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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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.

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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
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

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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

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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

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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

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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

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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.

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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.

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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.

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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

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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

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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

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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

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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

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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]

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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]

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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]

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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.

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- 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

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	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	

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	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

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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.

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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]

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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.

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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.

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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

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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	

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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)*".

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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]

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	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:

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	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.

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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)

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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

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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

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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

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- 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]

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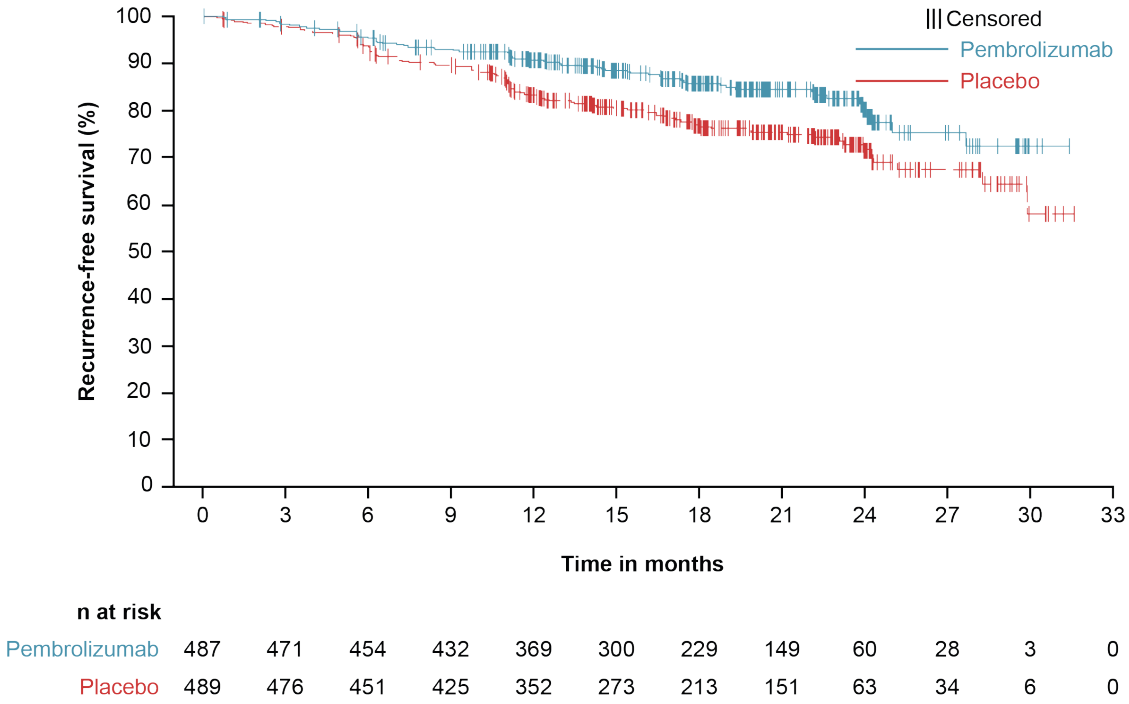
	(0.45, 0.82)	

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

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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.

