pembrolizumab (200 mg Q3W) and nivolumab (240 mg Q2W) in all settings (conservative dosing scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,823
24		Shorter dosing schedules used for pembrolizumab (200 mg Q3W) in all settings (conservative dosing scenario) (nivolumab schedule as per base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,727

#	Scenario	Description	Pembrolizumab		Routine surveillance		Incremental		
			Costs (£)	QALYs	Costs (£)	QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
25	Vial sharing permitted	For agents where weight-based dosing is used, vial sharing is permitted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,032
26	Discount rate	Discounting of costs and effects set to 1.5%.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,339
27		Discounting of costs at 3.5% and effects at 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,310

Abbreviations: DM, distant metastases; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; QALY, quality-adjusted life year; QxW, every x weeks; RF, recurrence-free.

† Scenario estimates a smaller treatment benefit for pembrolizumab versus routine surveillance compared with the base case scenario; ‡ Scenario estimates a larger treatment benefit for pembrolizumab versus routine surveillance compared with the base case scenario.

New scenarios added based on the IA3 model and technical engagement response are indicated in **bold**.

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Appendix A: Transition probabilities

Transitions from the RF health state

Transition parameters

Table 34: Parametric models for transitions starting from RF state, separately fitted to each arm of the KEYNOTE-716 trial – Approach #1

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

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.

Table 35: Parametric models for transitions starting from the RF state, using time-constant treatment effect – Approach #2

Distribution	Parameter	Parameter estimates			Pembrolizumab vs routine surveillance		
		RF→LRR	RF→DM	RF→ Death	RF→LRR	RF→DM	RF→ Death
Exponential	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Shape	[redacted]	[redacted]	-	[redacted]	[redacted]	-
	Scale	[redacted]	[redacted]	-			
Gompertz	Shape	[redacted]	[redacted]	-	[redacted]	[redacted]	-
	Rate	[redacted]	[redacted]	-			

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.

Table 36: Parametric models for transitions starting from the RF state, using a time-varying treatment effect – Approach #3

Distribution	Parameter	Parameter estimates			Pembrolizumab vs routine surveillance (year 1)			Pembrolizumab vs routine surveillance (post-year 1)		
		RF→LRR	RF→DM	RF→ Death	RF→LRR	RF→DM	RF→ Death	RF→LRR	RF→DM	RF→ Death
Exponential	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Shape	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
	Scale	[redacted]	[redacted]	-						
Gompertz	Shape	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
	Rate	[redacted]	[redacted]	-						

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.

Visual fit figures

Figure 17: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence (RF→LRR)
A) Routine surveillance

[redacted]

B) Pembrolizumab

[redacted]

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.
Each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→LRR. The different shades within a particular colour family represent the different distributions fitted to the cause-specific hazards of RF→DM. Solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1), dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2), and dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3).

Figure 18: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases (RF→DM)
A) Routine surveillance

[redacted]

B) Pembrolizumab

[redacted]

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.
Each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→DM. The different shades within a particular colour family represent the different distributions fitted to the cause-specific hazards of RF→LRR. Solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1), dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2), and dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3).

Figure 19: Predicted vs. observed cumulative incidence of transitions from recurrence-free to death (RF→Death)
A) Routine surveillance

[redacted]

B) Pembrolizumab

[redacted]

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free.
Each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→DM. The different shades within a particular colour family represent the different distributions fitted to the cause-specific hazards of RF→LRR. Solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1), dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2), and dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3).

Figure 20: Predicted vs. observed RFS

A) Routine surveillance

B) Pembrolizumab

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; RF, recurrence-free; RFS, recurrence-free survival.
Each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→DM. The different shades within a particular colour family represent the different distributions fitted to the cause-specific hazards of RF→LRR. Solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1), dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2), and dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3).

Figure 21: Predicted vs. observed DMFS

A) Routine surveillance

B) Pembrolizumab

Abbreviations: DM, distant metastases; DMFS, distant metastases free survival; LRR, locoregional recurrence; RF, recurrence-free.
Each colour family represents one of the different distributions fitted to the cause-specific hazards of RF→DM. The different shades within a particular colour family represent the different distributions fitted to the cause-specific hazards of RF→LRR. Solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1), dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2), and dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3).

Selection of base case parametric functions

As discussed in CS B.3.3.1, a range of assessment criteria (statistical fit, visual fit, and clinical plausibility) were applied to compare all 54 combinations of parametric functions and select the base case combination of functions. The performance of each of these combinations of functions against the criteria is presented in Table 37

Table 37: Comparison of parametric functions versus selection criteria (statistical fit and clinical plausibility)

Rank by MSE				Parametric functions		Function selection criteria					
Routine surveillance		Pembrolizumab		RF → LRR	RF → DM	MSE (placebo)†		Curves cross	RFS below KEYNOTE-054	RFS and/or DMFS >5% outside external sources	Comment
RFS	DMFS	RFS	DMFS			RFS	DMFS				
Approach #1: Parametric models separately fitted to each treatment arm											
1	4	17	18	Log-normal	Generalized gamma	0.0000872	0.0001052	Yes	No	Yes	Exclude based on external plausibility
2	5	2	12	Generalized gamma	Generalized gamma	0.0000887	0.0001060	Yes	No	Yes	Exclude based on external plausibility
3	3	5	11	Log-logistic	Generalized gamma	0.0000899	0.0001033	Yes	No	Yes	Exclude based on external plausibility
4	2	1	10	Weibull	Generalized gamma	0.0000908	0.0001028	Yes	No	Yes	Exclude based on external plausibility
5	6	18	16	Gompertz	Generalized gamma	0.0000923	0.0001060	Yes	No	Yes	Exclude based on external plausibility
6	1	19	5	Exponential	Generalized gamma	0.0001074	0.0001015	Yes	No	Yes	Exclude based on external plausibility
7	14	33	35	Generalized gamma	Log-normal	0.0001187	0.0001216	No	No	No	Explore for base case
8	13	38	39	Gompertz	Log-normal	0.0001228	0.0001207	No	No	No	Explore for base case
9	**15**	**37**	**42**	**Log-normal**	**Log-normal**	**0.0001264**	**0.0001220**	**No**	**No**	**No**	**Select for base case**
10	31	14	20	Generalized gamma	Log-logistic	0.0001515	0.0001368	No	No	Yes	Exclude based on external plausibility
11	17	32	32	Log-logistic	Log-normal	0.0001531	0.0001222	No	No	No	Explore for base case
12	28	26	23	Gompertz	Log-logistic	0.0001570	0.0001357	No	No	Yes	Exclude based on external plausibility
13	16	29	31	Weibull	Log-normal	0.0001607	0.0001220	No	No	No	Explore for base case
14	32	25	25	Log-normal	Log-logistic	0.0001616	0.0001378	No	No	Yes	Exclude based on external plausibility
15	38	9	15	Generalized gamma	Weibull	0.0001660	0.0001463	No	No	Yes	Exclude based on external plausibility
16	36	24	21	Gompertz	Weibull	0.0001714	0.0001450	No	No	Yes	Exclude based on external plausibility
17	8	3	4	Generalized gamma	Gompertz	0.0001762	0.0001124	Yes	Yes	Yes	Exclude based on external plausibility
20	19	47	47	Exponential	Exponential	0.0001766	0.0001305	No	No	No	Explore for base case

Rank by MSE				Parametric functions		Function selection criteria					
Routine surveillance		Pembrolizumab		RF → LRR	RF → DM	MSE (placebo)†		Curves cross	RFS below KEYNOTE-054	RFS and/or DMFS >5% outside external sources	Comment
RFS	DMFS	RFS	DMFS			RFS	DMFS				
21	39	23	22	Log-normal	Weibull	0.0001772	0.0001475	No	No	Yes	Exclude based on external plausibility
22	9	22	7	Log-normal	Gompertz	0.0001806	0.0001133	Yes	Yes	Yes	Exclude based on external plausibility
23	7	16	6	Gompertz	Gompertz	0.0001858	0.0001121	Yes	Yes	Yes	Exclude based on external plausibility
24	34	15	19	Log-logistic	Log-logistic	0.0001960	0.0001391	No	No	Yes	Exclude based on external plausibility
26	18	28	27	Exponential	Log-normal	0.0002003	0.0001258	No	No	No	Explore for base case
28	10	6	3	Log-logistic	Gompertz	0.0002057	0.0001151	Yes	Yes	Yes	Exclude based on external plausibility
29	35	12	17	Weibull	Log-logistic	0.0002063	0.0001393	No	No	Yes	Exclude based on external plausibility
30	24	50	50	Log-logistic	Exponential	0.0002087	0.0001338	No	No	No	Explore for base case
32	22	49	49	Weibull	Exponential	0.0002101	0.0001336	No	No	No	Explore for base case
35	40	11	14	Log-logistic	Weibull	0.0002151	0.0001496	No	No	Yes	Exclude based on external plausibility
36	11	4	2	Weibull	Gompertz	0.0002151	0.0001154	Yes	Yes	Yes	Exclude based on MSE & external plausibility
38	26	54	54	Log-normal	Exponential	0.0002166	0.0001348	No	No	Yes	Exclude based on external plausibility
39	27	51	51	Generalized gamma	Exponential	0.0002267	0.0001355	No	No	Yes	Exclude based on external plausibility
40	41	8	13	Weibull	Weibull	0.0002268	0.0001498	No	No	Yes	Exclude based on MSE & external plausibility
41	12	13	1	Exponential	Gompertz	0.0002314	0.0001198	Yes	Yes	Yes	Exclude based on MSE & external plausibility
43	30	52	52	Gompertz	Exponential	0.0002411	0.0001367	No	No	Yes	Exclude based on external plausibility
44	37	21	9	Exponential	Log-logistic	0.0002485	0.0001451	No	No	Yes	Exclude based on external plausibility
48	44	20	8	Exponential	Weibull	0.0002718	0.0001570	No	No	Yes	Exclude based on MSE & external plausibility

