Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Cancer Drugs Fund Review of TA553

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

Completed 6 September 2021

CONTAINS COMMERCIAL IN CONFIDENCE AND ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID3776] (Cancer Drugs Fund Review of TA553)
Produced by:	Liverpool Reviews & Implementation Group (LR*i*G)
Authors:	James Mahon, Director, Coldingham Analytical Services, Berwickshire Sophie Beale, Director, Hare Research, North Yorkshire Angela Boland, Director, LR*i*G, University of Liverpool Rebecca Bresnahan, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool
Correspondence to:	Angela Boland, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB
Date completed:	6 September 2021

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 131840.

Declared competing interests of the authors: None.

Acknowledgements: The authors would like to thank Dr Neil Steven, Honorary Consultant in Medical Oncology, University Hospitals Birmingham, who provided feedback on the final version of the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Mahon J, Beale S, Boland A, Bresnahan R. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID3776]: Cancer Drugs Fund Review of TA553. Liverpool Reviews and Implementation Group, University of Liverpool, 2021.

Contributions of authors:

James Mahon	Critical appraisal of the economic evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Rebecca Bresnahan	Critical appraisal of the clinical evidence

Table of contents

1 EXECUTIVE SUMMARY 7
1.1 Overview of the ERG's key issues 7
1.2 Clinical effectiveness evidence: summary of the ERG's key issues 8
1.3 The cost effectiveness evidence: summary of the ERG's key issues 8
1.4 Summary of ERG's preferred assumptions and resulting cost effectiveness results 10
1.5 Company cost effectiveness results 10
1.5.1 Company cost effectiveness results 10
2 BACKGROUND 11
2.1 Introduction 11
2.2 Pembrolizumab 11
2.3 Evidence sources 11
3 THE CLINICAL DECISION PROBLEM 14
3.1 Population 14
3.2 Comparators 15
3.3 Survival data 15
3.3.1 Updated KEYNOTE-054 trial results: RFS, DMFS and OS 15
3.3.2 SACT overall survival data 17
3.4 Recurrence-free survival hazard ratio analyses 17
3.5 Subsequent treatments 18
3.6 ERG clinical effectiveness conclusions 19
4 THE COST EFFECTIVENESS DECISION PROBLEM 20
4.1 Relapse-free survival 20
4.2 Distant metastasis-free survival 21
4.3 Overall survival 21
4.3.1 Validation of company model OS projections 21
4.4 Duration of treatment effect 23
4.5 Subsequent treatments 25
4.6 NICE End of Life criteria 25
4.7 ERG cost effectiveness conclusions 25
5 REFERENCES 27

List of tables

Table 1 Reasons for patients with a SACT record stopping treatment with pembrolizumab 12
Table 2 ERG summary of NICE AC preferred clinical assumptions 14
Table 3 Original and extended data analysis results (ITT population) 16
Table 4 Pembrolizumab SACT data 17
Table 5 SACT subsequent treatment data 19
Table 6 ERG summary of NICE AC preferred economic assumptions 20
Table 7 Company concerns and ERG comment relating to the company Gershenwald/AJCC analysis 22
Table 8 Risk of experiencing a first recurrence: KEYNOTE-054 trial and company model data 24
Table 9 Risk of experiencing a distant metastasis: KEYNOTE-054 trial and company model data 24

List of figures

Figure 1 KEYNOTE-054 trial diagram 12
Figure 2 OS estimates for patients receiving routine surveillance (company model and Gershenwald/AJCC) 22

List of boxes

Box 1 NICE Appraisal Committee's preferred assumption: population 14
Box 2 Appraisal Committee's preferred assumption: comparators 15
Box 3 NICE Appraisal Committee's preferred assumption: survival results 15
Box 4 NICE Appraisal Committee's preferred assumption: RFS HRs 17
Box 5 NICE Appraisal Committee's preferred assumption: subsequent treatments 18
Box 6 NICE Appraisal Committee's preferred assumption: relapse-free survival 20
Box 7 NICE Appraisal Committee's preferred assumption: distant metastasis-free survival 21
Box 8 NICE Appraisal Committee's preferred assumption: overall survival 21
Box 9 NICE Appraisal Committee's preferred assumption: duration of treatment effect 23
Box 10 NICE Appraisal Committee's preferred assumption: subsequent treatments 25
Box 11 NICE Appraisal Committee's preferred assumption: NICE End of Life criteria 25