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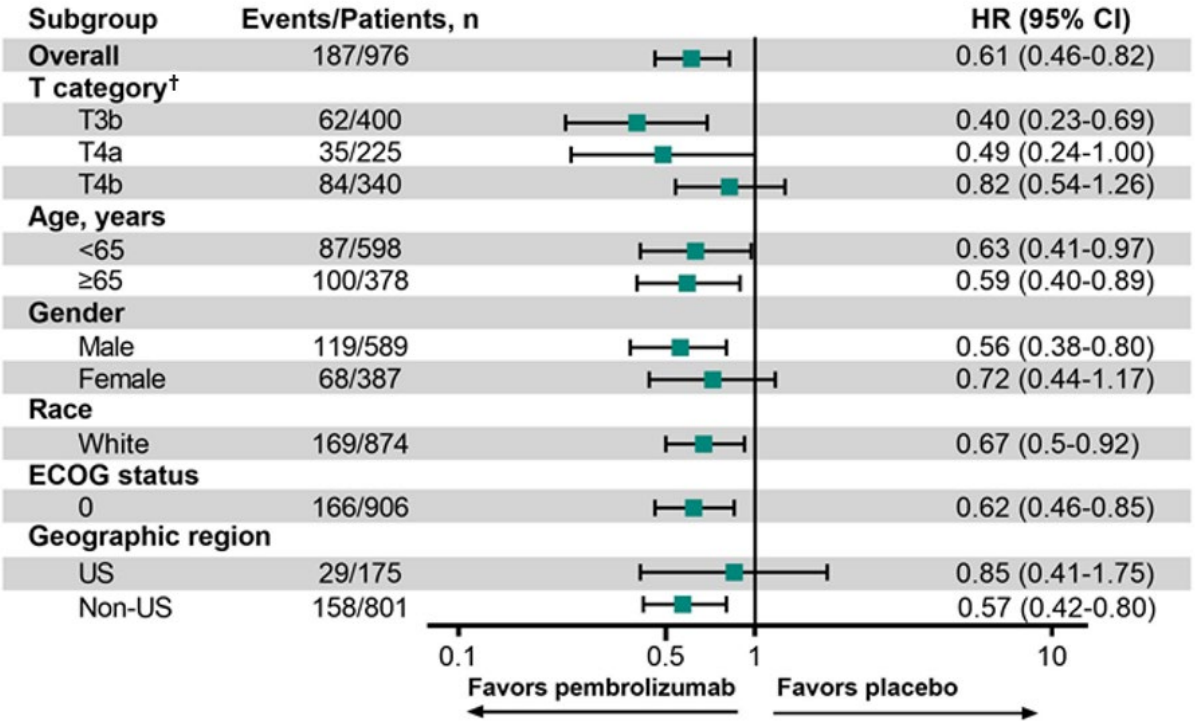
Figure 3.2: RFS stratified by prespecified subgroups



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.

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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.

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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			

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	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]

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	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]

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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]

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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]

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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]

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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]

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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]

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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]

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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

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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.

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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			

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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

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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.

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- 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

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	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)

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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.

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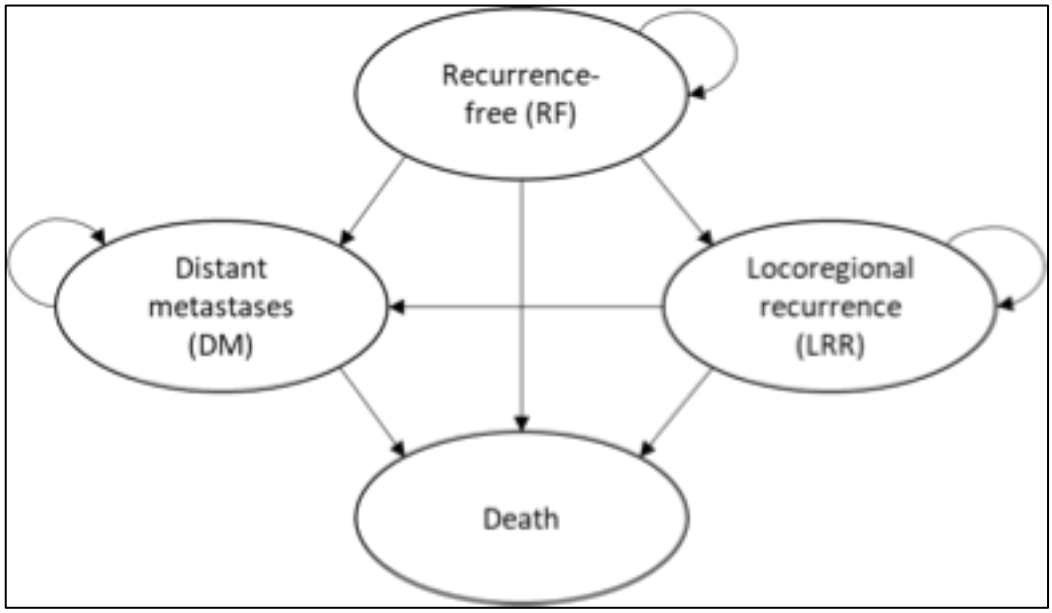
Figure 4.1: Model structure



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

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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

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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

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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

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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

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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

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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

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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-

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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

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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

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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),

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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]

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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

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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.

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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

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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.

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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.

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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

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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.

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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

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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).

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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

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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

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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

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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.

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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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8. REFERENCES

[1] 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.

[2] National Institute for Health and Care Excellence. *Pembrolizumab for djuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]: Final scope [Internet]*. London: NICE, 2021 [accessed 27.1.22] Available from: https://www.nice.org.uk/guidance/gid-ta10786/documents/final-scope

[3] Merck Sharp & Dohme (MSD) Ltd. *Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]: Response to request for clarification from the ERG*, 2022 [accessed 28.3.22]. 118p.