Rank by MSE				Parametric functions		Function selection criteria					
Routine surveillance		Pembrolizumab		RF → LRR	RF → DM	MSE (placebo)†		Curves cross	RFS below KEYNOTE-054	RFS and/or DMFS >5% outside external sources	Comment
RFS	DMFS	RFS	DMFS			RFS	DMFS				
Approach #2: Parametric proportional hazards models with a time-constant treatment effect											
19	20	46	46	Exponential	Exponential	0.0001766	0.0001305	No	No	No	Explore for base case
27	49	40	36	Gompertz	Weibull	0.0002028	0.0001888	No	No	Yes	Exclude based on external plausibility
34	25	48	48	Weibull	Exponential	0.0002148	0.0001340	No	No	No	Explore for base case
37	43	43	41	Gompertz	Gompertz	0.0002157	0.0001565	No	No	Yes	Exclude based on external plausibility
42	29	53	53	Gompertz	Exponential	0.0002374	0.0001365	No	No	Yes	Exclude based on external plausibility
46	50	27	28	Weibull	Weibull	0.0002680	0.0001940	No	No	Yes	Exclude based on MSE & external plausibility
47	45	34	30	Weibull	Gompertz	0.0002698	0.0001619	No	No	Yes	Exclude based on MSE & external plausibility
51	47	7	26	Exponential	Gompertz	0.0003119	0.0001713	No	No	Yes	Exclude based on MSE & external plausibility
53	52	10	24	Exponential	Weibull	0.0003328	0.0002045	No	No	Yes	Exclude based on MSE & external plausibility
Approach #3: Parametric proportional hazards models with a time-varying treatment effect											
18	21	42	43	Exponential	Exponential	0.0001766	0.0001305	No	No	No	Explore for base case
25	51	39	40	Gompertz	Weibull	0.0001994	0.0002020	No	No	Yes	Exclude based on external plausibility
31	42	41	37	Gompertz	Gompertz	0.0002098	0.0001562	No	No	Yes	Exclude based on external plausibility
33	23	44	44	Weibull	Exponential	0.0002114	0.0001338	No	No	No	Explore for base case
45	33	45	45	Gompertz	Exponential	0.0002572	0.0001378	No	No	Yes	Exclude based on external plausibility
49	46	36	33	Weibull	Gompertz	0.0002744	0.0001649	No	No	Yes	Exclude based on external plausibility
50	53	35	38	Weibull	Weibull	0.0002884	0.0002113	No	No	Yes	Exclude based on external plausibility
52	48	31	29	Exponential	Gompertz	0.0003153	0.0001738	No	No	Yes	Exclude based on external plausibility

Rank by MSE				Parametric functions		Function selection criteria					
Routine surveillance		Pembrolizumab		RF → LRR	RF → DM	MSE (placebo)†		Curves cross	RFS below KEYNOTE-054	RFS and/or DMFS >5% outside external sources	Comment
RFS	DMFS	RFS	DMFS			RFS	DMFS				
54	54	30	34	Exponential	Weibull	0.0003544	0.0002219	No	No	Yes	Exclude based on external plausibility

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LRR, locoregional recurrence; MSE, mean squared error; RF, recurrence-free; RFS, recurrence-free survival.
† Combinations of distributions were excluded if they ranked among the ten worst-fitting combinations in terms of both RFS and DMFS in the routine surveillance arm, regardless of their ranking in the pembrolizumab arm.

Appendix B: Subsequent treatments in KEYNOTE-716

Data on the first subsequent treatment received after first recurrence in KEYNOTE-716 are presented in Table 38 and Table 39, after LRR and DM respectively. Patients who received pembrolizumab monotherapy in part 2 of the trial are included but reported separately from patients who received pembrolizumab monotherapy but did not enter part 2.

Table 38: First subsequent treatment after LRR in KEYNOTE-716, IA3

Regimen	Subsequent treatments by adjuvant treatment arm			
	Pembrolizumab (N=487)		Placebo (N=489)	
	n	%	n	%
Patients with LRR as first event	**46**	**-**	**56**	**-**
Received any subsequent treatment following LRR	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab (Part 2)†	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Binimetinib + encorafenib	[redacted]	[redacted]	[redacted]	[redacted]
Cancer vaccines + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib mesilate	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Monoclonal antibodies + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + other antineoplastic agents	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + quavonlimab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + vibostolimab	[redacted]	[redacted]	[redacted]	[redacted]

† Patients who received pembrolizumab in Part 2 of the KEYNOTE-716 trial (crossover or rechallenge with pembrolizumab monotherapy).
Data cut-off 4th January 2022.

Table 39: First subsequent treatment after DM in KEYNOTE-716, IA3

Regimen	Subsequent treatments by adjuvant treatment arm			
	Pembrolizumab (N=487)		Placebo (N=489)	
	n	%	n	%
Patients with DM as first event	**45**	**-**	**77**	**-**
Received any subsequent treatment following DM	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab (Part 2)†	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Binimetinib + encorafenib	[redacted]	[redacted]	[redacted]	[redacted]

Regimen	Subsequent treatments by adjuvant treatment arm			
	Pembrolizumab (N=487)		Placebo (N=489)	
	n	%	n	%
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Cobimetinib + vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab + nivolumab + tocilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Other therapeutic products + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib malate	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]

† Patients who received pembrolizumab in Part 2 of the KEYNOTE-716 trial (crossover or rechallenge with pembrolizumab monotherapy).
Data cut-off 4th January 2022.

Appendix C: Model updates

Table 40: Summary of changes to the original submission model

Updates to originally submitted model		Model tabs where updates are implemented
1)	**Updated the following clinical inputs based on the clinical study report and supplemental results tables from the third interim analysis (IA3) of the KEYNOTE-716 trial:**	
	• Risks, mean number of episodes per patient with AE, and mean duration per episode of grade 2+ diarrhoea	'Raw - AEs'
	• Risks, mean number of episodes per patient with AE, and mean duration per episode of grade 3+ AEs	'Raw - AEs'
	• Plot points for pembrolizumab time on treatment Kaplan-Meier curve	'Raw_ToT KM curves'
	• Plot points for recurrence-free survival (RFS) Kaplan-Meier curve in each arm	'Raw_KM curves', 'Observed survival curves', 'Effectiveness', 'Specifications'
	• Plot points for distant metastases-free survival (DMFS) Kaplan-Meier curve in each arm (Note: The presentation of DMFS Kaplan-Meier curves from KEYNOTE-716 is a new addition to the model based on the third interim analysis of KEYNOTE-716. DMFS was not part of the pre-specified first interim analyses of KEYNOTE-716, and thus was not available at the time of the original submission)	'Raw_KM curves', 'Observed survival curves', 'Effectiveness', 'Specifications'
	• Pembrolizumab mean relative dose intensity	'Raw - Drug costs'
	• Percentages of patients who underwent salvage surgery in the locoregional recurrence state among those who entered the locoregional recurrence state	'HCRU'
	• AE-related disutility based on regression analysis of EQ-5D data	'Raw - AEs'
	• Health state utilities based on regression analyses of EQ-5D data	'Raw - Utilities'
2)	**Re-ran the competing-risk survival analyses of patient-level data from the KEYNOTE-716 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:**	

Updates to originally submitted model		Model tabs where updates are implemented
	• 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)	'Raw_Param Estimates'
	• Plot points for the cumulative incidences of RF→LR, RF→DM, and RF→Death in each arm	'Raw_KM curves', 'Observed survival curves', 'Efficacy Validation'
3)	**Given the new availability of DMFS outcomes from the third interim analysis of KEYNOTE-716, additional competing-risk survival analyses of patient-level KEYNOTE-716 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 based on the market shares of subsequent adjuvant treatments for stage III melanoma received in the LR state.) The cost-effectiveness model was updated as follows to incorporate these newly available transition probability inputs from KEYNOTE-716:**	
	1. Added dropdown menu in the Effectiveness tab to allow users to choose from the following two options for estimating transition probabilities starting from the LR state: 1. Use KEYNOTE-716 IA3 data (data cutoff date: 04Jan2022) to directly estimate transition probabilities starting from the LR state 2. Derive transition probabilities from market shares of subsequent adjuvant treatments received in LR state (i.e., original approach)	'Effectiveness'
	• Added a new table in the Effectiveness tab to store the exponential rates and corresponding standard errors from KEYNOTE-716	'Effectiveness'
	• Updated macro that loops through all 54 possible combinations of parametric distributions to also compute the mean squared error for observed vs. predicted DMFS in each model arm. (Originally, mean squared errors could only be calculated for the comparison of observed vs. predicted RFS in each arm.)	'Param Output'
	• Updated DSA/PSA to vary the KEYNOTE-716-based exponential rates of LR->DM and LR->death	'DSA Set-up', 'PSA Setup'
4)	**Re-ran the cross-validation exercise in which parametric curves are directly fitted to RFS as a composite endpoint, and compared the resulting extrapolations of RFS in each arm with those estimated from the Markov model**	'Raw_Param Estimates', 'Raw - Parametric RFS curves'

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Clinical expert statement and technical engagement response form

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

Thank you for agreeing to comment on the evidence review group (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 for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. 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. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

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.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

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. 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.

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.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 15 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

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.