LIST OF ABBREVIATIONS

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

1 EXECUTIVE SUMMARY

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

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

1.1 Overview of the ERG's key issues

Table A Summary of key issues

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

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

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

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

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

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

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

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

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

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

SACT=Systemtic Anti-Cancer Therapy

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

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

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

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

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

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

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

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

1.5 Company cost effectiveness results

1.5.1 Company cost effectiveness results

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

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

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

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

2 BACKGROUND

2.1 Introduction

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

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

2.2 Pembrolizumab

Key facts:

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

2.3 Evidence sources

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

KEYNOTE-054 trial

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

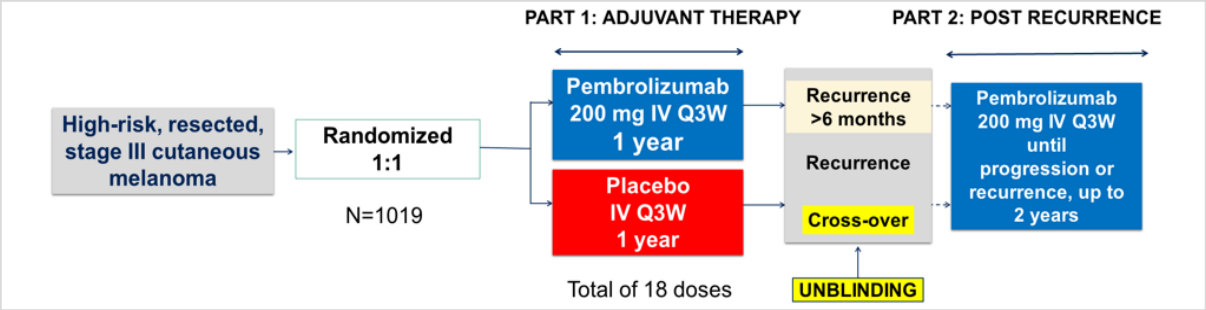

Figure 1 KEYNOTE-054 trial diagram

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

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

SACT data

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

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

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

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

Source: Public Health England report[5]

Comparison of KEYNOTE-054 trial and SACT patient populations

The main differences between the two populations are:

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

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

3 THE CLINICAL DECISION PROBLEM

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

Table 2 ERG summary of NICE AC preferred clinical assumptions

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

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

3.1 Population

Box 1 NICE Appraisal Committee's preferred assumption: population

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

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

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

The ERG is satisfied that the patients recruited to the KEYNOTE-054 trial are broadly representative of patients with resected Stage III melanoma who are treated in the NHS and appear to match the population specified in the final scope issued by NICE. However:

- clinical advice to the ERG is that approximately 20% of patients with Stage III melanoma treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than patients participating in the KEYNOTE-054 trial (ECOG PS 0: 94.4%; ECOG PS 1: 5.6%) or who contributed to the SACT dataset (only patients who had an ECOG PS of 0 or 1 were elegible to receive pembrolizumab)
- approximately four-fifths (83.3%) of patients enrolled in the KEYNOTE-054 trial were defined as having programmed death-ligand 1 (PD-L1) positive disease. However, as PD-L1 testing is not routinely carried out in the NHS, it is not known whether a similarly high proportion of NHS patients have PD-L1 positive disease.

3.2 Comparators

Box 2 Appraisal Committee's preferred assumption: comparators

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

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

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

3.3 Survival data

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

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

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

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

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

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

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

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

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

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

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

† Company clarification response

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

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

3.3.2 SACT overall survival data

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

Table 4 Pembrolizumab SACT data

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

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

3.4 Recurrence-free survival hazard ratio analyses

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

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

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

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

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

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

3.5 Subsequent treatments

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

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

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

KEYNOTE-054 trial

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

SACT data

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

Table 5 SACT subsequent treatment data

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

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

3.6 ERG clinical effectiveness conclusions

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

4 THE COST EFFECTIVENESS DECISION PROBLEM

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

Table 6 ERG summary of NICE AC preferred economic assumptions

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

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

The ERG is satisfied that the structure of the company model is appropriate for the assessment of the cost effectiveness of pembrolizumab as an adjunctive therapy versus routine surveillance for patients with Stage III melanoma. However, concerns remain around the validity of company model OS estimates and the ERG considers that company model cost effectiveness results remain highly uncertain.