[4] European Medicine Agency (EMA). *Keytruda: summary of product characteristics (SPC)*, 2021 [accessed 17.11.21] Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

[5] European Medicine Agency (EMA). *Keytruda: procedural steps taken and scientific information after the authorisation [Internet]*. Amsterdam: EMA, 2022 [accessed 10.3.22] Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/keytruda-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf

[6] Jacobs CR, Rapoport BL, Chan SW, Ruff P, Arance AM, Mujika K, et al. KEYNOTE-555 Cohort B: efficacy, safety, and PK of pembrolizumab (pembro) 400 mg every 6 weeks (Q6W) as 1L therapy for advanced melanoma. *J Clin Oncol* 2021;39(15 Suppl):9541.

[7] U.S. Food and Drug Administration (FDA). FDA approves new dosing regimen for pembrolizumab [Internet]. 2020 [accessed 12.4.22]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-pembrolizumab

[8] National Institute for Health and Care Excellence. *Melanoma: assessment and management: NICE guideline 14 [Internet]*. London: NICE, 2015 [accessed 18.11.21] Available from: https://www.nice.org.uk/guidance/ng14/

[9] Larkin J, Acland K, Algurafi H, Allan R, Barlow C, Board R, et al. *Position paper: follow-up of high risk cutaneous melanoma in the UK [Internet]*. Cambridge: Melanoma Focus 2013 [accessed 18.1.22] Available from: https://melanomafocus.org/members/follow-up-position-paper/

[10] National Institute for Health and Care Excellence. *Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma: NICE Technology appraisal guidance 766 [Internet]*. London: NICE, 2022 [accessed 2.2.22] Available from: https://www.nice.org.uk/guidance/ta766

[11] National Institute for Health and Care Excellence. *Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease: NICE Technology appraisal guidance 684. [Internet]*. London: NICE, 2021 [accessed 18.11.21] Available from: https://www.nice.org.uk/guidance/ta684

[12] National Institute for Health and Care Excellence. *Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma: NICE Technology appraisal guidance 544 [Internet]*. London: NICE, 2018 [accessed 18.11.21] Available from: https://www.nice.org.uk/guidance/TA544

[13] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline statement. *J Clin Epidemiol* 2016;75:40-6.

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[14] Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol* 2009;62(9):944-52.

[15] Merck Sharp & Dohme (UK) Ltd. *Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence [ID3908]: Appendices. Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*, 2022 [accessed 16.2.22]. 131p.

[16] Scottish Intercollegiate Guidelines Network. Search filters [Internet]. 2021 [accessed 27.1.22]. Available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/

[17] Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. *Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019) [Internet]*: Cochrane, 2019 [accessed 27.1.22] Available from: https://training.cochrane.org/handbook

[18] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

[19] Downs SH, Black NCP. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-84.

[20] Luke JJ, Ascierto PA, Carlino MS, Gershenwald JE, Grob JJ, Hauschild A, et al. KEYNOTE-716: Phase III study of adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma. *Future Oncol* 2020;16(3):4429-38.

[21] Eggermont AMM, Rutkowski P, Dutriaux C, Hofman-Wellenhof R, Dziewulski P, Marples M, et al. Adjuvant therapy with pegylated interferon-alfa2b vs observation in stage II B/C patients with ulcerated primary: results of the European Organisation for Research and Treatment of Cancer 18081 randomised trial. *Eur J Cancer* 2020;133:94-103.

[22] Maio M, Lewis K, Demidov L, Mandalà M, Bondarenko I, Ascierto PA, et al. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2018;19(4):510-20.

[23] Hansson J, Aamdal S, Bastholt L, Brandberg Y, Hernberg M, Nilsson B, et al. Two different durations of adjuvant therapy with intermediate-dose interferon alfa-2b in patients with high-risk melanoma (Nordic IFN trial): a randomised phase 3 trial. *Lancet Oncol* 2011;12(2):144-52.

[24] Wilson M, Geskin LJ, Carvajal RD, Mehnert JM, Chiuzan C, Leiby B, et al. Adjuvant nivolumab in high-risk stage IIb/IIc melanoma patients: results from investigator initiated clinical trial. *J Clin Oncol* 2021;39(15 Suppl):9583.

[25] Luke JJ, Rutkowski P, Queirolo P, Vecchio MD, Mackiewicz J, Sileni VC, et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. *Ann Oncol* 2021;32(Suppl 5):S1283-346.