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Part 1: Treating resected stage 2 melanoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

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 resected stage 2 melanoma? ☒ A specialist in the clinical evidence base for resected stage 2 melanoma 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 did not submit one, I do not 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
8. What is the main aim of treatment for resected stage 2 melanoma?	To reduce the risk of melanoma recurrence

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A statistically significant HR of 0.75
10. In your view, is there an unmet need for patients and healthcare professionals in resected stage 2 melanoma?	Yes
11. How is resected stage 2 melanoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently no systemic therapy is offered and patients are followed up and treated on relapse. This is well defined and as per NICE guidelines to date. If Pembrolizumab was available then this group of patients would have access to a treatment that can significantly reduce the risk of recurrence of the melanoma.
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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	This drug is widely used as adjuvant therapy for stage 3 melanoma in NHS. This would allow access to patients with Stage 2 melanoma. If adopted there will be an increase in the use of adjuvant therapy -with associated resource implications for drugs costs, SACT administration, toxicity management, outpatients vistis, AOS.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
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? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is a major advance for this group of patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Stage IIb and IIc.
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 treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	As mentioned the drug is already used for Stage 3 – so no difficulties to expand to offering to stage 2 patients.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – it will be given according to licence.
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?	N/A

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
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 improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes it is a step-change.
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?	Immunotherapy side effects are well managed as the drugs are widely prescribed.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. How do data on real-world experience compare with the trial data?	No real world data in stage 2 melanoma.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	N/A

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. 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 also 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.

Table 2 Issues arising from technical engagement

Key issue 1: The results described in the company submission are not generalisable to adolescent patients (aged 12 to 17 years) because only one patient in this age category was allocated to each treatment arm of the included randomised controlled trial (RCT) (2 patients in total). **(Report sections 1.3 and 2.1)** *Would you expect the outcomes in adults with resected stage 2 melanoma to be generalisable to adolescents?*	Yes
Key issue 2: The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W. No clinical data are	No – the 400mg 6-weekly schedule is widely used in stage 3 disease.

available to demonstrate the comparability of efficacy and safety outcomes between the two dosing regimens therefore the relative effects are uncertain. **(Report sections 1.3 and 2.2)** *Would you expect there to be any differences in clinical outcomes between people with resected stage 2 melanoma receiving pembrolizumab 200 mg every 3 weeks (Q3W) and 400 mg every 6 weeks (Q6W)?*	
Key issue 3: There is a larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in UK clinical practice. This may result in an overestimation of the therapeutic benefits of the product for the overall population with stage 2B or 2C melanoma in the UK. **(Report sections 1.4, 3.2.3 and 3.2.5.2)** *What proportion of people have stage 2B versus stage 2C melanoma in UK clinical practice?* *Would you expect there to be differences in clinical outcomes in people with stage 2B and stage 2C melanoma who are treated with pembrolizumab?*	Would this mean an underestimate of the benefits?

Key issue 4: No data were provided for overall survival (OS) or distant-metastasis free survival (DMFS) and this hinders a full evaluation of effectiveness and cost effectiveness of the product. **(Report sections 1.4, 3.2.5.1 and 3.2.5.3)**	OS data not yet available.
Key issue 5: The use of separate regression models for the estimation of utility in the recurrence-free (RF) health state and disutility associated with adverse events (regression model 1) and utilities in the locoregional recurrence (LRR) and distant metastases (DM) health states (regression model 2) may have had an effect on the incremental cost-effectiveness ratio (ICER) of unclear magnitude and direction. **(Report sections 1.5 and 4.2.8)**	
Key issue 6: The assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs may not be plausible. The ICER may increase or decrease depending on the specific assumptions made. **(Report sections 1.5, 4.2.9 and 5.1)** *Would people treated with adjuvant pembrolizumab for stage 2 melanoma receive further systemic therapy after a locoregional recurrence?*	

Clinical expert statement

What is the expected duration of subsequent treatments for people with pre-progression distant metastases and post-progression distant metastases, respectively? *Is it appropriate to only apply terminal care costs for people with stage 2 melanoma who die having had distant metastases? Would people who die when they are recurrence free or die following a locoregional recurrence require terminal care?*	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patients with Sage 2 melanoma have a significant risk of relapse and death from melanoma.

The use of pembrolizumab significantly reduces this risk.

The drug is already approved and used safely or stage 3 disease

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

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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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Thank you for your time.

Clinical expert statement

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Part 1: Treating resected stage 2 melanoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Cambridge University Hospitals NHS Foundation Trust
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 resected stage 2 melanoma? ☐ A specialist in the clinical evidence base for resected stage 2 melanoma 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 did not submit one, I do not 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.	No links
8. What is the main aim of treatment for resected stage 2 melanoma?	To prevent disease recurrence

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A 30% risk reduction in relapse
10. In your view, is there an unmet need for patients and healthcare professionals in resected stage 2 melanoma?	Yes – patients with resected stage 2B and 2C melanoma have outcomes similar to those of resected stage 3A and 3B melanoma. Adjuvant therapy is available for resected stage 3 melanoma but not for stage 2 melanoma. This is in part simply a misperception that if '2' is a lower number than '3', the stage 2 patients must be at lower risk than stage 3. This is not the case.
11. How is resected stage 2 melanoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The NICE melanoma management guidelines are currently being updated and should be finalised in July22 (draft guidance was recently out for consultation). MelanomaFocus, the national melanoma charity, also offers clinical guidelines on contemporary issues that have arisen since publication of previous NICE guidance – for example, they have provided guidance on melanoma patient surveillance after resection of locoregional disease that hopefully will be incorporated into the new NICE guidance. The standard pathway is well defined: patients with primary melanoma undergo surgical excision. The Breslow depth of the primary melanoma +/- ulceration define the disease T stage. Stage 2 melanomas are >1mm thickness and will usually be offered wide local excision (WLE) and sentinel lymph node (SLN) biopsy. If the SLN is free of melanoma and there are no microsatellite lesions in the WLE, then the tumour stage is confirmed to be Stage 2. Since recurrence after resection of Stage 2b and 2c melanoma is relatively high, these patients are offered routine surveillance with 6 monthly imaging for 3 years and then annually to 5 years. This is usually undertaken by the dermatology or plastic surgery team responsible for the patient's initial tumour resection.

	The technology would mean offering these patients the opportunity to receive 1 year of adjuvant therapy. These patients would therefore be identified at MDT meetings and referred on to specialist oncology teams who would manage their treatment and most likely refer the patients back to the original dermatology/plastic surgery team for their ongoing surveillance.
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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is exactly the same as that already being used to treat resected stage 3 melanoma. Nb. We routinely use the 400mg 6 weekly schedule and although the Keynote 176 trial tested 200mng 3 weekly schedule, we see these as being equivalent in both efficacy and toxicity and given resource implications, would want to continue to utilise the 6 weeklyl regimen. The setting remains secondary care, specialist oncology teams. Because of the high prevalence of stage 2 melanoma, the volume of work for melanoma clinics as well as oncology day units and pharmacies will likely increase significantly and require additional resources. It is essentially 'more of the same' as opposed to requiring any new training etc.
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? • Do you expect the technology to increase health-related quality of life more than current care?	The goal of this treatment is to reduce recurrence and the number of melanoma patients developing metastatic disease from which they have a high chance of death and for which an increasing number of high cost, complex treatments are now being made available, which prolong median life expectancy and cure only the minority. Overall, it is expected to increase overall survival as well as health related QOL
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The benefits of treatment are best realised by people with a reasonable life expectancy. Given also the risk of life threatening and life changing side effects, there are some people less likely to benefit. These include elderly (eg.few people over the age of 80yrs I suspect will realistically benefit), or frail people, or those with multiple co-morbidities, or auto-immune diseases
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	From my personal experience of recruiting patients to the Keynote 716 trial, there may be a reticence of some people to accept treatment believing that if

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)	their SLN was negative, they are essentially cured. We may actually have to do some educational work to encourage patients to take up the offer of treatment!
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients should stop treatment if they relapse on treatment or experience significant 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	-
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 improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is a step change to addressing an unmet need and will help to address the need to recognise that stage 2b/c melanoma is equivalent to stage 3a/b melanoma in terms of its serious health risk.
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?	The immune-related adverse effects of pembrolizumab are well described and clinicians are familiar with their management. About 2 in 10 patients treated may have a serious adverse event requiring medical intervention such as use of immunosuppressive medications. About 1 in 10 will have a permananent life

	changing event, such as hypothyroidism requiring long term thyroxine replacement. The risk of treatment-related death is extremely low.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes Key outcomes – recurrence-free survival, distant-metastasis-free survival, patient QOL, all measured in the trial No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	The treatment is not available to this patient group outside of a clinical trial
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	-

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. 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 also 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.