4.1 Relapse-free survival

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

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

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

4.2 Distant metastasis-free survival

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

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

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

4.3 Overall survival

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

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

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

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

4.3.1 Validation of company model OS projections

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

Pembrolizumab overall survival data

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

Routine surveillance overall survival data

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

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

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

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

Source: CDF Review CS, pp70-71

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

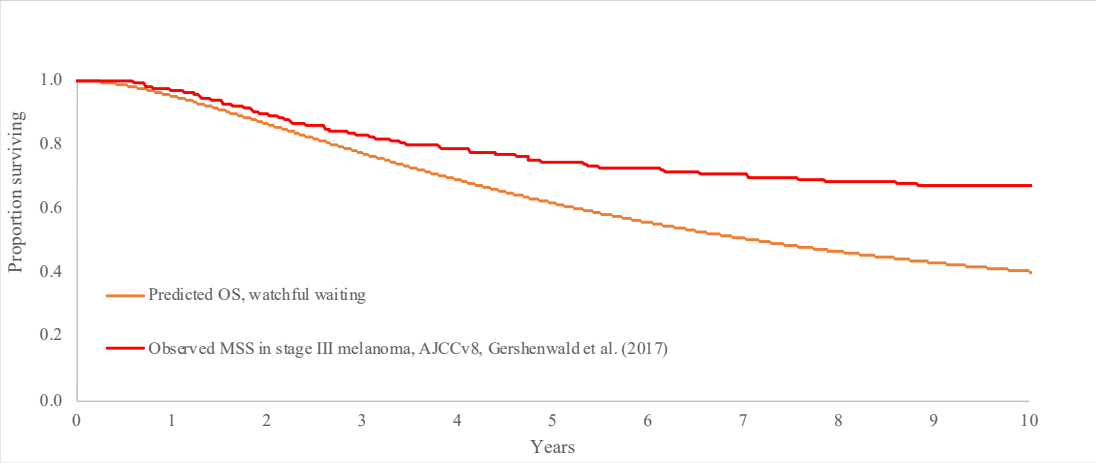

Figure 2 OS estimates for patients receiving routine surveillance (company model and Gershenwald/AJCC)

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

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

4.4 Duration of treatment effect

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

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

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

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

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

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

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

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

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

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

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

4.5 Subsequent treatments

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

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

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

4.6 NICE End of Life criteria

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

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

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

4.7 ERG cost effectiveness conclusions

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

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

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

5 REFERENCES

1. National Institute for Health and Care Excellence. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [TA553]. Published 19 December 2018; Available from: www.nice.org.uk/guidance/ta553/history. Accessed 16 August 2021.
2. National Institute for Health and Care Excellence. Cancer Drugs Fund. Managed Access Agreement. Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence. Published December 2018; Available from: www.nice.org.uk/guidance/ta553/resources/managed-access-agreement-december-2018-pdf-6606117613. Accessed 16 August 2021.
3. National Institute for Health and Care Excellence. Terms of engagement for CDF Review of TA553: Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence. 2019.
4. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, *et al.* Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2021; 22:643-54.
5. Public Health England. SACT: Pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage III malignant melanoma – data review2021 [Confidential report for the NICE Appraisal Committee for the Review of TA553].
6. Eggermont AM, Meshcheryakov A, Atkinson V, Blank CU, Mandala M, Long GV, *et al.* Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase 3 trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma. J Clin Oncol. 2021; 39:abstr 9500.
7. 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; 67:472-92.

Cresected melanoma with high risk of recurrence. Final scope. Published 6 April 2018; Available from: www.nice.org.uk/guidance/ta553/documents/final-scope. Accessed 17 August 2021.

9. Merck Sharp & Dohme B.V. Pembrolizumab (KEYTRUDA). Annex I. Summary of Product Characteristics Published 14 July 2021; Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Accessed 18 August 2021.
10. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994; 81(3):515-26.
11. Lin DY, Wei LJ, Ying Z. Checking the Cox Model with Cumulative Sums of Martingale-Based Residuals. Biometrika. 1993; 80:557-72.
12. National Institute for Health and Care Excellence. NICE Pathways. Melanoma overview. Published 30 July 2021; Available from: www.pathways.nice.org.uk/pathways/melanoma. Accessed 18 August 2021.
13. National Institute for Health and Care Excellence. Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma [TA562]. Published 27 February 2019; Available from: https://www.nice.org.uk/guidance/TA562. Accessed 18 August 2021.
14. National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER). Published 8 July 2021; Available from: www.seer.cancer.gov/. Accessed 31 August 2021.
15. National Institute for Health and Care Excellence. Pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366]. Published 12 September 2017; Available from: www.nice.org.uk/guidance/ta366. Accessed 31 August 2021.
16. National Institute for Health and Care Excellence. Appraising life-extending, end of life treatments. Published July 2009; Available from: www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2. Accessed 20 August 2021.