[26] Akman T, Oztop I, Baskin Y, Akbarpour M, Unal OU, Oflazoglu U, et al. The role of BRAF mutation in patients with high-risk malignant melanoma treated with high-dose adjuvant interferon therapy. *Med Oncol* 2015;32(1):440.

[27] Bilgin Ç, Çetinkünar S, Bilgen K, Celep B, Tokgöz S, Sözen S, et al. Impact of high dose chemoimmunotherapy after surgery on the overall and disease-free survivals in advanced stage malignant melanoma. *Ann Ital Chir* 2012;83(6):529-33.

[28] Luke JJ, Long GV, Khattak MA, de la Cruz Merino L, Del Vecchio M, Spagnolo F, et al. *Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: updated results from KEYNOTE-716. Presented at the 2021 Society for Melanoma Research Congress [PowerPoint]*, 2021 [accessed 17.2.22] Available from: https://bit.ly/3DOhtCH

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[29] Merck Sharp & Dohme (MSD) Ltd. *Data on File. KEYNOTE-716 Clinical Study Report (IA2 data cut-off June 2021)[PDF provided by the company]*

[30] Merck Sharp & Dohme (MSD) Ltd. *Data on File. KEYNOTE 716 Protocol (Number 716-04)[PDF provided by the company]*

[31] Cancer Research UK. Melanoma skin cancer incidence statistics [Internet]. London: Cancer Research UK, [accessed 17.11.21]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/incidence

[32] Merck Sharp & Dohme (MSD) Ltd. *Data on File. UK Melanoma Advisory Board (December 2021) [PDF provided by the company]*, 2021

[33] National Cancer Registration and Analysis Service (NCRAS). Cancer registration: epidemiology of melanoma (1995-2017) [Internet]. London: Public Health England, 2019 [accessed 27.1.22]. Available from: https://data.gov.uk/dataset/bc207b50-8ead-48fb-a026-f9bec0764d1b/cancer-registration-epidemiology-of-melanoma-1995-2017.

[34] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017;67(6):472-92.

[35] Merck. KEYTRUDA® (pembrolizumab) demonstrated significant improvement in distant metastasis-free survival (DMFS) compared to placebo as adjuvant therapy for patients with resected stage IIB and IIC melanoma in phase 3 KEYNOTE-716 trial. New results build on previously reported significant recurrence-free survival (RFS) benefit seen in these patients. News release [Internet]. Merck, 2022 [accessed 15.3.22]. Available from: https://www.merck.com/news/mercks-keytruda-pembrolizumab-demonstrated-significant-improvement-in-distant-metastasis-free-survival-dmfs-compared-to-placebo-as-adjuvant-therapy-for-patients-with-resected-stage/

[36] Sashegyi A, Ferry D. On the interpretation of the hazard ratio and communication of survival benefit. *Oncologist* 2017;22(4):484-6.

[37] Samlowski W, Silver M, Hohlbauch A, Zhang S, Scherrer E, Fukunaga-Kalabis M, et al. Real-world clinical outcomes in US Oncology Network (USON) patients with stage IIB and IIC cutaneous melanoma. Presented at the 18th International Congress of the Society for Melanoma Research (SMR); 28-31 Oct 2021; Virtual Congress [PDF provided by the company]. 2021.

[38] Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer* 2009;101(3):387-9.

[39] van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-15.

[40] Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13(5):509-18.

[41] Georghiou T, Bardsley M. *Exploring the cost of care at the end of life [Internet]*. London: Nuffield Trust 2014 [accessed 2.2.22] Available from: https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life

[42] British Association of Dermatologists. Melanoma stage 4 [Internet]. London: BAD, 2019 [accessed 21.4.22]. Available from: https://www.skinhealthinfo.org.uk/condition/stage-4-melanoma/

[43] Bajaj S, Donnelly D, Call M, Johannet P, Moran U, Polsky D, et al. Melanoma prognosis: accuracy of the American Joint Committee on Cancer Staging Manual Eighth Edition. *J Natl Cancer Inst* 2020;112(9):921-8.

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[44] Grimm SE, Pouwels X, Ramaekers BLT, Wijnen B, Knies S, Grutters J, et al. Development and Validation of the TRansparent Uncertainty ASsessmenT (TRUST) Tool for assessing uncertainties in health economic decision models. *Pharmacoeconomics* 2020;38(2):205-16.

[45] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

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