Table 2 Issues arising from technical engagement

Key issue 1: The results described in the company submission are not generalisable to adolescent patients (aged 12 to 17 years) because only one patient in this age category was allocated to each treatment arm of the included randomised controlled trial (RCT) (2 patients in total). **(Report sections 1.3 and 2.1)** *Would you expect the outcomes in adults with resected stage 2 melanoma to be generalisable to adolescents?*	Diagnosis of melanoma in adolescent patients is very rare so this is to be expected. Yes – completely – we would very much want to offer this treatment to adolescents if approved for adults
Key issue 2: The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W. No clinical data are	We would not expect there to be a difference between the 2 schedules. There is published data suggesting equivalent PK parameters. I have led a UK health service

available to demonstrate the comparability of efficacy and safety outcomes between the two dosing regimens therefore the relative effects are uncertain. **(Report sections 1.3 and 2.2)** *Would you expect there to be any differences in clinical outcomes between people with resected stage 2 melanoma receiving pembrolizumab 200 mg every 3 weeks (Q3W) and 400 mg every 6 weeks (Q6W)?*	evaluation of the 2 schedules and shown no difference in either efficacy or toxicity between the 2 regimens (data not yet published, but abstract submitted to ESMO 2022). It would be very important to the NHS for us to be able to use the 6 weekly schedule in order to manage the impact on clinics, oncology day units and pharmacies.
Key issue 3: There is a larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in UK clinical practice. This may result in an overestimation of the therapeutic benefits of the product for the overall population with stage 2B or 2C melanoma in the UK. **(Report sections 1.4, 3.2.3 and 3.2.5.2)** *What proportion of people have stage 2B versus stage 2C melanoma in UK clinical practice?* *Would you expect there to be differences in clinical outcomes in people with stage 2B and stage 2C melanoma who are treated with pembrolizumab?*	I would imagine the proportion might be somewhere around 50:50, but I don't know for sure. I would not expect there to be a difference

Key issue 4: No data were provided for overall survival (OS) or distant-metastasis free survival (DMFS) and this hinders a full evaluation of effectiveness and cost effectiveness of the product. **(Report sections 1.4, 3.2.5.1 and 3.2.5.3)**	An update including DMFS data was presented at ASCO 2022 and is consistent with the fully published data - Median f/up 27mo DMFS @ 24mo: 88.1% vs 82.2% (treatment arm) HR 0.64 p=0.029 Consistent across all T categories and other subgroups 45 vs 79 distant mets as first event RFS @ 24mo: 81.2 vs 72.8% (treatment arm) HR 0.64 Consistent across all T categories
Key issue 5: The use of separate regression models for the estimation of utility in the recurrence-free (RF) health state and disutility associated with adverse events (regression model 1) and utilities in the locoregional recurrence (LRR) and distant metastases (DM) health states (regression model 2) may have had an effect on the incremental cost-effectiveness ratio (ICER) of unclear magnitude and direction. **(Report sections 1.5 and 4.2.8)**	-
Key issue 6: The assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs may not be plausible. The ICER may increase or decrease depending on	

Clinical expert statement

the specific assumptions made. **(Report sections 1.5, 4.2.9 and 5.1)** *Would people treated with adjuvant pembrolizumab for stage 2 melanoma receive further systemic therapy after a locoregional recurrence?* *What is the expected duration of subsequent treatments for people with pre-progression distant metastases and post-progression distant metastases, respectively?* *Is it appropriate to only apply terminal care costs for people with stage 2 melanoma who die having had distant metastases? Would people who die when they are recurrence free or die following a locoregional recurrence require terminal care?*	This is an interesting issue, which may be impacted by timing of recurrence and BRAF status. If disease recurred during or shortly after completing treatment, I think they would not be treated again. If a patient recurred many years down the line, it is possible that this might be considered. In addition, for BRAF mutant patients, the question is whether they might be offered BRAF-targeted therapy which is currently approved for resected stage 3 melanoma. The median duration of treatment for patients with distant metastases receiving systemic therapy is probably now around 12 – 18 months. Median duration post progression (ie 2nd line) I suspect is around 6 months I think the type of terminal care needed in general will be different for someone dying from metastatic melanoma compared with someone dying of most other causes. The former would reasonably be attributed higher costs, in my view. However, it is fair to say that nowadays people are kept alive with many chronic conditions due to intensive medical and care support such that people dying of non-melanoma cause probably use up just as many resources, just in different packages – perhaps not necessarily a classical terminal/end of life care package that we have historically attributed to cancer care.
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The Keynote 716 trial has shown a clinically significant and meaningful benefit of adjuvant pembrolizumab in terms of reducing risk of recurrence and distant metastases in patients with resected stage 2b and 2c melanoma
Patients with stage 2b and 2c melanoma have outcomes similar to that of stage 3a and 3b melanoma, to whom adjuvant pembrolizumab is already routinely offered
Pembrolizumab is generally well tolerated by patients
Preventing the need to treat people for distant metastatic melanoma has got to be a good thing for patients as well as our health service and our health economy
Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

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

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (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 about living with resected stage 2 melanoma or caring for a patient with resected stage 2 melanoma.

The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. 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. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient 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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

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. 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.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by the end of **Friday 15 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Part 1: Living with this condition or caring for a patient with resected stage 2 melanoma

Table 1 About you, resected stage 2 melanoma, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with melanoma? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with melanoma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Melanoma Focus
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with melanoma? **If you are a carer (for someone with melanoma) please share your experience of caring for them**	My late wife developed Stage 4 melanoma in 2016 and died in October 2018. I cared for her during the later period when she became very unwell. About 12 months later, in December 2019, I developed what turned out to be Stage 2B melanoma on my ankle. It was removed very quickly and I later had a lymph node removed and an area around the cancer taken off. Both were clear. I volunteered for the trial and did it for about 5 months. I assume that I had the active treatment as I developed severe discoid eczema coupled with less severe constipation and a dry mouth. The eczema took some time to clear (and has since recurred, but less severely). I would have continued if I was actually being treated but I decided not to continue. I have had regular scans since without any recurrence.
7a. What do you think of the current treatments and care available for resected stage 2 melanoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**I was treated very speedily and efficiently to remove my melanoma.** **My treatment and the trials have not been affected by Covid, unlike some others.**
8. If there are disadvantages for patients of current NHS treatments for resected stage 2 melanoma (for example, how the treatment is given or taken, side effects of treatment, and any others) please describe these	Not for the treatment I underwent.
9a. If there are advantages of pembrolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your	**Not relevant save that I suffered the adverse consequences which I assume came from the pembrolizumab.**

ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pembrolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of pembrolizumab over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	See above- adverse side effects. However if the risk of recurrence is reduced it is worth doing.
11. Are there any groups of patients who might benefit more from pembrolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering resected stage 2 melanoma and pembrolizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	I think those on the trial should be told after completion whether they have been on placebo.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also 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, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Key issue 1: The results described in the company submission are not generalisable to adolescent patients (aged 12 to 17 years) because only one patient in this age category was allocated to each treatment arm of the included randomised controlled trial (RCT) (2 patients in total). **(Report sections 1.3 and 2.1)** *Would you expect the outcomes in adults with resected stage 2 melanoma to be generalisable to adolescents?*	

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Key issue 2: The recommended dose of pembrolizumab in adults is either 200 mg Q3W or 400 mg Q6W. No clinical data are available to demonstrate the comparability of efficacy and safety outcomes between the two dosing regimens therefore the relative effects are uncertain. **(Report sections 1.3 and 2.2)** *Would you expect there to be any differences in clinical outcomes between people with resected stage 2 melanoma receiving pembrolizumab 200 mg every 3 weeks (Q3W) and 400 mg every 6 weeks (Q6W)?*	
Key issue 3: There is a larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in UK clinical practice. This may result in an overestimation of the therapeutic benefits of the product for the overall population with stage 2B or 2C melanoma in the UK. **(Report sections 1.4, 3.2.3 and 3.2.5.2)** *What proportion of people have stage 2B versus stage 2C melanoma in UK clinical practice?*	

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Would you expect there to be differences in clinical outcomes in people with stage 2B and stage 2C melanoma who are treated with pembrolizumab?	
Key issue 4: No data were provided for overall survival (OS) or distant-metastasis free survival (DMFS) and this hinders a full evaluation of effectiveness and cost effectiveness of the product. **(Report sections 1.4, 3.2.5.1 and 3.2.5.3)**	
Key issue 5: The use of separate regression models for the estimation of utility in the recurrence-free (RF) health state and disutility associated with adverse events (regression model 1) and utilities in the locoregional recurrence (LRR) and distant metastases (DM) health states (regression model 2) may have had an effect on the incremental cost-effectiveness ratio (ICER) of unclear magnitude and direction. **(Report sections 1.5 and 4.2.8)**	
Key issue 6: The assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs may not be plausible. The ICER may	

Patient expert statement

increase or decrease depending on the specific assumptions made. **(Report sections 1.5, 4.2.9 and 5.1)** *Would people treated with adjuvant pembrolizumab for stage 2 melanoma receive further systemic therapy after a locoregional recurrence?* *What is the expected duration of subsequent treatments for people with pre-progression distant metastases and post-progression distant metastases, respectively?* *Is it appropriate to only apply terminal care costs for people with stage 2 melanoma who die having had distant metastases? Would people who die when they are recurrence free or die following a locoregional recurrence require terminal care?*	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Anything that can be done to reduce the risk of recurrence of melanoma is worth careful consideration.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]

ERG response to the technical engagement response form

Produced by	Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)
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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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Abbreviations

1L	First-line
AACR	American Association for Cancer Research
ADR	Adverse drug reaction
AE	Adverse events
AEOSI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ApaT	All-patients-as-treated
ASCO	American Society of Clinical Oncology
BCG	Bacillus Calmette-Guérin
BIC	Bayesian information criterion
bw	Body weight
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CS	Company submission
CSF	Colony stimulating factor
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DM	Distant metastases
DMFS	Distant metastasis-free survival
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
EBM	Evidence-based medicine
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EHR	Electronic health record
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EuroQol-5 Dimension
EQ-5D-5L	EuroQol-5 Dimension-5 level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE	Fixing errors
FV	Fixing violations
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HSUV	Health State Utility Value

HUI	Health Utilities Index
IA2	Second interim analysis
IA3	Third interim analysis
ICER	Incremental cost-effectiveness ratio
IFNα-2b	Interferon-alpha 2b
ITT	Intention-to-treat
KM	Kaplan–Meier
KN-716	KEYNOTE-716 (trial)
KPS	Karnofsky performance status
KSR	Kleijnen Systematic Reviews Ltd
LPI	Last patient in
LPLV	Last-patient-last-visit
LPS	Lansky performance status
LRR	Locoregional recurrence
LS	Least squares
LY	Life year
M0	Metastases not present
M1C	Metastases present in a non-central nervous system location
M1D	Metastases present in a central nervous system location
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities (MIMS
MJ	Matters of judgement
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme
N	Number of patients
N/A	Not available
N0	(Lymph) node has no cancer
N1C	(Lymph) node has presence of in-transit, satellite and/or microsatellite metastases
NCI	National Cancer Institute
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Heath and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reached
NX	(Lymph) node cannot be evaluated
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD-1	Programmed (cell) death protein 1
PD-L 1/2	Programmed (cell) death ligand ½
PEG-IFNα-2b	Pegylated interferon-alpha 2b
Pembro	Pembrolizumab
PFS	Progression-free survival
PHE	Public Health England
PICOTS	Population, interventions, comparators, outcomes, timeframe, study design
PK	Pharmacokinetic(s)
POL-103A	Polyvalent melanoma vaccine 103A
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRFS	Progression/recurrence-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
QxW	Every x weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RF	Recurrence-free
RFS	Recurrence-free survival
rhGM-CSF	Recombinant human granulocyte macrophage-colony stimulating factor
RoB	Risk of bias
RoB2	Cochrane risk of bias tool version 2
SAE	Serious adverse event
SD	Standard deviation
SF-6D	Short-form-6 dimension
SIGN	Scottish Intercollegiate Guidelines Network
SITC	Society for Immunotherapy of Cancer
SLN	Sentinel lymph node
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Society for Melanoma Research
STA	Single technology appraisal
TA	Technology appraisal
TE	Technical engagement
TEAE	Treatment-emergent adverse event
TNM	Tumour, nodes, metastases
TRAE	Treatment-related adverse event
TSD	Technical Support Document
T-Stage	Tumour stage
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
UMC	University Medical Centre
US	United States
USON	United States Oncology Network
UV	Ultraviolet
VAS	Visual analogue scale

Introduction

This document is the Evidence Review Group's (ERG's) response to comments and additional data provided by the company as part of the technical engagement (TE) process for pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence.[1]

Key issues

Key issue 1: The results described in the company submission (CS) are not generalisable to adolescent patients (aged 12 to 17 years) because only one patient in this age category was allocated to each treatment arm of the included randomised controlled trial (RCT; 2 patients in total).

The company provided some further comments in relation to generalisability of results to adolescent patients, together with cited literature intended to support the points made. No new evidence, data or analyses were provided.[1]

ERG comment: The ERG acknowledges the arguments proposed by the company. The ERG would like to clarify that whilst criticism of the trial recruitment strategy was not intended, it is important to highlight the persisting uncertainty around generalisability to adolescent patients in light of the very small number of trial participants within this age category.

Of note, the company actually highlighted this point themselves within their TE response, i.e. *"the rarity of adolescent melanoma has meant that adjuvant treatment for patients in this age group has been understudied"*,[1] and provide supporting evidence of incidence estimates for European patients with melanoma aged under 20 years.[2] Therefore, the ERG still stands by its original comments.

Key issue 2: The recommended dose of pembrolizumab in adults is either 200 mg every three weeks (Q3W) or 400 mg every six weeks (Q6W). No clinical data are available to demonstrate the comparability of efficacy and safety outcomes between the two dosing regimens therefore the relative effects are uncertain.

The company proposed further comments in relation to the comparability between the two dosing regimens of pembrolizumab in adults with resected stage 2 melanoma and cited references that were intended to substantiate its arguments. No new evidence, data or analyses were provided.[1]

ERG comment: In its response to technical engagement (TE), the company claimed that *"clinical evidence, alongside dose/exposure modelling and simulation of dose/exposure relationships for efficacy and safety, has demonstrated that there are no clinically significant differences in efficacy or safety among the different posology options"*.[1] Several references were cited with the intention of supporting this claim and these are discussed further in the following paragraphs.

The European Medicines Agency (EMA) Summary of Product Characteristics for Keytruda[3] confirms the dosing options for pembrolizumab as outlined in the CS[4] and in the company's TE response.[1] Under a sub-heading *"Clinical efficacy and safety"* (Section 5.1), the following is stated: *"Pembrolizumab doses of 2 mg/kg body weight (bw) every 3 weeks, 10 mg/kg bw every 3 weeks, and 10 mg/kg bw every 2 weeks were evaluated in melanoma or previously treated non-small cell lung carcinoma (NSCLC) clinical studies. Based on the modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg every 3 weeks, 2 mg/kg bw every 3 weeks, and 400 mg every 6 weeks"*.

The document went on to summarise findings from several KEYNOTE studies involving a variety of study designs, dosing regimens of pembrolizumab and a range of indications including melanoma and

NSCLC. None of the results related to direct comparisons between pembrolizumab 200 mg Q3W and 400 mg Q6W and several of the cited studies did not evaluate either of these doses. Furthermore, there was no mention of an indirect treatment comparison to assess the relative clinical effectiveness of the two dosing regimens.[3]

A second EMA document (Keytruda: Procedural steps taken and scientific information after the authorisation) described the process leading to the approval of the 400 mg Q6W dose of pembrolizumab.[5] This document cited the KEYNOTE-555 study, an interventional pharmacokinetic (PK) evaluation comparing pembrolizumab 200 mg Q3W with pembrolizumab 400 mg Q6W in patients with advanced melanoma, highlighted by the company to support its arguments about the presence of clinical evidence. However, scrutiny of the KEYNOTE-555 reference (a conference abstract) indicated that whilst PK metrics were provided in a table for both dosing regimen groups, clinical efficacy and safety outcomes (objective response rate [ORR], complete response [CR], partial response [PR], progression-free survival [PFS] and adverse events [AEs]) were only reported for patients receiving the Q6W regimen[6] therefore evaluation of a between-group comparisons was not possible.

A report of the Melanoma Virtual National Advisory Board Meeting held during December 2021 suggested that the consensus from a group of eight clinical experts indicated a preference for the Q6W dosing regimen in light of NHS capacity issues and concerns relating to coronavirus disease 2019 (COVID-19).[7] Clinicians' preference for the Q6W regimen was also reported from a technology appraisal (TA766) of pembrolizumab evaluated in patients with a different disease stage (completely resected stage 3 melanoma).[8]

Following on from the above, the company cited *"an ongoing real-world study of the prescribing pattern of pembrolizumab across stage 2-4 melanoma following the Q6W licensing date"* claiming that "[redacted]." The company also asserted that "[redacted]".[9]

This document was only made available to the ERG at a very late stage during the TE critique period. The presented data include [redacted]. The adjustment covariates included baseline: [redacted]. The different types of toxicity outcomes included: [redacted].

The presented estimates (see pages 8 and 9 of document provided by the company) suggested [redacted]: adjusted OR [redacted].[9] Estimates for two treatment response outcomes/populations were presented: [redacted] respectively.[9]

The ERG noted several issues with the above reference.[9] The Table of baseline characteristics indicated that n=[redacted] and n=[redacted] participants received the Q3W and Q6W regimens respectively and analyses were based on all patients described at baseline. There was no information about the source or methods of recruiting these participants. A small proportion of participants were classified as having stage 2 disease: [redacted]%) in the Q3W group and [redacted]%) receiving the Q6W regimen. The proportions of participants receiving treatment in the adjuvant and metastatic/unresectable settings were: [redacted]% and [redacted]%; and [redacted]% and [redacted]% for Q3W and Q6W, respectively. Therefore this study population had very limited relevant to the NICE Final Scope[10] or the CS.[4] No details of the study methods were provided and the nature of the treatment response outcomes were not clear from the definitions given. The two outcomes [redacted]) were not explained further and do not appear as part of the NICE Final Scope[10] or the CS.[4]

In summary, the ERG acknowledges the arguments proposed by the company and has considered these along with the cited references. The company highlights the related approvals for the Q6W dosing regimen and the evidence that the higher and less frequent dose of pembrolizumab is preferred by clinicians and patients within the adjuvant setting. However, these aspects are not the same as clinical evidence to demonstrate the relative effectiveness of pembrolizumab 200 mg Q3W versus pembrolizumab 400 mg Q6W in the relevant population and none of the cited references substantiate the company's claims that efficacy and safety profiles are comparable. Therefore, the ERG maintains its original critique, i.e. the relative clinical effectiveness of the two dosing regimens in patients with stage 2 resected melanoma is uncertain.

Key issue 3: There is a larger proportion of patients with less severe disease (stage 2B melanoma) recruited to the included RCT compared with those seen in UK clinical practice. This may result in an overestimation of the therapeutic benefits of the product for the overall population with stage 2B or 2C melanoma in the UK.

The company commented on the generalisability of results to the UK population in relation to the distribution of disease stage. Three references were cited as supporting evidence. No new evidence, data or analyses were provided.[1]

ERG comment: One of the cited references was the report of the Melanoma Virtual National Advisory Board Meeting held during December 2021 already mentioned under Key issue 2 above.[7] There appeared to be no information in this report to support the company's claim that *"clinical experts have confirmed at an advisory board that the baseline characteristics of patients in the KEYNOTE-716 are representative of the population in England"*. The ERG noted an item on the meeting agenda entitled *"How accurately does this pathway reflect current clinical practice"* but no information about the content of the ensuing discussion was provided.[1]

The company cited a document from Public Health England (PHE) (now called the UK Health Security Agency [UKHSA]) that was also cited in the CS,[4] providing separate prevalence estimates for patients with stage 2B and 2C melanoma in England during the period 1995 to 2017.[11] The PHE estimates reported in the CS were checked for accuracy by the ERG (and found to be correct) at the time of preparing the ERG report.[12]

In its TE response, the company describes the differences between the staging distribution for KEYNOTE-716 and PHE as being minor, i.e. *"a comparison between the KEYNOTE-716 population and Public Health England (PHE) data indicates that that a slightly lower proportion of patients have stage 2B melanoma – and therefore a slightly higher proportion of patients have stage 2C melanoma –*

in clinical practice compared with KEYNOTE-716. However, the observed differences in staging between the KEYNOTE-716 and PHE datasets are relatively small (64.0% versus 57.0% for stage 2B, and 34.8% versus 43.0% for stage 2C)".[1] The ERG does not agree that the percentage point differences between the prevalence estimates are trivial (7.0 for stage 2B and 8.2 for 2C). In the TE response, the company also urges caution when comparing estimates between the two different data sources.[1] The ERG agrees that care in interpretation is merited because of possible differences in data collection methods and quality of retrieval.

The company also mentioned the clinical study report (CSR) for KEYNOTE-716[13] within their TE response,[1] highlighting the signposting of this during the response to clarification questions (question A10).[14] The clarification response specified tables in the CSR (14.2-12 and 14.2-13) that presented the results of subgroup analyses according to stage 2B and 2C disease.[13] As noted in the ERG report (Sections 3.2.3 and 3.2.5.2), the hazard ratio (HR) estimates for pembrolizumab versus placebo for recurrence-free survival (RFS) were [redacted] and 0.82 (95% CI 0.54 to 1.26), respectively.[12] These data suggest a finding in favour of pembrolizumab compared with placebo for patients with stage 2B melanoma and no between-group difference for those with stage 2C melanoma. In their TE response the company stated that *"subgroup analyses in the KEYNOTE-716 trial were not statistically powered to detect differences in efficacy and therefore, any observed difference in efficacy of pembrolizumab in stage 2B compared with stage 2C patients could simply be due to chance"*.[1] The ERG is of the view that for this very reason (i.e. the potential for lack of statistical power), the possibility of between-subgroup differences (e.g. type II error) cannot be discounted.

After considering the company's arguments, the ERG considers that there is persisting uncertainty about (1) the comparability of clinical effectiveness between patients with stage 2B and 2C melanoma; and the extent to which results from the KEYNOTE-716 trial can be generalised to the population in the UK in terms of disease stage distribution. The ERG concludes that the risk of overestimation of the therapeutic benefits of pembrolizumab for the overall population with stage 2B or 2C melanoma in the UK still stands.

Key issue 4: No data were provided for overall survival (OS) or distant metastasis-free survival (DMFS) and this hinders a full evaluation of effectiveness and cost effectiveness of the product.

The company provided new data on several outcomes including recurrence-free survival (RFS), DMFS and OS in their TE response document[1] and an accompanying appendix.[15] These data (interim analysis [IA] 3 of the KEYNOTE-716 trial; data cut-off 4th January 2022) served to update those in the original CS (based on IA2 of the same trial; data cut-off 21st June 2021). According to the company, the analyses derived from IA3 presented in the TE appendix were an update to Sections B.2.4.2, B.2.6 and B.2.10 of Document B of the CS.[15] The following sections provide a summary of results from IA3 of KEYNOTE-716 as presented by the company.[1, 15]

4.1. Patient disposition in at the time of IA3

Table 1 summarises the disposition of patients in the intention-to-treat (ITT) population at IA3 and shows the reasons for patients discontinuing the trial and study treatment. The median duration of follow-up at IA3 (defined as time from randomisation to data cut-off) was reported as 27.4 months (range 14.0 to 39.4 months).[15]

Table 1. Disposition of patients in the ITT population at the time of IA3

	Pembrolizumab (N=487)	Placebo (N=489)
Trial disposition		
Discontinued	[redacted]	[redacted]
Death	[redacted]	[redacted]
Associated with COVID-19	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Not associated with COVID-19, no further information	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Associated with COVID-19, no further information	[redacted]	[redacted]
Not associated with COVID-19, no further information	[redacted]	[redacted]
Not associated with COVID-19, subsequently died	[redacted]	[redacted]
Participants ongoing	[redacted]	[redacted]
Participant study medication disposition in Part 1		
Started	483	486
Completed	320 (66.3)	368 (75.7)
Discontinued	163 (33.7)	118 (24.3)
AE	85 (17.6)	23 (4.7)
Associated with Covid-19	1 (0.2)	1 (0.2)
Lost to follow-up	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]
Physician decision	10 (2.1)	4 (0.8)
Associated with COVID-19	0 (0.0)	2 (0.4)
Protocol violation	[redacted]	[redacted]
Relapse/recurrence	24 (5.0)	61 (12.6)
Withdrawal by subject	40 (8.3)	27 (5.6)
Associated with COVID-19	6 (1.2)	7 (1.4)

Based on Table 1 of the TE response appendix[15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17]
AE = adverse event; COVID-19 = coronavirus disease 2019; CSR = clinical study report; ITT = intention-to-treat; TE = technical engagement

4.2. Recurrence-free survival at the time of IA3

The results of the RFS analysis (summarised in Table 2 and Figure 1) suggest a more favourable result for pembrolizumab compared with placebo.

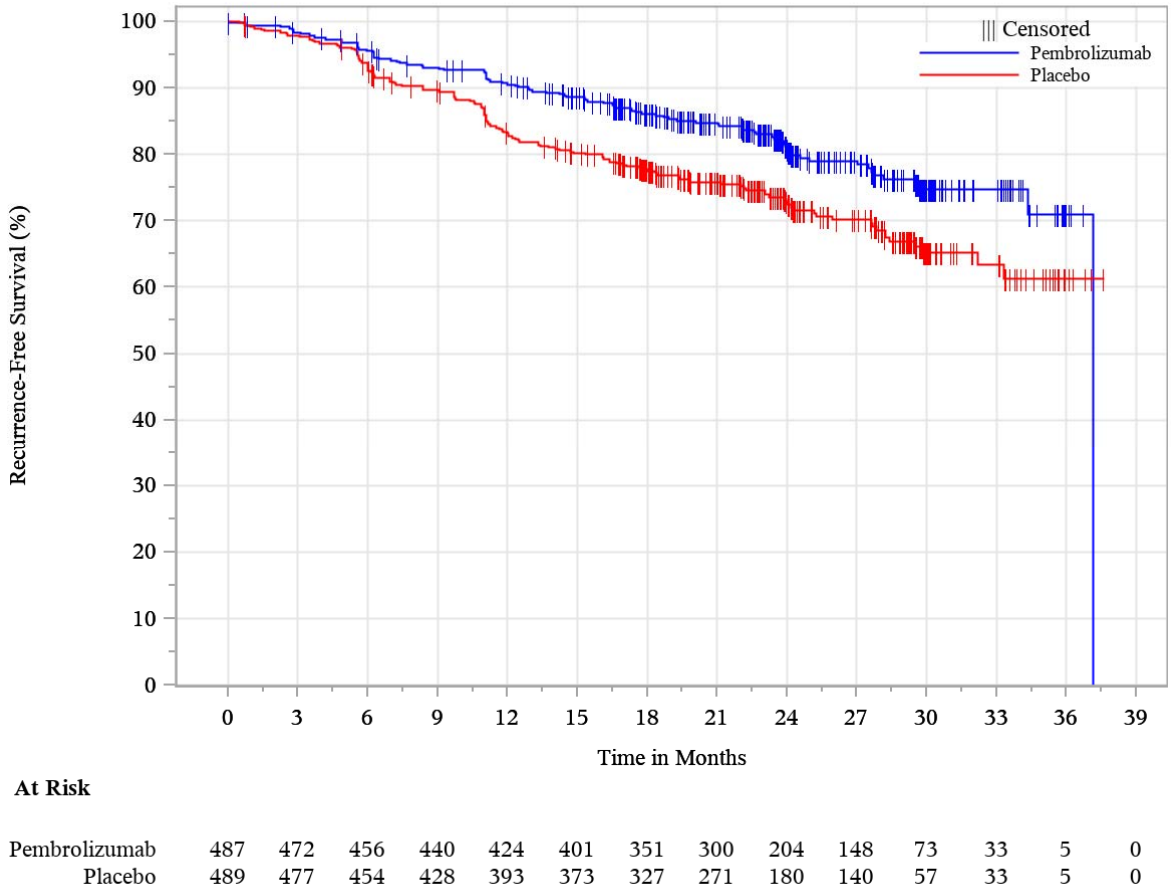
Table 2. Analysis of RFS (primary censoring rule) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/100 Person-months	Median RFS† (months) (95% CI)	RFS Rate at 24 months† (%) (95% CI)
Pembrolizumab	487	95 (19.5)	10653.6	0.9	37.2 (NR, NR)	81.2 [redacted]
Placebo	489	139 (28.4)	10200.7	1.4	NR (NR, NR)	72.8 [redacted]

Pairwise Comparisons	HR‡, (95% CI)
Pembrolizumab vs. Placebo	0.64 (0.50, 0.84)

Based on Table 2 of the TE response appendix[15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
†From product-limit (Kaplan–Meier) method for censored data.
‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
CI = confidence interval; CSR = clinical study report; HR = hazard ratio; ITT = intention to treat; NR = not reached; RFS = recurrence-free survival; TE = technical engagement

Figure 1. Kaplan-Meier estimates of RFS (primary censoring rule; ITT population)



Based on Figure 1 of the TE response appendix[15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
CSR = clinical study report; ITT = intention-to-treat; RFS = recurrence-free survival; TE = technical engagement

The RFS rate over time is summarised in Table 3 and a breakdown of the type of first RFS event is presented in Table 4.

Table 4.3. RFS rate over time

RFS rate at time point	Pembrolizumab (N=487), % (95% CI)†	Placebo (N=489), % (95% CI)†
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	81.2 [redacted]	72.8 [redacted]

30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

Based on Table 3 of the TE response appendix [15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
[†]From product-limit (Kaplan-Meier) method for censored data.
CI = confidence interval; CSR = clinical study report; RFS = recurrence-free survival; TE = technical engagement

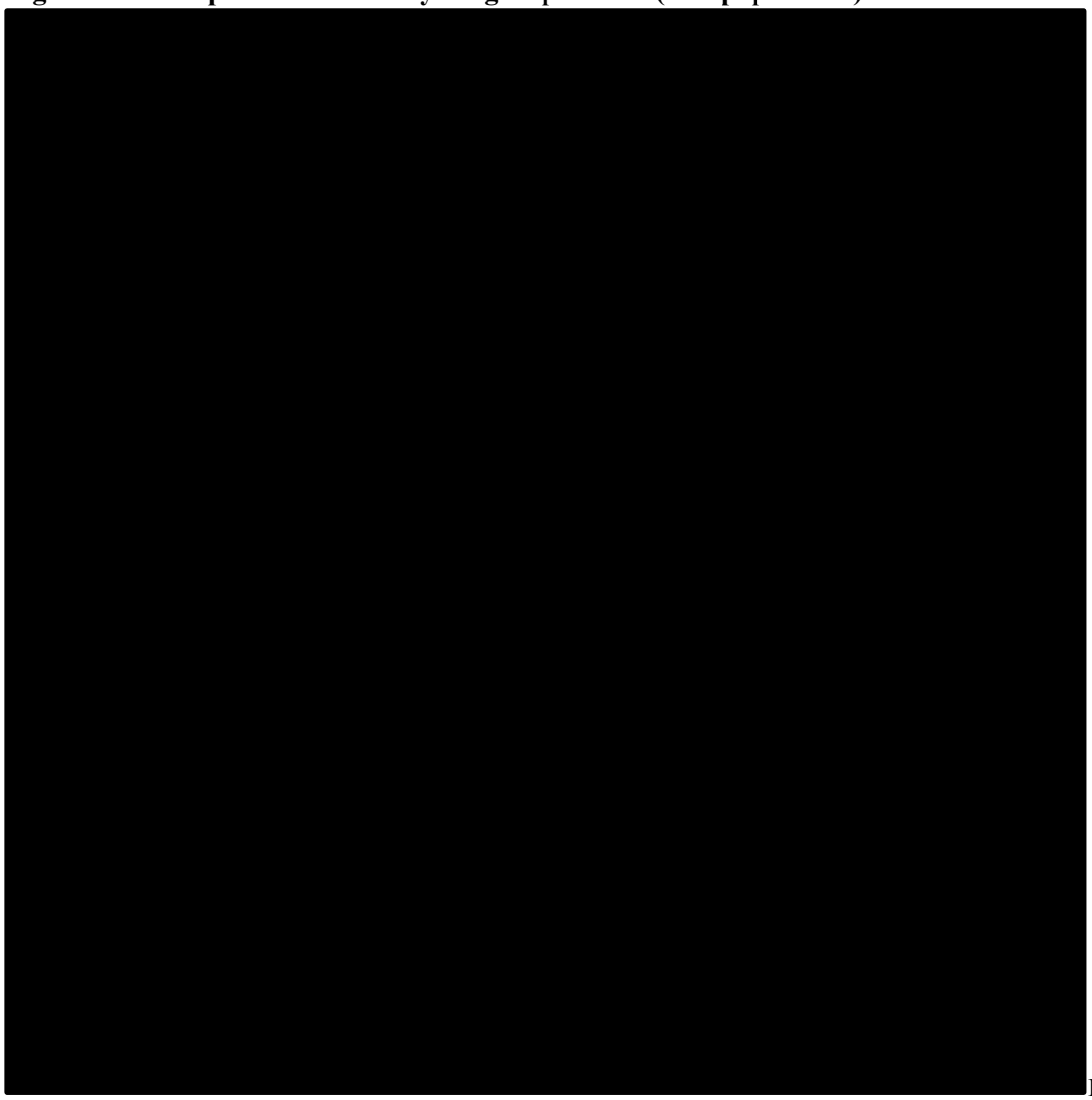
Table 4. Type of first RFS event (ITT population)

Type of first event in RFS analysis	Pembrolizumab (N=487), n (%)	Placebo (N=489), n (%)
All events	95 (20)	139 (28)
Local[†], regional[‡] and loco-regional[§]	46 (9)	56 (11)
Distant[¶,††]	45 (9)	77 (16)
Death	4 (1)	6 (1)

Based on Table 4 of the TE response appendix [15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
[†]Local: Tumour recurrence is in the immediate vicinity of primary tumour (i.e. skin, in transit lesions, micro-satellite metastases);
[‡]Regional: Regional Lymph node basin involvement;
[§]Loco-regional: Tumour recurrence is in the immediate vicinity of primary tumour and regional lymph node basin metastasis is noted. Tumour has not spread beyond regional lymph nodes;
[¶]Distant: Metastasis is beyond the regional lymph node basin;
[††]Includes distant event diagnosed within 30 days from Local/Regional/Locoregional event.
CSR = clinical study report; ITT = intention-to-treat; RFS = recurrence-free survival; TE = technical engagement

The company also provided a forest plot of subgroup data for RFS (Figure 2). This suggested similar results to the main analysis (Table 2) i.e., more favourable results for pembrolizumab when compared with placebo, except for the following subgroups: T-Stage T4b; female sex; and United States geographical region.[15]

Figure 2. Forest plot of RFS HR by subgroup factors (ITT population)



Based on Figure 5 of the TE response appendix [15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.

A subgroup with number of participants <10% of the ITT population is not displayed on the plot.

*Based on actual baseline tumour stage collected on eCRF

CI = confidence interval; CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intention to treat; RFS = recurrence-free survival; TE = technical engagement

4.3. Distant metastasis-free survival at the time of IA3

The results of the DMFS analysis (summarised in Table 5 and Figure 3) suggest a more favourable result for pembrolizumab compared with placebo. The company commented that *"data remain immature with median DMFS not being reached in either treatment arm as of the data cut-off"*[1] (this is indicated in Table 5). The DMFS rate over time is shown in Table 6.

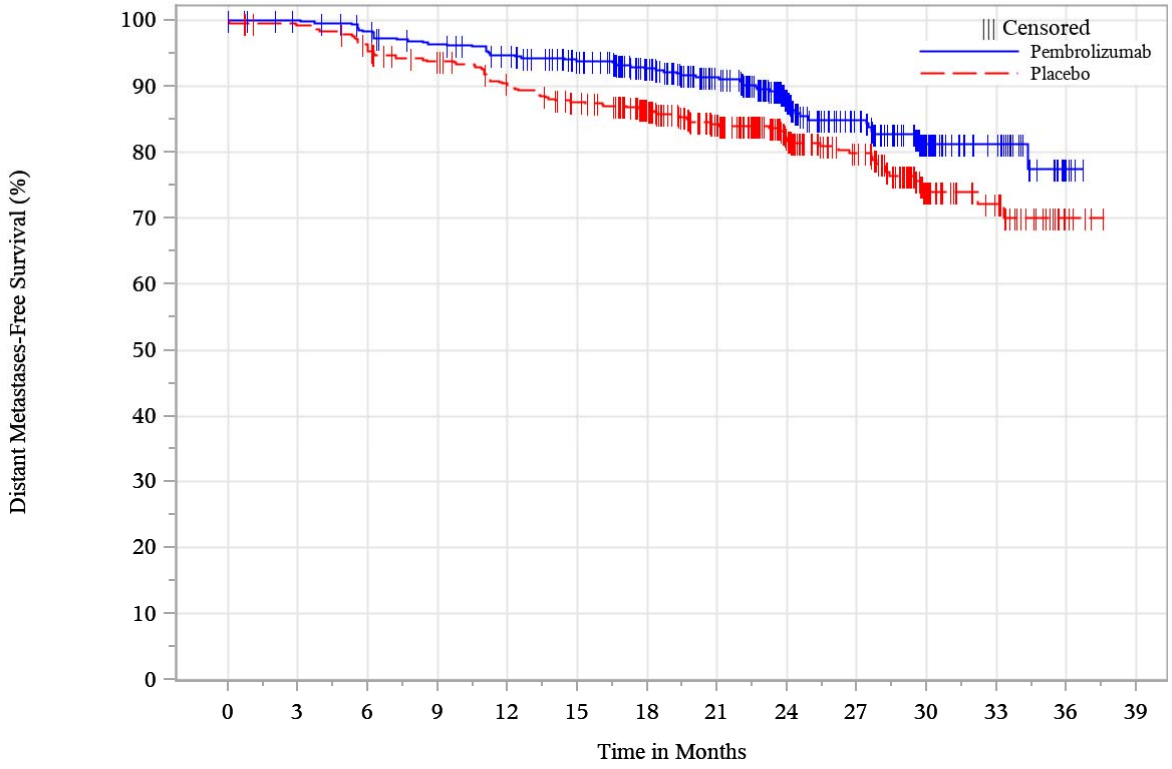
Table 4.5. Analysis of DMFS (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/100 Person-months	Median DMFS† (months) (95% CI)	DMFS Rate at 24 months† (%) (95% CI)

Pembrolizumab	487	63 (12.9)	11100.8	0.6	NR (NR, NR)	88.1 [redacted]
Placebo	489	95 (19.4)	10870.0	0.9	NR (NR, NR)	82.2 [redacted]
Pairwise Comparisons					**HR[‡] (95% CI)**	**P value[§,¶]**
Pembrolizumab vs. Placebo					0.64 (0.47, 0.88)	0.00292

Based on Table 5 of the TE response appendix [15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
[†]From product-limit (Kaplan–Meier) method for censored data.
[‡]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
[§]One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b).
CI = confidence interval; CSR = clinical study report; DMFS = distant metastasis-free survival; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; TE = technical engagement

Figure 3. Kaplan-Meier estimates of DMFS (ITT population)



At Risk

Pembrolizumab	487	480	469	456	443	421	375	318	217	157	79	35	5	0
Placebo	489	482	465	448	424	406	363	303	204	156	65	37	5	0

Based on Figure 2 of the TE response appendix [15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
CSR = clinical study report; DMFS = distant metastasis-free survival; ITT = intention-to-treat; TE = technical engagement

Table 6. DMFS rate over time

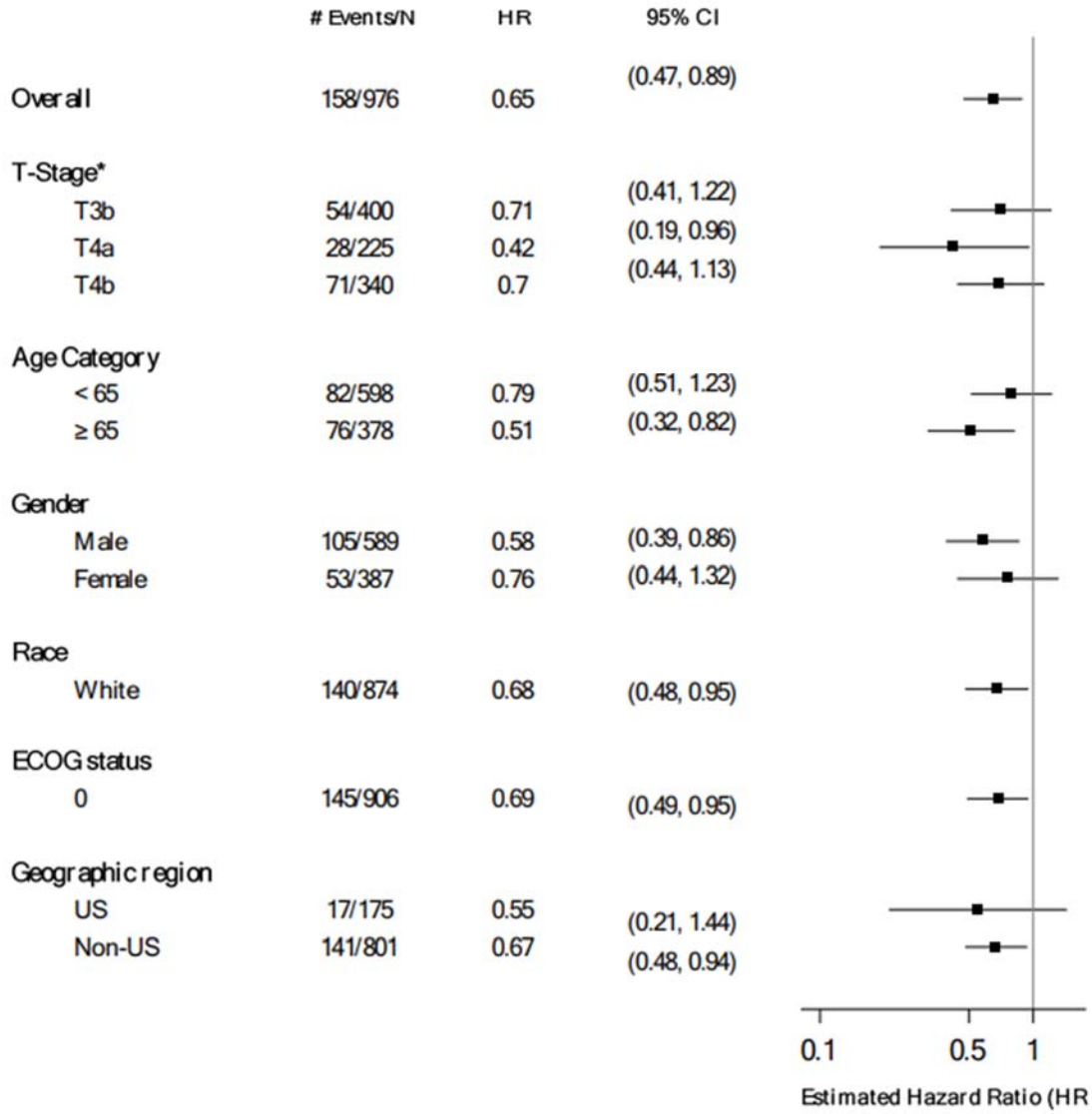
RFS rate at time point	Pembrolizumab (N=487), % (95% CI)[†]	Placebo (N=489), % (95% CI)[†]
6 months	[redacted]	[redacted]
12 months	94.7 [redacted]	90.2 [redacted]
18 months	[redacted]	[redacted]

24 months	88.1 [redacted]	82.2 [redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

Based on Table 6 of the TE response appendix [15] which cites the CSR of KEYNOTE-716[16] and Long et al. 2022[17] as the primary sources.
[†]From product-limit (Kaplan–Meier) method for censored data.
CI = confidence interval; CSR = clinical study report; DMFS = distant metastasis-free survival; TE = technical engagement

The company also provided a forest plot of subgroup data for DMFS (Figure 4). This suggested similar results to the main analysis (Table 5) i.e., more favourable results for pembrolizumab when compared with placebo, except for the following subgroups: T-Stages T3b and T4b; age younger than 65 years; female sex; and US geographical region.[15]

Figure 4. Forest plot of DMFS HR by subgroup factors (ITT population)



Based on Figure 6 of the TE response appendix [15] which cites Long et al. 2022[17] as the primary source.
A subgroup with number of participants < 10% of the ITT population is not displayed on the plot.
*Based on actual baseline tumour stage collected on eCRF

CI = confidence interval; DMFS = distant metastasis-free survival; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; HR = hazard ratio; ITT = intention to treat; TE = technical engagement

In terms of further analyses, the company mentioned that *"as per the protocol, the final analysis of DMFS is scheduled at the fourth interim analysis (IA4; after [redacted] observed DMFS events). The last-patient-last-visit (LPLV) for IA4 is currently projected between [redacted]"*.[1]

4.4 Overall survival at the time of IA3

In the TE appendix, the company reported that *"as of the IA3 data cut-off, insufficient events had occurred to enable analysis of OS to be conducted; [redacted] OS events were reported representing [redacted]% of the final number of events needed for analysis. This secondary endpoint will be analysed at a separate future IA once the prespecified protocol criteria of target event numbers has been reached"*.[15]

In the main TE document, the following additional details were outlined:[1]

"As of IA3, [redacted] OS events were reported representing [redacted]% of the final number of events needed for analysis. The current projected timings listed below are assuming events continue to accrue as expected for the protocol specified analyses:
First interim analysis for OS (IA5; ~[redacted] events): [redacted]
Final analysis for OS (~[redacted] events): [redacted]".

4.5 Other outcomes at the time of IA3

The company reported results for health-related quality of life (HRQoL) outcomes at week 72: EuroQol-5 Dimension-5 level visual analogue score (EQ-5D-5L VAS); and the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30). Further details of these can be found in the TE appendix.[15]

ERG comment: In the main TE response document, the company also proposed arguments in relation to the use of RFS and DMFS as surrogate measures for OS and cited references intended to support the points made.[1] Although the company try to make a case for a robust relationship between OS and these other outcome variables, the cited evidence is not convincing being related to an irrelevant population (those with stage 3 melanoma),[8] or based on correlation analysis[18] or brief details within a conference abstract.[19]

Key issue 5: The use of separate regression models for the estimation of RF utility and AE disutility (regression model 1) and LRR and DM utilities (regression model 2) may have had an effect on the ICER of unclear magnitude and direction.

ERG comment: The company's scenario analysis indicated that the impact of using separate regression models or a single regression model to estimate health state utilities is minimal. Hence this key issue can be considered as resolved.

Key issue 6: The assumptions regarding the proportion and duration of subsequent treatments and the application of terminal care costs may not be plausible. The ICER may increase or decrease depending on the specific assumptions made.

ERG comment: The company provides additional information to support its base-case. However, the ERG regards this issue as a matter of judgement that is relevant for the committee to consider, also given that assuming alternative subsequent treatment proportions/market share in the locoregional recurrence (LRR) health state was the most influential adjustments in the ERG base-case while

assuming no subsequent treatment costs in the distant metastases (DM) health state was among the most influential ERG scenarios.

References

[1] Merck Sharp & Dohme (UK) Limited. *Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]: Technical engagement response* 2022

[2] Merck Sharp & Dohme (MSD) Limited. EU5 (DE, ES, FR, IT, UK) / Melanoma / Incidence and Newly Metastatic: Data from Epiphany Partners Inc. (http://www.time4epi.com) epic oncology™ [Data on file]. [accessed 6.11.21].

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[4] Merck Sharp & Dohme (UK) Ltd. *Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]: Document B. Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*, 2022 [accessed 16.2.22]. 54p.

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